MIZOSIN TABLET

DESCRIPTION:
Mizosin Tablet 1mg: An orange, 7 mm round, biconvex, with '1' scored on one side and plain on the other side, uncoated tablet.
Mizosin Tablet 2mg: A white, 8 mm round, biconvex, with '2' scored on one side and plain on the other side, uncoated tablet.

COMPOSITION:
Mizosin Tablet 1mg: Each tablet contains (Sigma) Prazosin Hydrochloride equivalent to Prazosin 1 mg.
Mizosin Tablet 2mg: Each tablet contains (Sigma) Prazosin Hydrochloride equivalent to Prazosin 2 mg.

PHARMACODYNAMICS:
Prazosin HCl causes a decrease in total peripheral resistance but the exact mechanism of action is unknown. Animal studies suggest that the vasodilator effect of Prazosin HCl is related to the blockade of post-synaptic alpha-adreno-receptors. The results of dog forelimb experiments demonstrate that the peripheral vasodilator effect is confined mainly to the level of the resistance vessels (arterioles). Unlike conventional alpha-blockers the antihypertensive action of Prazosin HCl is usually not accompanied by reflex tachycardia. Haemodynamic studies have been carried out in hypertensive patients following acute single dose administration 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 significant change in cardiac output, heart rate, renal blood flow, and glomerular filtration rate. There is no measurable negative chronotropic effect.
Prazosin HCl may increase plasma renin activity in patients with congestive cardiac failure.
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 does not appear to develop in long-term clinical use in the treatment of hypertension. Rebound elevation of blood pressure does not occur following abrupt cessation of Prazosin HCl therapy.
In patients with congestive heart failure there is reduction in left ventricular filling pressure, reduction in cardiac impedance and augmentation of cardiac output. It does not provoke a reflex tachycardia in such patients.
Enucleated hyperplastic glandular tissue and hyperthrophied 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 a pharmacological treatment of benign prostatic hyperplasia (BPH) involving alpha-adrenoceptor antagonism. There is evidence of statistically significant improvement in urinary flow following Prazosin HCl therapy in patients with BPH. There is also evidence for a reduction in the volume of residual bladder urine and for improvement in symptoms of BPH such as frequency of micturition.
Raynaud's phenomenon and Raynaud's disease have been successfully treated with Prazosin HCl. The vasodilator action of the drug may increase blood flow to affected parts to reduce the severity of the sign and symptoms and the frequency and duration of attacks.

PHARMACOKINETICS:
Following oral administration to 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 congestive cardiac failure, most of whom showed evidence of hepatic congestion, indicate that peak plasma concentrations are reached in 2.5 hours and plasma half-life is approximately seven hours. The bioavailability of oral prazosin was also increased 2-3 times in patients with congestive cardiac failure but the time to reach the peak was not affected in patients compared to normal volunteers. The mechanism of increase in plasma half-life and bioavailability of prazosin in congestive heart failure has not been satisfactorily explained. The drug is highly bound to plasma protein. Animal studies indicate that Prazosin HCl is extensively metabolized primarily by demethylation and conjugation, and excreted mainly via bile and faeces. Less extensive human studies suggest similar metabolism and excretion in man.

INDICATIONS:
In Patients with Hypertension: Prazosin HCl is indicated in the treatment of hypertension of varied aetiology and all grades of severity. It can be used as the initial and sole agent or it may be employed in a general treatment programme in conjunction with other antihypertensive agents. Renal blood flow and glomerular filtration rate are not impaired by long-term oral administration. Prazosin HCl can be used with safety in hypertensive patients with impaired renal function.
In Patient with Congestive Heart Failure: Prazosin HCl is indicated in the treatment of severe refractory congestive heart failure. Prazosin HCl may be added to the therapeutic regime in those patients who have become refractory to conventional therapy with cardiac glycosides and diuretics.
In Patients with Raynaud's Phenomenon and Raynaud's Disease: Prazosin HCl is indicated in the treatment of Raynaud's phenomenon and Raynaud's disease.
Benign Prostatic Hyperplasia: Prazosin HCl is indicated as an adjunct in the symptomatic treatment of urinary obstruction caused by benign prostatic hyperplasia in patients awaiting prostatic surgery.

RECOMMENDED DOSAGE:
General Comment: There is evidence that patient toleration is best when therapy is best when therapy is initiated with a low starting dose. The dose is to be adjusted on the basis of the patient's individual blood pressure response.
Response is usually seen early (1 to 14 days) if it is to occur at a given dose. If a response is seen, therapy should be continued at the dose until the degree of response has reached the optimum possible before adding the next increment.
Specific Recommendations: In patients with hypertension: Suggested Initial Dose Range: 0.5mg twice daily (b.d.) increasing to 1.0mg b.d. or three times daily (t.i.d.).
Usual Maintenance Dose: 3.0mg to 20mg daily in divided dose.
The following are given as guides to administration.
Patients receiving No Antihypertensive Therapy: It is recommended that therapy be initiated at 0.5mg b.d. for three days. Unless the patient is unusually sensitive, this dose should be increased to 1.0mg b.d. or t.i.d. for a further three days and then to 2mg two or three times daily. Thereafter, as determined by the patient's response to the blood pressure lowering effect, the daily dose should be increased gradually to 20mg. The optimal response may take up to six weeks. After initial titration some patients can be maintained on a twice daily dosage regimen.
A diuretic may be added to enhance the efficacy. It is recommended that this addition be considered when the Prazosin HCl dose is at 2mg b.d. or t.i.d.
Patients Receiving Diuretic Therapy with Inadequate Control of Blood Pressure: The diuretic should be reduced to a maintenance dose level for the particular agent and Prazosin HCl initiated at 0.5mg b.d.
*The manufacturer's instructions for gradual dose reduction should be followed particularly in the case of clonidine to avoid, possible rebound hypertension.
After the initial period of observation, the dose of Prazosin HCl should be gradually increased as determined by the patient's response.
Patients Receiving Other Antihypertensive Agents but with Inadequate Control: Because some additive effect is anticipated, the other agent (eg: beta-adrenergic blocking agent alpha methyldopa, reserpine, clonidine etc.)* should be reduced and Prazosin HCl initiated at 0.5mg b.d. subsequent dosage increase should be made depending upon the patient's response.
Though experience is limited, there is evidence that adding Prazosin HCl to beta-adrenergic blocking agents may bring about a substantial reduction in blood pressure. Thus, the low initial dose regimen is strongly recommended.
Patients with Moderate to Severe Grades of Renal Impairment: Evidence to date show that Prazosin HCl does not further compromise renal function when used in patients with renal impairment. Because some patients in this category has responded to small doses of Prazosin HCl, it is recommended that therapy be initiated at 0.5mg daily and that dose increases be instituted cautiously.
In Patients with Congestive heart Failure: Suggested Initial Daily Dose Range: 0.5mg increasing to 4.0mg in divided doses.
Usual Daily Maintenance Dose: 4.0mg to 20mg divided dose.
In recumbent patients the recommended starting dose is 0.5mg three to four times a day. Dosage should be titrated according to the patient's clinical response based on careful monitoring of cardiopulmonary signs and symptoms or haemodynamic studies when indicated. Dosage titration steps may be performed as often as every two to three days in patients under close medical supervision. In severely ill, decompensated patients, rapid dose titration over 1 or 2 days may be indicated and is best done when haemodynamic monitoring is available. In clinical studies to date the mean optimal daily dose during the initial treatment period was 11.5mg with therapeutic dosages ranging from 4mg to 20mg daily in divided doses. Retitration may be required in some patients to maintain optimal clinical improvement.
Raynaud's Phenomenon and Raynaud's Disease: Suggested Starting Dosage – 0.5mg b.d. Usual daily Maintenance Dosage – 1mg and 2mg b.d.
The recommended starting dosage is 0.5mg b.d. given for a period of three to seven days. Dosage should be adjusted according to the patient's clinical response.
Benign Prostatic Hyperplasia: The recommended starting dose is 0.5mg twice daily, given for a period of 3 to 7 days and then adjusted according to clinical response. The recommended maintenance dosage is 2mg twice daily. The use of doses over 4mg daily has not been studied, and cannot be recommended at present. Doses up to 4mg daily have produced amelioration of symptoms for periods of up to 4 weeks but currently longer term date are not available. Postural hypotension may occur: refer to "Precaution – General (All Patients)".

ROUTE OF ADMINISTRATION: Oral

CONTRAINDICATIONS:
Prazosin HCl is contraindicated in patients with a known sensitivity to the drug.

WARNING & PRECAUTIONS:
Use in Patients with Congestive Heart Failure: Prazosin HCl is not recommended in the treatment of congestive heart failure due to mechanical obstruction such as aortic valve stenosis, mitral valve stenosis, pulmonary embolism and restrictive pericardial disease. Adequate rate are not yet available to establish efficacy in patients with congestive heart failure due to recent myocardial infarction.
General (All Patients): Prazosin HCl 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 about severe tachycardia with heart rates of 120-160 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 HCl. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2mg 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 0.5mg, by subsequently increasing the dosage slowly by introducing any additional antihypertensive drugs into the patient's regimen with caution (see Dosage and Administration). Hypotension may develop in patients given Prazosin HCl are also receiving a beta-blocker or a diuretic.
Addition of a diuretic or other antihypertensive agent to Prazosin HCl therapy has been shown to cause an additive hypotensive effect. This effect can be minimized by reducing the dose of Prazosin HCl to 1mg or

2mg twice daily, by introducing additional antihypertensive drugs cautiously and then retitrating Prazosin HCl on clinical response.
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.
Patient should always be started at a dose of 0.5mg of Prazosin HCl. The 2mg and 5mg tablets are not indicated for initial therapy. Both lying and standing blood pressure should be measured.
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 the 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 HCl therapy.
In Patients with Raynaud's Phenomenon or Raynaud's Disease: Because Prazosin HCl decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration of Prazosin HCl is suggested (See" General All Patients").
In Patients with Congestive Heart Failure: In patients with acute or chronic left ventricular failure who have undergone vigorous diuretic and vasodilator treatment, the resultant decrease in left ventricular failure who have undergone vigorous diuretic and vasodilator treatment, the resultant decreases in left ventricular filling may be associated with a significant fall in cardiac output and systemic blood pressure when Prazosin is administered. In such patients, a low initial dose of Prazosin and gradual titration with close observation is recommended (See "Dosage and Administration").
The haemodynamic response to prazosin in patients with congestive heart failure should be carefully monitored to ensure sustained clinical improvement as rapid attenuation of improved cardiac performance might occur in some patients.
In occasional patients with congestive heart failure, the clinical efficacy of Prazosin has been reported to diminish due to complete or partial tolerance to haemodynamic effects of Prazosin. Evidence of efficacy for periods exceeding 6 months is lacking. In these patients there is usually evidence of weight gain or peripheral oedema indicating fluid retention. Since spontaneous deterioration may occur in such severely ill patients a casual relationship to Prazosin therapy has not been established. Thus, as with all patients with congestive heart failure, careful adjustment of diuretic dosage according to the patient's clinical condition is required to prevent excessive fluid retention and consequent recurrence of symptoms. In those patients without evidence of fluid retention, when clinical improvement has diminished, an increase in the dosage of Prazosin HCl temporary withdrawal of the drug and / or addition of an aldosterone antagonist (eg: spironolactone) to the treatment regimen will usually restore clinical efficacy.
Patients with Benign Prostatic Hyperplasia: Prazosin HCl decreases peripheral vascular resistance and since many patients with this disorder are elderly, standing and lying blood pressure should be carefully monitored during initial administration and during adjustment of the dose of Prazosin HCl. Refer to "general-All Patients". Close observation is especially recommended for patients taking medications are known to lower blood pressure.
Use in Children: Prazosin HCl is not recommended for the treatment of children under the age of twelve years since safe conditions for its use have not been established.
Patients with Angina: Prazosin HCl should be used cautiously in patients with ischaemic heart disease as angina may be exacerbated.
Patients with Impaired Liver Function: There is no data available on the use of Prazosin in liver disease. However, as the drug is primarily metabolized by the liver and excreted in the bile and faeces, patients with impaired hepatic function may require a lower dose.

USE IN PREGNANCY & LACTATION:
Use in Pregnancy: When both male and female rats were treated with Prazosin HCl at a dose of 75mg/kg/day and then mated, there was a significant impairment of fertility. There is no information available as to whether Prazosin HCl crosses the placenta. No teratogenic effects were seen in animal testing. However, the safety of Prazosin HCl used during pregnancy has not been established. Accordingly, it should be used only when, in the opinion of the physician, expected benefit to the pregnant patient outweighs any potential risk.
Use in Lactation: Prazosin HCl has been shown to appear in breast milk, it should be administered to a nursing mother only when, in the opinion of the physician, the expected benefit outweighs any potential risk. Consideration should be given to not breast-feeding the baby.

SIDE EFFECTS:
The following percentages are derived from reports of clinical trials but it should not be noted that the dosage used in some of these trials were higher than the current recommendations.
More Common Reactions:
Cardiovascular: Postural hypotension (14%), palpitations (5%), oedema (4%).
Gastrointestinal: Nausea (5%), dry mouth (4%).
General: Lack of energy (7%), weakness (7%)
Nervous System: Headache (8%), drowsiness (8%)
Ocular: Blurred vision (4%)
Respiratory: Nasal Congestion (4%)
Less Common Reactions:
Cardiovascular: Tachycardia (1%), syncope (1%). There are reports of exacerbation of pre-existing angina.
Dermatological: Rash and pruritus (1%), alopecia; lichen planus.
Gastrointestinal: Vomiting (3%), constipation (3%), diarrhoea (2%); liver function abnormalities; pancreatitis.
Genitourinary: Urinary incontinence, priapism, impotence (1 case reported).
Nervous System: Nervousness (2%), depression (2%), paraesthesiae, hallucinations, reddened sclera, tinnitus.
Respiratory: dyspnoea (2%), epistaxis.
General: Fever diaphoresis, positive ANA titre, arthralgia.
Serious or Life Threatening Reactions:
Postural hypotension, especially in elderly patients with cerebrovascular disease, may be dangerous. Exacerbation of pre-existing angina, new-onset angina and myocardial infarction have been associated with prazosin, although a casual relationship has been established.

SYMPTOMS AND TREATMENT OF OVERDOSE:
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 accompanied 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 HCl is not dialyzable because it is protein bound.

STORAGE CONDITION: Store below 30°C. Protect from light. Keep out of reach of children. *Jauhkan daripada kanak-kanak.*

PACK SIZE: Mizosin Tablet 1mg: Blister of 10 x 10's and 100 x 10's tablets.
Mizosin Tablet 2mg: Blister of 10 x 10's, 50 x 10's and 100 x 10's tablets.

SHELF LIFE: Please refer to outer package.

PRODUCT REGISTRATION HOLDER & MANUFACTURER:
DUOPHARMA (M) SDN BHD
Lot 2599 Jalan Seruling 59 Kawasan 3, Taman Klang Jaya,
41200 Klang, Selangor, MALAYSIA.