1. NAME OF THE MEDICINAL PRODUCT

Doxazosin Mylan 1 mg Tablets
Doxazosin Mylan 2 mg Tablets
Doxazosin Mylan 4 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxazosin Mylan tablets 1 mg, 2 mg or 4 mg contain 1 mg, 2 mg or 4 mg doxazosin as doxazosin mesilate.

Excipient with known effect: lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

1 mg tablets: white, round tablets marked DX1 on one side
2 mg tablets: white, capsule shaped, scored tablets marked DX|2 on one side
4 mg tablets: white, capsule shaped, scored tablets marked DX|4 on one side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential Hypertension. Treatment of clinical symptoms in benign prostatic hyperplasia

4.2 Posology and method of administration

Posology
In hypertension
Doxazosin tablets are administered once daily. The initial dose is 1 mg. Depending on the therapeutic response, the dose can be increased to 2 mg after 1 – 2 weeks. If necessary, the dose can then be doubled at intervals of 1 – 2 weeks. The maximum dose is 16 mg doxazosin once daily, but daily doses over 8 mg seldom give further reductions in blood pressure.

Doxazosin tablets can be used as monotherapy or in combination with a thiazide diuretic or beta-blocking agent when treatment with these alone has not given the desired effect or is unsuitable.

In Benign Prostatic Hyperplasia
Doxazosin tablets are administered once daily. The initial dose is 1 mg increasing at 1 – 2 weekly intervals until a satisfactory response is obtained. The usual effective dosage is 2 – 4 mg once daily. The maximum daily dose is 8 mg doxazosin once daily.

Use in the elderly and in patients with renal impairment:
Since the pharmacokinetics of doxazosin are unchanged in the elderly and in patients with renal insufficiency, the usual dose may be used in these patients. However, dosage should be kept as low as possible and increments made under close supervision. As doxazosin is highly protein bound it is not removed by dialysis.

Use in hepatically impaired patients:

Doxazosin should be administered with particular caution to patients with evidence of impaired hepatic function. In patients with severe hepatic impairment there is no clinical experience (see section 4.4 and section 5.2).

Paediatric population
The safety and efficacy of doxazosin mesilate in children and adolescents have not been established.

Method of administration
For oral use.

4.3 Contraindications

Doxazosin is contraindicated in
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to other quinazolines (e.g. prazosin, terazosin).
- 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 (for the hypertension indication only, see section 4.6).
- Patients with hypotension (for the benign prostatic hyperplasia indication only).

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

4.4 Special warnings and precautions for use

Postural hypotension /Syncope
On initiation of therapy or increasing of dose the patient should be monitored as patients may experience postural hypotension evidenced by dizziness and weakness, or rarely loss of consciousness (syncope).

Patients should be instructed to avoid abrupt changes of positions or activities which may be adversely affected by dizziness or asthenia. During the dose titration period, blood pressure should be monitored carefully.

Special care should be taken with elderly patients, patients with hepatic or renal insufficiency, patients on a low-sodium diet or those treated with diuretics.

In patients treated for benign prostatic hyperplasia and without hypertension mean blood pressure changes are small, but hypotension, dizziness, fatigue occur in 10 – 20% of the patients and oedema and dyspnoea occur in less than 5% of patients.

Patients with benign prostatic hyperplasia and having simultaneously obstruction of the upper urinary tract, chronic infection of the urinary tract or bladder stone should not be treated with doxazosin.

Caution is recommended when doxazosin is administered concomitantly with drugs which may influence hepatic metabolism (e.g. cimetidine).

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 haemodynamically stable on the alpha-blocker therapy before initiating use of phosphodiesterase-5-inhibitors. 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.

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.

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.

Use in patients with acute cardiac conditions:
Because of its vasodilatory effect cautions is advised when administering doxazosin to patients with the following acute 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.

In hypertensive patients with one or more additional risk factors for cardiovascular disease, doxazosin should not be used as a single agent for the first-line treatment of hypertension due to a possible increased risk for development of heart failure (see section 5.1)

Use in hepatically impaired patients:
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. Until further experience has been obtained, patients with mild to moderate impaired liver function should be closely monitored.

Paediatric population:
There is insufficient experience to recommend the use of doxazosin in children.

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

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 potentiates the blood pressure lowering activity of other alpha-blockers and other anti-hypertensives.

In an open-label, randomised, 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.

The antihypertensive effect may be increased, when doxazosin is administered concomitantly with other antihypertensive agents, vasodilators and nitrates.

As for other antihypertensive agents, non-steroidal antirheumatics or oestrogens may reduce the antihypertensive effect of doxazosin.

Sympathomimetics may reduce the antihypertensive effect of doxazosin; doxazosin may reduce blood pressure and vascular reactions to dopamine, ephedrine, epinephrine, metaraminol, methoxamine and phenylephrine.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and doxazosin may lead to symptomatic hypotension in some patients (see section 4.4).

There are no studies concerning interactions with agents influencing hepatic metabolism.

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

4.6 Fertility, pregnancy and lactation

For the hypertension indication:
Pregnancy
As there are no adequate and well controlled studies in pregnant women, the safety of doxazosin during pregnancy has not yet 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).

Breast-feeding
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 breast-feeding when treatment with doxazosin is necessary (see section 5.3).

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

Undesirable effects arise mainly from the pharmacological properties of the preparation. Most of the undesirable effects have been transient or have been tolerated on continued treatment.

Adverse reactions are ranked under heading of frequency, the most frequent first, using the following convention: 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	Common	Uncommon	Rare	Very rare	Not known
Infections and infestations	Respiratory tract infection, urinary tract infection				
Blood and lymphatic system disorders			Anaemia	Leucopenia, thrombocytopenia	
Immune System disorders		Allergic drug reaction			
Metabolism and nutrition disorders		Increased appetite, anorexia, thirst, hypokalaemia, gout, disturbed sense of taste	Hypoglycaemia		
Psychiatric disorders	Apathy	Agitation, depression, anxiety, insomnia, nervousness, nightmares, memory loss, emotional liability			
Nervous system disorders	Dizziness, headache, giddiness, somnolence	Cerebrovascular accident, hypoesthesia, syncope, tremor		Postural dizziness, paresthesia	
Eye disorders	Accommodation disturbances	Abnormal tear flow, photophobia	Conjunctivitis	Blurred vision	Intraoperative Floppy Iris Syndrome (IFIS) (see section 4.4)
Ear and labyrinth disorders	Vertigo	Tinnitus			
Cardiac disorders	Palpitations, tachycardia	Angina pectoris, myocardial infarction		Bradycardia, cardiac arrythmias	
Vascular disorders	Hypotension, postural hypotension	Peripheral ischaemia	Cerebrovascular disturbances	Hot flushes	

Respiratory, thoracic and mediastinal disorders	Bronchitis, cough, dyspnoea, nasal congestion, rhinitis	Epistaxis, bronchospasm, pharyngitis	Laryngeal oedema	Bronchospasm aggravated	
Gastrointestinal disorders	Abdominal pain, dyspepsia, dry mouth, nausea	Constipation, flatulence,vomiting, gastroenteritis, diarrhoea			Taste disturbances
Hepatobiliary disorders		Abnormal liver function tests	Icterus	Cholestasis, hepatitis, jaundice	
Skin and subcutaneous tissue disorders	Pruritus	Skin rash	Itching, sweating	Urticaria, alopecia, purpura	
Musculoskeletal and connective tissue disorders	Back pain, myalgia	Muscle stiffness, muscle pains, arthralgia	Muscle cramps, muscle weakness		
Renal and urinary disorders	Cystitis, urinary incontinence	Micturition frequency, haematuria, urinary disturbances, dysuria	Increases in plasma urea and creatinine polyuria	Increased diuresis, micturition disorder, nocturia	
Reproductive system and breast disorders	Delayed ejaculation	Impotence		Gynecomastia, priapism	Retrograde ejaculation
General disorders and administration site conditions	Peripheral oedema, chest pain, influenza-like symptoms, asthenia,	Pain, facial/general oedema, facial redness, fever/shivering, paleness	Decreased body temperature in the elderly	Fatigue, malaise	
Investigations		Weight increase			

Postural hypotension and, in rare cases, syncope can occur initially during treatment, especially at too high doses, but can also arise if therapy is restarted after a short break.

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 [To be completed nationally].

4.9 Overdose

Toxicity:
Experience of overdosing is limited. A 16 mg dose to a fasting adult caused syncope, a maximum of 40 mg to a 13 year old produced moderate intoxication. A 22-year-old male, who stated that he had

ingested 40 mg of doxazosin, experienced sinus bradycardia with sinus arrhythmia and ST-segment elevation in the precordial leads.

Symptoms:
Headache, dizziness, confusion, syncope, dyspnoea, hypotension, palpitations, tachycardia, arrythmias, sinus bradycardia, ST-segment elevation, nausea, vomiting and possibly hypoglycaemia, hypokalaemia.

Treatment:
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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: C02C A04 Antihypertensives, alpha adrenoreceptor antagonists.

Doxazosin is a chinazolin derivative and exercises its vasodilating effect by selective and competitive blockade of post-synaptic alpha$_1$-receptors.

In clinical studies it has been shown that the blood pressure-reducing effect remains 24 hours after intake of doxazosin tablets. Tolerance development has not been observed during long-term treatment with doxazosin. Increased plasma renin activity and tachycardia are rare during maintenance therapy. Doxazosin has shown effects on blood lipids with a significant increase of the HDL/total cholesterol ratio (approximately 4% to 13% of baseline). The clinical significance of these findings remains to be established. No negative metabolic effects have been demonstrated. Doxazosin increases insulin sensitivity in hypertensive patients.

Treatment with doxazosin has been shown to produce regression of left ventricular hypertrophy by reducing wall thickness and left ventricular mass.

Interim Analysis of the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) indicated that hypertensive patients with at least 1 other major risk factor for coronary heart disease (CHD) treated with doxazosin experienced a double risk of congestive heart failure (CHF) with a 25% higher risk of major cardiovascular disease (CVD) events as compared to chlorthalidone-treated patients. The doxazosin arm of ALLHAT was discontinued as a result of these findings. No difference regarding mortality was present. The results may be confounded by various issues such as differences in effect on systolic blood pressure and withdrawal of diuretics in the doxazosin treated group before treatment was started.

Doxazosin has been shown to inhibit the phenylephrine-induced prostatic contractions of the prostate. High concentrations of α_1-adrenoreceptors are found in the smooth muscle of the prostate, proximal urethra and bladder base and mediate the smooth muscle tone of the prostatic urethra. Blockade of α_1-adrenoreceptors with doxazosin brings about a reduction in muscle tone of the prostatic urethra thereby improving the rate of urinary flow. This is the pharmacological basis for its clinical use in the treatment of benign prostatic hyperplasia.

5.2 Pharmacokinetic properties

Doxazosin is almost totally absorbed after oral administration. Bioavailability is about 63%. Maximal plasma concentration occurs after about 2 hours. The maximal blood pressure reduction is normally seen after 2 – 6 hours. Protein binding is high (98%). Distribution volume: 1 l/kg. Clearance: 1.3 ml/min/kg.

Doxazosin is metabolised mainly in the liver and is primarily excreted in the faeces as metabolites (63 to 65%) or unchanged drug (5%). The effective half-life at steady state is about 10 hours. The terminal half-life is about 22 hours.

Elderly persons and patients with kidney insufficiency have not shown changed pharmacokinetics.

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 patients 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 30%. Therefore doxazosin should be administered with particular caution to patients with impaired hepatic function (see also Section 4.4 Special Warnings and Special Precautions for Use).

Major metabolites of doxazosin in man include the 6-O and 7-O-demethyl doxazosin, 6-hydroxy- and 7-hydroxy-doxazosin. 6-hydroxy-doxazosin is a potent and selective α-blocker and in man accounts for 5% of the oral dose. Therefore 6-hydroxy-doxazosin contributes little to the antihypertensive effect of doxazosin.

Other less significant metabolites of doxazosin include the 2-piperazinyl and the 2-amino compounds.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction, genotoxicity or carcinogenicity. For further information see section 4.6.

Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at doses approximately 300 times greater than the maximum human recommended dose.

Doxazosin accumulates in milk of lactating rats. There is no information about the excretion of the drug into the milk of lactating women. The use of doxazosin is contraindicated during lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Lactose anhydrous
Sodium starch glycollate Type A
Magnesium stearate
Sodium laurilsulfate

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

10, 20, 28, 30, 50, 60, 90, 100, 250, 500 and 1000 tablets in HDPE plastic bottles with tamper evident polypropylene cap.
10, 20, 28, 30, 50, 60, 90 and 100 tablets in aluminium foil/aclar blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused medicinal product should be disposed of in accordance with the local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1998-05-15
Date of last renewal: 2008-05-15

10. DATE OF THE REVISION OF THE TEXT

2017-04-07