Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxazosin Aurobindo 1mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 1.21 mg doxazosin mesilate equivalent to 1mg doxazosin.

Excipients with known effect:
Each Doxazosin Aurobindo 1 mg tablet contains 24 mg lactose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off white coloured circular biconvex shaped uncoated tablet debossed with H on one side and 01 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- Essential hypertension. Doxazosin Aurobindo 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 of administration

Method of administration:
The tablets should be administered once daily with a sufficient amount of water. The duration of treatment should be established by a physician.

Posology:
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 le 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 wi patients with severe hepatic impairment (see section 4.4).

Paediatric population:
'The safety and efficacy of Doxazosin Aurobindo in children and adolescents have not been established

4.3 Contraindications

Doxazosin is contraindicated in:

- Patients with a known hypersensitivity to quinazolines (e.g. prazosin, terazosin, doxazosin), or any of the excipients listed in section 6.1.
- 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
- Patients with a history of Gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastrointestinal tract (for patients taking sustained release tablets only
- During lactation (please see section 4.6)[1]
- Patients with hypotension[2]

Doxazosin is contraindicated as monotherapy in patients with either overflow bladder or anuria with or without progressive renal insufficiency.

[1] For Hypertension indication only

[2] For the benign prostatic hyperplasia indication only

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 anti-hypertensive 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 PDE-5 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. No studies have been conducted with doxazosin prolonged release formulations.

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 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.

Priapism
Prolonged erections and priapism have been reported with alpha-1 blockers including doxazosin in post marketing experience. If priapism is not treated immediately, it could result in penile tissue damage and permanent loss of potency, therefore the patient should seek immediate medical assistance.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of doxazosin with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients (see section 4.4, Special Warnings and Special Precautions for Use). No studies have been conducted with doxazosin prolonged release formulations.).

Most (98%) of plasma doxazosin is protein bound. *In vitro* data in human plasma indicate that doxazosin has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin.

Conventional doxazosin has been administered without any adverse drug interaction in clinical experience with thiazide diuretics, furosemide, beta-blockers, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents, and 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.

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

Pregnancy:
For the hypertension indication:
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 extremely high doses (see section 5.3: Preclinical Safety Data).

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.

Breastfeeding
Alternatively, mothers should stop breast-feeding when treatment with Doxazosin Aurobindo is necessary (please see section 5.3: Preclinical safety data).

For the benign prostatic hyperplasia indication:
This section is not applicable.

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

The following undesirable effects have been observed and reported during treatment with Doxazosin with the following frequencies.
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).

System Organ Class	**Frequency**	**Undesirable Effects**
Infections and infestations	Common	Respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	Very Rare	Leukopenia, thrombocytopenia
Immune System Disorders	Uncommon	Allergic drug reaction
Metabolism and Nutrition Disorders		
	Uncommon	gout, increased appetite, anorexia
Psychiatric Disorders		
	Uncommon	Agitation, depression, anxiety, insomnia, nervousness
Nervous System Disorders		Dizziness, headache
	Common	Somnolence, Dizziness, headache
	Uncommon	Cerebrovascular accident, hypoesthesia, syncope, tremor
	Very Rare	Dizziness postural, paresthesia
Eye Disorders	Very Rare	Blurred vision
	Unknown	Intraoperative floppy iris syndrome (see Section 4.4)
Ear and Labyrinth Disorders	Common	Vertigo
	Uncommon	Tinnitus
Cardiac Disorders	Common	Palpitation, tachycardia
	Uncommon	Angina pectoris, myocardial infarction
	Very Rare	Bradycardia, cardiac arrhythmias
Vascular Disorders	Common	Hypotension, postural hypotension
Respiratory, Thoracic and Mediastinal Disorders	Common	Bronchitis, cough, dyspnea, rhinitis
	Uncommon	Epistaxis
	Very Rare	Bronchospasm
Gastrointestinal Disorders	Common	Abdominal pain, dyspepsia, dry mouth, nausea,
	Uncommon	Constipation, flatulence, vomiting, gastroenteritis, diarrhoea

Hepatobiliary Disorders	Uncommon	Abnormal liver function tests
	Very Rare	Cholestasis, hepatitis, jaundice
Skin and Subcutaneous Tissue Disorders	Common	Pruritus
	Uncommon	Skin rash
	Very Rare	urticaria, alopecia, purpura
Musculoskeletal and Connective Tissue Disorders	Common	Back pain, myalgia
	Uncommon	Arthralgia
	Very rare	Muscle cramps, muscle weakness
Renal and Urinary Disorders	Common	Cystitis, urinary incontinence
	Uncommon	Dysuria, micturition frequency, hematuria
	Very Rare	Increased diuresis, micturition disorder, polyuria nocturia
Reproductive System and Breast Disorders	Uncommon	Impotence
	Very Rare	Gynecomastia, priapism
	Unknown	Retrograde ejaculation
General Disorders and Administration Site Conditions	Common	Asthenia, chest pain, influenza-like symptoms, peripheral oedema
	Uncommon	Pain, facial oedema
	Very Rare	Fatigue, malaise
Investigations	Uncommon	Weight increase

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 via HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

Should overdosage 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.
Since doxazosin is highly protein bound, dialysis is not indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoceptor antagonists
ATC code: C02CA04

Doxazosin is a selective and competitive antagonist of postsynaptic alpha-1-adrenergic 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 non-selective alpha-adrenergic-receptor 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

Absorption:
Following oral administration, doxazosin is well absorbed. The peak plasma levels are achieved after 2 hours, and the absolute bioavailability is approximately 63%.

Biotransformation/Elimination:
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 doxazos 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 doxazosi 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

Non-clinical 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 (C_{max} 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 labelled doxazosin to pregnant rats.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose microcrystalline
Lactose anhydrous
Sodium starch glycolate (Type A)
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage condition.

6.5 Nature and contents of container

PVC-PVDC Aluminium blisters:
Pack size: 10, 14, 15, 20, 28, 30, 50, 56, 60, 90, 98, 100 and 140 tablets

HDPE bottle:
Pack size: 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Aurobindo Pharma (Malta) Limited
Vault 14, Level 2, Valletta Waterfront
Floriana FRN 1913
Malta

8 MARKETING AUTHORISATION NUMBER

PA1445/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11th March 2011

10 DATE OF REVISION OF THE TEXT

May 2017