Prazosin Hydrochloride GITS Tablets
MINIPRESS® XL GITS Tablets

1. NAME OF THE MEDICINAL PRODUCT

MINIPRESS XL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated GITS tablet contains Prazosin Hydrochloride I.P. equivalent to 2.5 or 5 mg prazosin.

For full list of excipients, please see section 6.1.

All strengths/presentations mentioned in this document might not be available in the market.

3. PHARMACEUTICAL FORM

Controlled release tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension

Prazosin hydrochloride GITS is indicated in the treatment of all grades of essential (primary) hypertension and of all grades of secondary hypertension of varied etiology. It can be used as the initial and sole agent, or it may be employed in a treatment program in conjunction with a diuretic and/or other antihypertensive drugs as needed for proper patient response.

Benign Prostatic Hyperplasia (BPH)

Prazosin hydrochloride GITS 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.

4.2 Posology and Method of Administration

Prazosin hydrochloride GITS can be taken with or without food.

The GITS tablets could be swallowed whole with a sufficient amount of liquid. Patients should not chew, divide, or crush the tablets (see section 4.4 Special Warnings and Special Precautions for Use: *Information for Patients*).

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

Hypertension

The initial dose is 2.5 mg given once daily (see section 4.4 Special Warnings and Special Precautions for Use: *Hypertension*). Dosage may be increased gradually as clinically indicated to 20 mg given in once daily doses.

Benign Prostatic Hyperplasia

The recommended starting dose is 2.5 mg given once daily for a period of 3 to 7 days and should be adjusted according to clinical response. The usual maintenance dosage is 5 mg given once daily. This dose should not be exceeded.

Use in Renally Impaired Patients

Renal blood flow and glomerular filtration rate are not impaired by long-term oral administration and thus prazosin hydrochloride GITS can be used with safety in hypertensive patients with impaired renal function.

Use in Children

Prazosin hydrochloride GITS is not recommended for the treatment of children under the age of 12 years since safe conditions for its use have not been established.

4.3 Contraindications

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

4.4 Special Warnings and Special Precautions for Use

Gastrointestinal Disorders

Markedly reduced GI retention times of prazosin hydrochloride GITS may influence the pharmacokinetic profile and hence the clinical efficacy of the drug. As with any other nondeformable material, caution should be used when administering prazosin hydrochloride GITS in patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic).

There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this nondeformable sustained release formulation.

Priapism

Since marketing, cases of prolonged erection and priapism have been reported with alpha-1 blockers, including prazosin. If an erection persists for more than 4 hours, the patient should immediately consult a doctor. If the priapism is not treated immediately, penile tissue lesions and permanent impotence may result.

Information for Patients

Patients should be informed that prazosin hydrochloride GITS should be swallowed whole. Patients should not chew, divide or crush the tablets. Patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. In prazosin hydrochloride GITS the medication is contained within a nonabsorbable shell that has been specially designed to slowly release the drug so the body can absorb it. When this process is completed, the empty tablet is eliminated from the body.

Hypertension

A very small percentage of patients have responded in an abrupt and exaggerated manner to the initial dose of prazosin hydrochloride. 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 prazosin hydrochloride and with small increases in dosage during the first 1 to 2 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 dizziness or weakness occur during the initiation of prazosin hydrochloride therapy.

Benign Prostatic Hyperplasia

Prazosin hydrochloride decreases peripheral vascular resistance and since many patients with this disorder are elderly, careful monitoring of blood pressure during initial administration and during adjustment of the dose of prazosin hydrochloride GITS is suggested. Close observation is especially recommended for patients taking medications that are known to lower blood pressure.

Use with PDE-5 Inhibitors[1]

As with other alpha-1 blockers, concomitant administration of prazosin hydrochloride GITS with a PDE-5 inhibitor should be used with caution as it may lead to symptomatic

hypotension in some patients. No studies have been conducted with prazosin hydrochloride GITS.

4.5 Interactions with Other Medicaments and Other Forms of Interaction

Prazosin hydrochloride has been administered without any adverse drug interaction in 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, propranolol and quinidine; and (6) analgesics, antipyretics and anti-inflammatory agents- propoxyphene, aspirin, indomethacin, and phenylbutazone type.

Addition of a diuretic or other antihypertensive agent to prazosin hydrochloride has been shown to cause an additive hypotensive effect. This effect can be minimized by reducing the dose of prazosin hydrochloride GITS to 2.5 mg or 5 mg once a day, by introducing additional antihypertensive drugs cautiously and then by retitrating prazosin hydrochloride GITS based on clinical response.

Concomitant administration of prazosin hydrochloride GITS with PDE-5 inhibitors: see section 4.4 Special Warnings and Special Precautions for Use (*Use with PDE-5 Inhibitors*).

False positive results may occur in screening tests for pheochromocytoma (urinary vanillylmandelic acid [VMA] and methoxyhydroxyphenyl glycol [MHPG], urinary metabolites of norepinephrine) in patients who are being treated with prazosin hydrochloride.

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

4.6 Fertility, Pregnancy and Lactation

Fertility

Animal studies have shown that prazosin hydrochloride may alter fertility (see section 5.3).

Pregnancy

Although no teratogenic effects were seen in animal testing, the safety of prazosin hydrochloride use during pregnancy has not yet been established. The use of prazosin hydrochloride 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 hydrochloride was continued for as long as 14 weeks.

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

There are no adequate and well controlled studies which establish the safety of prazosin hydrochloride in pregnant women. Prazosin hydrochloride 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.

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

4.7 Effects on Ability to Drive and Use Machines

The ability to engage in activities such as operating machinery or operating a motor vehicle may be impaired, especially when initiating prazosin hydrochloride GITS therapy.

4.8 Undesirable Effects

The most common reactions associated with prazosin hydrochloride therapy are:

Body as a Whole: Lack of energy, weakness (asthenia)

Central & Peripheral Nervous: Dizziness (faintness), headache

Gastrointestinal: Nausea

Heart Rate/Rhythm: Palpitations

Psychiatric: Drowsiness

In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dosage of the drug.

In addition, the following reactions have been associated with prazosin hydrochloride therapy:

Autonomic Nervous: Diaphoresis, dry mouth, flushing, priapism

Body as a Whole: Allergic reaction, asthenia (weakness), fever, malaise, pain

Cardiovascular, General: Angina pectoris, edema, hypotension, orthostatic hypotension, syncope

Central & Peripheral Nervous: Faintness (dizziness), paresthesia, vertigo

Collagen: Positive ANA titer

Endocrine: Gynecomastia

Gastrointestinal: Abdominal discomfort and/or pain, constipation, diarrhea, pancreatitis, vomiting

Hearing/Vestibular: Tinnitus

Heart Rate/Rhythm: Bradycardia, tachycardia

Liver/Biliary: Liver function abnormalities

Musculoskeletal: Arthralgia

Psychiatric: Depression, hallucinations, impotence, insomnia, nervousness

Respiratory: Dyspnea, epistaxis, nasal congestion

Skin & Appendages: Alopecia, pruritus, rash, lichen planus, urticaria

Urinary: Incontinence, urinary frequency

Vascular (Extracardiac): Vasculitis

Vision: Blurred vision, reddened sclera, eye pain

Some of these reactions have occurred rarely, and in many instances the exact causal relationships have not been established.

Literature reports exist associating prazosin hydrochloride therapy with a worsening of pre-existing narcolepsy. A causal relationship is uncertain in these cases.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

4.9 Overdose

Accidental ingestion of at least 50 mg of prazosin hydrochloride in a 2 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 prazosin hydrochloride is not dialyzable because it is protein bound.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Hypertension

Prazosin hydrochloride causes a decrease in total peripheral vascular resistance. Animal studies suggest that the vasodilator effect of prazosin hydrochloride is related to blockade of postsynaptic 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 prazosin hydrochloride is usually not accompanied by reflex tachycardia.

Most studies indicate that chronic therapy with prazosin hydrochloride 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 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, 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 prazosin hydrochloride.

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) cholesterol and an increased risk of coronary heart disease. Clinical studies have shown that prazosin hydrochloride lowers LDL levels and either has no effect or increases levels of HDL.

Benign Prostatic Hyperplasia

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 a pharmacological treatment of benign prostatic hyperplasia (BPH) involving alpha-adrenoceptor antagonism.

There is evidence of statistically significant improvement in urinary flow following therapy with prazosin hydrochloride 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.

5.2 Pharmacokinetic Properties

Prazosin hydrochloride is readily absorbed from the gastrointestinal tract as assessed by plasma drug concentrations after oral administration. Plasma drug concentrations rise at a slow, controlled rate after dosing with prazosin hydrochloride GITS and reach a plateau at approximately six 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. Steady-state plasma levels are achieved by the second dose. At steady-state, the bioavailability of the GITS tablet is 86% relative to prazosin hydrochloride capsules. Bioavailability is not influenced by morning versus evening administration nor by concurrent food ingestion. The pharmacokinetics of prazosin hydrochloride GITS tablets are linear over the 2.5 to 30 mg dose range in that plasma prazosin hydrochloride concentrations are proportional to dose administered and the multiple-dose profile can be predicted from the single-dose profile. There was no evidence of dose-dumping either in the presence or absence of food in over 180 subjects who participated in pharmacokinetic studies.

5.3. Preclinical Safety Data

Conventional genotoxicity study results for prazosin hydrochloride have been negative. Toxicity studies at repeated doses have shown modifications at the testicular level (atrophy and necrosis) in rats and dogs at doses of 25 mg/kg/day (corresponding to, respectively, 12 and 40 times the maximum recommended dose in humans).

In conventional peri- and postnatal fertility and toxicity studies in rats respectively, a decrease in male and female fertility, and a decrease in size from the time of birth until weaning were observed at high doses of 75 mg/kg/day (corresponding to 36 times the maximum dose in humans). These effects were not observed at the dose of 25 mg/kg/day (corresponding to 12 times the maximum recommended dose in humans). Prazosin has not been shown to be teratogenic in rats and rabbits.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Polyethylene oxide, sodium chloride, methylhydroxypropylcellulose, ferric oxide, magnesium stearate, cellulose acetate, polyethylene glycol.

6.2 Incompatibilities

None known.

6.3 Shelf Life

MINIPRESS XL tablets 2.5 mg: 36 months

MINIPRESS XL tablets 5 mg: 36 months

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Nature and Contents of Container

Blister PVC/Aluminium.

MINIPRESS XL tablets 2.5 mg: One strip of 15 tablets each, 5 strips in one carton.
One strip of 30 tablets each, 10 strips in one carton.

MINIPRESS XL tablets 5 mg: One strip of 15 tablets each, 5 strips in one carton.
One strip of 30 tablets each, 10 strips in one carton.

6.6 Instruction for Use/Handling

Tablets should be swallowed whole. Do not break, crush or chew.

REFERENCES

1. Clinical Expert Report: *Co-Administration of Prazosin with PDE-5 Inhibitors*. D.L. Bell Pfizer Inc. January 31, 2004