1. NAME OF THE MEDICINAL PRODUCT

UNIPROST® 4 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each cross scored tablet contains 4 mg of Doxazosin (as mesylate). For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets. White round biconvex uncoated tablets with one side lip type cross scored and side BP13.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

• Essential hypertension. Doxazosin is not appropriate for first-line treatment. It may be used as a monotherapy in patients who have failed to respond to or have contraindications to other agents. Alternatively, use should be limited to second or third line treatment in combination with other antihypertensives.
• Symptomatic treatment of benign prostatic hyperplasia.

4.2 Posology And Method Administration

treatment should be established by a physician. Hypertension:
Doxazosin is used in a once daily regimen: the initial dose is 1mg, to minimise the potential for postural hypotension and/or syncope (see section 4.4). Dosage may then be increased to 2mg after an additional one or two weeks of therapy and thereafter, if necessary to 4mg. The majority of patients who respond to Doxazosin will do so at a dose of 4mg or less. Dosage can be further increased if necessary to 8mg or the maximum recommended dose of 16mg. Benign Prostatic Hyperplasia:
The recommended initial dosage of Doxazosin is 1mg given once daily to minimise the potential for postural hypotension and/or syncope (see section 4.4). Depending on the individual patient's urodynamics and BPH symptomatology dosage may then be increased to 2mg and thereafter to 4mg and up to the maximum recommended dose of 8mg. The recommended titration interval is 1-2 weeks. The usual recommended dose is 2-4mg daily.

Use in elderly:
Same dosage as for adults.
Use in patients with renal impairment:
There is no change in pharmacokinetics of doxazosin in patients with renal impairment. Therefore, the usual dose is generally recommended. Due to possible hypersensitivity in some of these patients, it may be necessary to take special care at the beginning of treatment. Doxazosin is not dialysable due to the fact that it is highly protein-bound.

Use in patients with hepatic impairment:
The dosage should be increased with special care in patients with hepatic impairment. There is no clinical experience with patients with severe hepatic impairment (see section 4.4).
Paediatric population:
'The safety and efficacy of Doxazosin in children and adolescents have not been established.

4.3 Contraindications

UNIPROST® is contraindicated in: • Patients with a known hypersensitivity to quinazolines (e.g. prazosin, terazosin, doxazosin), or any of the excipients. • Patients with a history of orthostatic hypotension. • Patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infection or bladder stones • During lactation. • Patients with hypotension. • As monotherapy in patients with either overflow bladder or anuria with or without progressive renal insufficiency.

4.4. Special warnings and precautions for use

Initiation of therapy:
In relation with the alpha blocking properties of doxazosin, patients may experience postural hypotension evidenced by dizziness and weakness, or rarely loss of consciousness (syncope), particularly with the commencement of therapy. Therefore, it is prudent medical practice to monitor blood pressure on initiation of therapy to minimize the potential for postural effects. The patient should be cautioned to avoid situations where injury could result should dizziness or weakness occur during the initiation of doxazosin therapy.
Use in patients with acute cardiac conditions:
As with other vasodilatory antihypertensive agent it is prudent medical practice to advise caution when administering doxazosin to patients with following cardiac conditions:

- Pulmonary oedema due to aortic or mitral stenosis.
- Heart failure at high output.
- Right-sided heart failure due to pulmonary embolism or pericardial effusion.
- Left ventricular heart failure with low filling pressure.

Use in hepatically impaired patients:
As with any drug wholly metabolized by the liver, doxazosin should be administered with particular caution to patients with evidence of impaired hepatic function. Since there is no clinical experience in patients with severe hepatic impairment use in these patients is not recommended.
Use with PDE5 inhibitors:
Concomitant administration of doxazosin with phosphodiesterase 5 inhibitors (e.g. sildenafil, tadalafil, and vardenafil) should be done with caution as both drugs have vasodilating effects and may lead to symptomatic hypotension in some patients. To reduce the risk of orthostatic hypotension it is recommended to initiate the treatment with phosphodiesterase 5 inhibitors only if the patient is hemodynamically stabilized on alpha blocker therapy. Furthermore, it is recommended to initiate phosphodiesterase 5 inhibitor treatment with the lowest possible dose and to respect a 6 hour time interval from intake of doxazosin.
Use in patients undergoing cataract surgery:
The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamsulosin. Isolated reports

have also been received with other alpha1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation current or past use of alpha1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

4.5. Interactions with other medicinal products

• Concomitant administration of doxazosin with phosphodiesterase-5-inhibitors (eg. sildenafil, tadalafil, vardenafil) may lead to symptomatic hypotension in some patients.
• Doxazosin is highly bound to plasma proteins (98%). In vitro data in human plasma indicates that doxazosin has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin or indometacin).
• Conventional doxazosin has been administered without any adverse drug interaction in clinical experience with thiazide diuretics, furosemide, beta-blocking agents, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents, or anticoagulants. However, data from formal drug/drug interaction studies are not present.

• Doxazosin potentiates the blood pressure lowering activity of other alpha-blockers and other antihypertensives.

4.6. Fertility, pregnancy and lactation

Use during pregnancy:
As there are no adequate and well controlled studies in pregnant women, the safety of doxazosin during pregnancy has not been established. Accordingly, during pregnancy, doxazosin should be used only if the potential benefit outweighs the risk. Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at high doses.
Use during lactation:
Doxazosin is contraindicated during lactation as the drug accumulates in milk of lactating rats and there is no information about the excretion of the drug into the milk of lactating women. Alternatively, mothers should stop breastfeeding when treatment with doxazosin is necessary

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 therapy.

4.8. Undesirable effects

Frequencies used are as follows: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Common: Respiratory tract infection, urinary tract infection

Very Rare: Leukopenia, thrombocytopenia

Uncommon: Allergic drug reaction

Common: Anorexia

Uncommon: gout, increased appetite

Common: Anxiety, insomnia, nervousness

Uncommon: Agitation, depression

Very common: Dizziness, headache

Common: Dizziness postural, paresthesia, somnolence

Uncommon:Cerebrovascular accident, hypoesthesia, syncope, tremor

Very Rare:Blurred vision

Unknown:Introperative floppy iris syndrome (see Section 4.4)

Common:Vertigo

Uncommon:Tinnitus

Common:Palpitation, tachycardia

Uncommon:Angina pectoris, myocardial infarction, cardiac arrhythmias

Very Rare:Bradycardia

Common:Hypotension, postural hypotension

Uncommon:Hot flushes

Common:Bronchitis, cough, dyspnea, rhinitis

Uncommon:Epistaxis, cough

Very Rare:Bronchospasm aggravated

Common:Abdominal pain, dyspepsia, dry mouth, nausea, diarrhoea
Uncommon:Constipation, flatulence, vomiting, gastroenteritis
Unknown:Taste disturbances

Uncommon:Abnormal liver function tests
Very Rare:Cholestasis, hepatitis, jaundice, abnormal liver function tests

Common:Pruritus
Uncommon:Skin rash, alopecia, purpura
Very Rare:urticaria
Common:Back pain, myalgia
Uncommon:Arthralgia, muscle cramps, muscle weakness

Common:Cystitis, urinary incontinence
Uncommon:Dysuria, micturition frequency, hematuria, polyuria, urinary incontinence
Very Rare:Increased diuresis, micturition disorder, nocturia

Uncommon:Impotence
Very Rare:Gynecomastia, priapism
Unknown:Retrograde ejaculation

Common:Asthenia, chest pain, influenza-like symptoms, peripheral oedema, fatigue, malaise
Uncommon: Pain, facial oedema

Uncommon:Weight increase

- To report any side effect(s) in Saudi Arabia;
- National Pharmacovigilance Center (NPC)
• Fax: +966-11-205-7662
• Call NPC at +966-11-2038222 Exts: 2317- 2356- 2353- 2354- 2334- 2340.
• Toll- free number: 8002490000
• E-mail: npc.drug@sfda.gov.sa
• Website: www.sfda.gov.sa/npc

4.9. Overdoes

Should over dosage lead to hypotension, the patient should be immediately placed in a supine, head down position.
Other supportive measures should be performed if thought appropriate in individual cases. Since doxazosin is highly protein bound, dialysis is not indicated.
If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressor should then be used. Renal function should be monitored and supported as needed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Alpha-adrenoceptor antagonists.
ATC code: C02CA04
Doxazosin is a selective and competitive antagonist of postsynaptic alpha1adrenergic receptors.
The administration of doxazosin causes a significant reduction in blood pressure due to decreased pheripheral vascular resistance. One daily dosage results in a clinically significant reduction in blood pressure, which will continue for 24 hours. After administration, a gradual reduction in blood pressure occurs; orthostatic effects at the start of treatment may occur. The largest decrease in blood pressure is obtained approximately 2 to 6 hours after administration.
During treatment with doxazosin, regression of left ventricle hypertrophy has been reported.
Contrary to the nonselective alpha-adrenergicreceptor blocking substances, no tolerance has been observed during long term treatment with doxazosin.

Clinical studies have demonstrated that doxazosin causes a small decrease in triglyceride plasma concentrations, total cholesterol and LDL fraction. A small increase in HDL/total cholesterol ratio has been observed (approximately 4 to 13% of the initial value). The clinical relevance of these results has to be established. Doxazosin increases sensitivity to insulin in patients with alteration of glucidic metabolism.

Administration of doxazosin to patients with symptomatic BPH results in an improvement of urodynamic complaints. Studies have shown that this effect results from selective blockade of the alpha-adrenoreceptors in the smooth muscles of the bladder neck, the bladder, the capsule of the prostate and the urethra.

5.2. Pharmacokinetic Properties

Following oral administration, doxazosin is well absorbed. The peak plasma levels are achieved after 2 hours, and the absolute bioavailability is approximately 63%. Doxazosin is highly protein bound in plasma (approximately 98%). The plasma elimination occurs in two phases. The terminal half-life is 16-30 hours thus making the drug suitable for once daily administration. Doxazosin is predominantly metabolized by the liver and is mainly excreted by the faeces (63-65%) ; less than 5% of the dose is excreted as unchanged doxazosin. 6-Hydroxy-doxazosin is a strong and selective alpha-adrenergic receptor blocking substance and in humans 5% of the oral dose is metabolized in this substance. Pharmacokinetic studies in elderly and patients with renal insufficiency did not show significant pharmacokinetic differences compared to patients with a normal renal function. There are only limited data concerning the use of doxazosin in patients with liver impairment and concerning the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). In a clinical study in 12 patients with mild hepatic insufficiency, single oral dose administration of doxazosin resulted in an increase in the area under the concentration-time-curve (AUC) of 43% and a decrease in clearance of 40%.

5.3 Preclinical Safety Data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and gastrointestinal tolerance. Studies in pregnant rabbits and rats at daily doses resulting in plasma concentrations 4 and 10 times the human exposure (Cmax and AUC), respectively, revealed no evidence of harm to the fetus. A dosage regimen of 82 mg/kg/day (8 times the human exposure) was associated with reduced fetal survival.

A male fertility study performed in the rat revealed that doxazosin can adversely affect fertility and reproductive performance. Alpha-adrenergic blocking agents may inhibit labour in rats.
Studies in lactating rats given a single oral dose of radioactive doxazosin gave an accumulation in the breast milk with a maximum concentration of about 20 times greater than the maternal plasma concentration. Radioactivity was found to cross the placenta following oral administration of labeled doxazosin to pregnant rats.

6. PHARMACEUTICAL PARTICULARS

6.1 Excipients List

- Lactose monohydrate
- Povidone
- Polysorbate 80
- Magnesium stearate
- Microcrystalline cellulose

• Colloidal silicon dioxide
• Sodium starch glycolate
• Isopropyl alcohol

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

24 Months.

6.4. Special precautions for storage

Store at temperature not exceeding 30ºC.

6.5. Nature and contents of container

Carton box containing 20 tablets in blisters along with a patient information leaflet.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

BATTERJEE PHARMA Jeddah Industrial City Jeddah-KSA

8. DATE OF REVISION OF THE TEXT

10-May-17