Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxane 2 mg Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg Doxazosin (as Mesilate).

For excipients see 6.1.

3 PHARMACEUTICAL FORM

Tablet.

White, oblong, biconvex tablets with a breakline on one side. The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension: DOXANE is indicated for the treatment of hypertension and can be used as a sole agent to control blood pressure in hypertensive patients.

In patients inadequately controlled on single antihypertensive therapy, DOXANE may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an angiotensin-converting enzyme inhibitor.

Benign prostatic hyperplasia: Doxazocin is indicated as an adjunct in the treatment of urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH). It may therefore be of value in patients awaiting prostatic surgery or for whom surgery is not possible.
Doxazocin may be used in BPH patients who are either hypertensive or normotensive.

4.2 Posology and method of administration

Route of Administration: Oral

Recommended Dosage Schedule:

Hypertension:
Adults: DOXANE is used in a once daily regimen and may be administered in the morning or evening.

It is recommended that therapy be initiated at 1 mg given once daily for one or two weeks to minimize the potential for postural hypotension and/or syncope *(see section 4.4 Special Warnings and Special Precautions for use).* The dosage may then be increased to 2 mg once daily for an additional one or two weeks. If necessary the daily dosage should then be increased gradually at similar intervals to 4 mg, 8 mg, and 16 mg as determined by patient response to achieve the desired reduction in blood pressure. The usual dose is 2-4 mg once daily. The maximum daily dose should not exceed 16 mg.

Diuretic therapy may be introduced, if required.

Benign prostatic hyperplasia (BPH)

The recommended initial dosage of doxazocin is 1mg given once daily to minimize the potential for postural hypotension and/or syncope *(see section 4.4 Special Warnings and Special Precautions for use)*. Depending on the individual patients 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 once daily.

Children: There is insufficient experience to recommend the use of DOXANE in children under 12 years of age.

Elderly: Normal adult dosage. In common with other drugs of this class, dosage should be kept as low as possible and increments made under close supervision.

Patients with renal impairment: Since there is no change in pharmacokinetics in patients with impaired renal function the usual adult dose of DOXANE is recommended. DOXANE is not dialyzable.

Patients with hepatic impairment: DOXANE should be used with care in patients with significant existing hepatic dysfunction. *(See also Special Warnings and Precautions for Use and section 5.2 Pharmacokinetic Properties.)*

4.3 Contraindications

DOXANE is contra-indicated in patients with a known hypersensitivity to quinazolines, doxazocin or to any of the excipients used BPH patients with hypotension or a history of orthostatic hypotension should not use doxazocin.

- Patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infections or bladder stones should not be treated with doxazocin.
- In accordance with prudent medical practice, this drug class should not be used in patients with:
- Overflow bladder, anuria or progressive renal insufficiency
- History of esophageal or gastrointestinal obstruction or decreased lumen diameter of the gastrointestinal tract or judged to be at increased risk for such obstruction.

Use during lactation: Animal studies have shown that doxazosin accumulates in breast milk. The clinical safety of DOXANE during lactation has not been established, consequently DOXANE is contra-indicated in nursing mothers.

4.4 Special warnings and precautions for use

Patients with renal impairment: There is no evidence that DOXANE aggravates renal dysfunction. However, DOXANE dosage introduction and adjustment should be carried out with great care.

Patients with hepatic impairment: There are only limited data in patients with liver impairment, therefore DOXANE should be used with care in patients with significant existing hepatic dysfunction. There have been no studies on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine) on the pharmacokinetics of DOXANE.

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. 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.

It is recommended that the initial dosage should be given when the patient is not required to undertake any activity such as driving or operating machinery.

The mean terminal half-life of doxazosin is 22 hours. This may be prolonged in patients with congestive heart failure. The rate of dose adjustment may need to be slowed.

In some patients with left ventricular failure, the decrease in left ventricular filling associated with vigorous therapy may result in a significant fall in cardiac output and systemic blood pressure after administration of doxazosin. These effects should be kept in mind when introducing therapy and continuous adjustment of dose used.

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

Doxazosin should be used with care in patients with Diabetic Autonomic Neuropathy.

Concomitant administration of PDE-5-inhibitors (such as sildenafil, tadalafil and vardenafil) and doxazocin should be exercised with caution, as this may lead to symptomatic hypotension in some patients *(see section 4.5 Interaction with other medicinal products and other forms of interaction).*

The 'intraopeative 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 or surgery.

Doxazosin may influence plasma renin activity and urinary excretion of vanillylmandelic acid. This should be considered when interpreting laboratory data.

4.5 Interaction with other medicinal products and other forms of interaction

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 indomethacin), however the theoretical potential for interaction with other protein bound drugs should be borne in mind.

No adverse drug interactions have been observed with thiazide diuretics, frusemide, beta-blocking agents, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents, or anticoagulants.

Doxazosin increases the blood pressure lowering effect of other antihypertensive drugs. The antihypertensive effect may be increased when doxazosin is administered concomitantly with vasodilators and nitrates.

Concomitant administration of PDE-5-inhibitors (such as sildenafil, tadaladil and vardenafil) and doxazocin should be exercised with caution, as this may lead to symptomatic hypotension in some patients.

4.6 Pregnancy and lactation

Use during pregnancy: Doxazosin crosses the placenta. 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 DOXANE's use during pregnancy has not yet been established. Accordingly, DOXANE should be used only when, in the opinion of the physician, potential benefit outweighs potential risk.

Use during lactation: Contraindicated. See 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. The drug may also induce drowsiness. Patients should not drive or operate machinery unless it has been shown not to affect their alertness or dexterity.

4.8 Undesirable effects

The following adverse reactions have been reported:

Very common (>1/10);common (>1/100,<1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

Blood and the lymphatic system disorders:
Very rare: Reduction of erythrocytes, leucocytopenia and thrombocytopenia.

Metabolism and nutrition disorders:
Uncommon: thirst, hypokalaemia, gout
Rare: hypoglycaemia

Psychiatric disorders:
Common: apathia
Uncommon: nighmares, amnesia, emotional instability
Rare: depression, agitation

Nervous system disorders:
Common: fatigue, malaise, headache, somnolence
Uncommon: tremor, muscular stiffness
Rare: paraesthesia

Eye disorders;
Common: accommodation disturbances
Uncommon: lacrimation, photophobia
Rare: blurred vision

Ear and labyrinth disorders:
Uncommon: tinnitus, vertigo

Cardiac disorders:
Common: palpitations, chest pain
Uncommon: arrhythmia, angina pectoris, bradycardia, tachycardia, myocardial infarction

Vascular disorders:
Common: giddiness, dizziness, oedema, orthostatic dysregulation
Uncommon: postural hypotension, peripheral ischaemia, syncope
Rare: cerebrovascular disturbances

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea, rhinitis
Uncommon: epistaxis, bronchospasms, cough, pharyngitis
Rare: oedema of larynx

Gastrointestinal disorders:
Common: constipation, dyspepsia, nausea
Uncommon: anorexia, increased appetite, taste disturbances
Rare: abdominal pain, diarrhoea, vomiting

Hepato-biliary disorders:
Rare: icterus, increased liver values, hepatitis and jaundice

Skin and subcutaneous tissue disorders:
Uncommon: alopecia, oedema of the face/general oedema
Rare: rash, pruritus, purpura.

Musculoskeletal, connective tissue and bone disorders:
Common: muscle cramps
Uncommon: muscular pain, swelling of joints/arthralgia, muscle weakness

Renal and urinary disorders:
Common: frequent desire to micturate, increased micturation
Uncommon: incontinence, micturation disturbances, dysuria
Very rare: increase of serum creatinine and serum urea.

Reproductive System and breast disorders:
Common: delayed ejaculation, gynaecomastia
Rare: impotence, priapism

General disorders and administration site conditions:
Common: asthenia
Uncommon: flushing, fever/shiver, paleness
Rare: low body temperature in elderly

Particular caution:
Postural hypotension and in rare cases syncope may occur at the beginning of therapy, especially at very high doses but also when treatment is recommended after a break.

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

ATC code: CO2C AO4**, GO4CA**

Pharmacotherapeutic classification: Alpha-adrenoceptor antagonists Urologicals.

Administration of DOXANE reduces blood pressure due to a decrease in systemic vascular resistance. With once daily dosing, clinically significant reductions in blood pressure are maintained throughout the day and 24 hours post-dose. During the onset of therapy, a gradual reduction in blood pressure occurs, and orthostatic effects are comparable with those of other antihypertensives.

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

DOXANE is suitable to use in patients with co-existent asthma, left ventricular hypertrophy and in elderly patients.

Treatment with DOXANE has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation and enhanced activity of tissue plasminogen activator. Additionally, DOXANE improves insulin sensitivity in patients who have impairment.

DOXANE produces favourable effects on blood lipids, with a significant increase in the HDL/total cholesterol ratio and trends to a favourable reduction in total triglycerides.

5.2 Pharmacokinetic properties

Following oral administration in humans (young male adults or the elderly or either sex), doxazosin is well absorbed and approximately two thirds of the dose is bioavailable. The mean plasma elimination half life is 22 hours thus making the drug suitable for once daily administration.

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

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

Pharmacokinetic studies in the elderly and patients with renal insufficiency have shown no significant alterations compared to younger patients with normal renal function. There are only limited data in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). As with any drug wholly metabolized by the liver, use of doxazosin in patients with altered liver function should be undertaken with caution *(see Special warnings and special precautions for use).*

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose Monohydrate
Magnesium Stearate
Microcrystalline Cellulose
Sodium Laurilsulfate
Sodium Starch Glycolate (Type A).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Clear blisters of Aluminium/PVdc of PVC-Aclar/Alu Blisters available in sales packs of 10 and 30 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Limited
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA 0711/098/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 November 2005

10 DATE OF REVISION OF THE TEXT

August 2008.