SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxazosin 2mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2.425mg of doxazosin mesilate equivalent to 2mg doxazosin.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets
White, oblong tablets, scored and embossed D2 on the same side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension:
Doxazosin is indicated for the treatment of hypertension and can be used as the sole agent to control blood pressure in the majority of patients. In patients inadequately controlled on single antihypertensive therapy, doxazosin may be used in combination with a thiazide diuretic, beta-adrenoreceptor blocking agent, calcium antagonist or an angiotensin converting enzyme inhibitor.

Benign Prostatic Hyperplasia:
Doxazosin is indicated for the treatment of urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH). Doxazosin may also be used in BPH patients who are either hypertensive or normotensive.

4.2 Posology and method of administration

Doxazosin may be administered in the morning or in the evening.

Hypertension:
Doxazosin is used in a once daily regimen: the initial dose is 1mg to minimize the potential for postural hypotension and/or syncope (see section 4.4 Special Warnings and Precautions for Use). Dosage may be increased after one or two weeks of therapy to 2 mg and thereafter, if necessary, to 4 mg. 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 8 mg or the maximum recommended dose of 16 mg.

Benign Prostatic Hyperplasia:
The recommended initial dose of doxazosin is 1mg given once daily to minimise the potential for postural hypotension and/or syncope (see section 4.4 Special Warnings and Precautions for Use). Depending on the individual patients urodynamics and BPH symptomatology dosage may be increased to 2 mg and thereafter to 4 mg and up to the maximum recommended dose of 8 mg. The recommended titration interval is 1-2 weeks. The recommended dose is 2-4mg daily.

Children:
The safety and efficacy of doxazosin in children have not been established.

Elderly:
Normal adult dose.

Patients with renal impairment:
Since there is no change in pharmacokinetics in patients with impaired renal function, the usual adult dose of doxazosin is recommended. Doxazosin is not dialysable.

Patients with hepatic impairment:
There are only limited data in patients with liver impairment and on the effect of drugs known to influence hepatic metabolism (e.g. cimetidine). As with any drug wholly metabolised by the liver, doxazosin should be administered with caution to patients with evidence of impaired liver function (see section 4.4 Special Warnings and Precautions for Use, and section 5.2 Pharmacokinetic properties).

4.3 Contraindications

Doxazosin is contraindicated in patients with a known hypersensitivity to quinazolines (e.g. doxazosin), or any of the inert ingredients.
Use during lactation:
Animal studies have shown that doxazosin accumulates in breast milk. The clinical safety of doxazosin during lactation has not been established, consequently doxazosin is contraindicated in nursing mothers.

4.4 Special warnings and precautions for use

Postural Hypotension/Syncope:

As with all alpha-blockers, a very small percentage of patients have experienced postural hypotension evidenced by dizziness and weakness, or rarely loss of consciousness (syncope), particularly with the commencement of therapy (see section 4.2 Posology and method of administration). When

instituting therapy with any effective alpha-blocker, 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 doxazosin therapy.

Use with PDE-5 Inhibitors:

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and doxazosin may lead to symptomatic hypotension in some patients. In order to minimise the risk for developing postural hypotension the patient should be stable on the alpha-blocker therapy before initiating use of phosphodiesterase-5-inhibitors.

Impaired liver function:

As with any other drug wholly metabolised by the liver, doxazosin should be administered with caution to patients with evidence of impaired hepatic function (see section 4.2 Posology and method of administration).

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 alpha-1 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 alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Doxazosin is highly bound to plasma protein (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). No adverse drug interactions have been observed with thiazide diuretics, furosemide, beta-blocking agents, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents or anticoagulants.

Phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) (see section 4.4).

In an open-label, randomised, placebo-controlled trial in 22 healthy male volunteers, the administration of a single 1mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in 10% increase in mean AUC of doxazosin, and no statistically significant changes in

mean Cmax and mean half-life of doxazosin. The 10% increase in the mean AUC for doxazosin with cimetidine is within intersubject variation (27%) of the mean AUC for doxazosin with placebo.

4.6 Pregnancy and lactation

Use during pregnancy: Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at extremely high doses. These doses were approximately 300 times the maximum recommended human dose. As there are no adequate and well controlled studies in pregnant women, the safety of doxazosin's use during pregnancy has not been established. Accordingly, doxazosin should be used only when in the opinion of the physician, potential benefit outweighs potential risk.

Use during lactation: Contraindicated. See section 4.3 Contraindications above.

4.7. Effects on Ability to Drive and Use Machines

The ability to drive or use machinery may be impaired, especially when initiating therapy.

4.8 Undesirable effects

Hypertension: In clinical trials involving patients with hypertension, the most common reaction associated with doxazosin therapy were of a postural type (rarely associated with fainting) or non-specific and include:

Ear and Labyrinth Disorders: vertigo

Gastrointestinal Disorders: nausea

General Disorders and Administration Site Conditions: asthenia, oedema, fatigue, malaise

Nervous System Disorders: dizziness, headache, postural dizziness, somnolence, syncope

Respiratory, Thoraic and Mediastinal Disorders: rhinitis

Benign prostatic hyperplasia: Experience in controlled clinical trials in BPH indicates a similar adverse event profile to that seen in hypertension.

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

Blood and Lymphatic Disorders: leucopenia, thrombocytopenia

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: blurred vision

Gastrointestinal Disorders: abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, dry mouth, vomiting

General Disorders and Administration Site Conditions: pain

Hepatobiliary Disorders: cholestasis, hepatitis, jaundice

Immune System Disorders: allergic reaction

Investigations: abnormal liver function tests, weight increase

Metabolism and Nutrition: anorexia

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain, muscle cramps, muscle weakness, myalgia

Nervous System Disorders: hypoaesthesia, paraesthesia, tremor

Psychiatric Disorders: agitation, anxiety, depression, insomnia, nervousness

Renal and Urinary System Disorders: dysuria, haematuria, micturition disorder, micturition frequency, nocturia, polyuria, urinary incontinence

Reproductive System and Breast Disorders: gynaecomastia, impotence, priapism, retrograde ejaculation

Respiratory, Thoraic and Mediastinal Disorders: aggravated bronchospasm, coughing, dyspnoea, epistaxis

Skin and Subcutaneous Tissue Disorders: alopecia, pruritus, purpura, skin rash, urticaria

Vascular Disorders: hot flushes, hypotension, postural hypotension

The following additional adverse events have been reported in marketing experience among patients treated for hypotension. In general, these are not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin: bradycardia, tachycardia, palpitations, chest pain, angina pectoris, myocardial infarction, cerebrovasuclar accidents and cardiac arrythmias.

4.9 Overdose

Should overdosage lead to hypotension, the patient should be immediately placed in a supine, head down position. Other supportive measures may be appropriate in individual cases. Since doxazosin is highly protein bound, dialysis is not indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Doxazosin is a potent selective post-junctional alpha-1-adrenoceptor antagonist. This action results in a decrease in systemic blood pressure. Doxazosin is appropriate for oral administration in a once a day regimen in patients with essential hypertension.

Doxazosin has been shown to be free of adverse metabolic effects and is suitable for use in patients with co-existent diabetes mellitus, gout and insulin resistance.

Doxazosin is suitable for use in patients with co-existent asthma, left ventricular hypertrophy, and in elderly patients. Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation and enhanced activity of tissue plasminogen activator.

Additionally, doxazosin improves insulin sensitivity in patients with impairment.

Doxazosin, in addition to its anti-hypertensive effect, has in long term studies produced a modest reduction in plasma total cholesterol, LDL-cholesterol and triglyceride concentrations, therefore may be of particular benefit to hypertensive patients with concomitant hyperlipidaemia.

Administration of doxazosin to patients with symptomatic benign prostatic hypertrophy results in a significant improvement in urodynamics and symptoms. The effect in BPH is thought to result from selective blockade of the alpha-adrenoceptors located in the prostatic muscular stroma, capsule of the prostate and in the bladder neck.

5.2 Pharmacokinetic properties

Absorption: Following oral administration in humans (young male and adults or the elderly of either sex), doxazosin is well absorbed and approximately two-thirds of the dose is bioavailable.

Biotransformation/Elimination: Approximately 98% of doxazosin is protein-bound in plasma.

Doxazosin is extensively metabolised in man and in animal species tested, with the faeces being the predominant route of excretion.

The mean plasma elimination half-life is 22 hours thus making the drug suitable for once daily administration.

After oral administration of doxazosin, the plasma concentration of metabolites are low. The most active metabolite (6' hydroxy) is present in man at one-fortieth of the plasma concentration of the parent compound, which suggests that the anti-hypertensive activity is in the main due to doxazosin.

There are only limited data in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). In a clinical study in 12 subjects with moderate hepatic impairment, single dose administration of doxazosin resulted in an increase in AUC of 43% and a decrease in apparent oral clearance of 40%. As with any drug wholly metabolised by the liver, doxazosin should be administered with caution to patients with impaired liver function (see section 4.4 Special Warnings and Precautions for Use).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional animal studies in safety pharmacology, repeated dose toxicity, genotoxicity and carcinogeneticity. For further information see section 4.6 Pregnancy and lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose
Sodium starch glycollate
Magnesium stearate
Colloidal anhydrous silica
Sodium lauryl sulphate.

6.2. Incompatibilities

Not applicable

6.3 Shelf life

60 months

6.4. Special Precautions for Storage

Do not store above 25°C. Store in the original package.

6.5. Nature and Contents of Container

PVC/PVDC aluminium blisters containing 14 tablets per strip, 2 strips per carton box (28 tablets per pack).

6.6. Instruction for Use/Handling

None

7. MARKETING AUTHORISATION HOLDER

Waymade plc
Trading as Sovereign Medical
Sovereign House
Miles Gray Road
Basildon
Essex, SS14 3FR
United Kingdom.

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30/07/2008

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