SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

DoxaduraTM XL 4mg Prolonged-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One prolonged-release tablet contains 4 mg doxazosin (as mesilate).

For the full list of excipients, see section 6.1.

Excipient(s) with known effect
Each prolonged-release tablet contains 0.1mg sodium.

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round, biconvex tablets, with bossing “DL” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Essential hypertension.

Symptomatic treatment of benign prostatic hyperplasia.

4.2 Posology and method of administration

Posology
The maximum recommended dose is 8 mg doxazosin once daily.

Essential hypertension
Adults
Most patients treated with Doxadura XL 4 mg prolonged release tablets once daily achieve control of blood pressure. It may take up to four weeks to reach optimal effect. If necessary, the dose can thereafter be increased to 8 mg once daily depending on the clinical response.

Doxadura XL 4 mg prolonged release tablets can be used as monotherapy or in combination with another medicinal product e.g. a thiazide diuretic, a beta-adrenoceptor blocking agent, a calcium antagonist or an ACE-inhibitor if either of them alone does not provide sufficient effect.

Symptomatic treatment of benign prostatic hyperplasia

Adults
Recommended dose is 4 mg once daily. Depending on clinical response, the dosage may be increased to 8 mg doxazosin once daily.

Doxazosin may be used in benign prostatic hyperplasia patients who are either hypertensive or normotensive, as the blood pressure reduction in normotensive patients is generally slight. Patients should be closely monitored in the initial phase of the treatment due to the risk of postural adverse events.

Special populations
Elderly
Same dosage recommendations as for adults.

Renal impairment
Since there is no change in pharmacokinetics in patients with impaired renal function and since there are no signs that doxazosin aggravates existing renal impairment, normal dose can generally be used in these patients.

Hepatic impairment
Doxazosin should be administered with caution in patients with signs of minor to moderate hepatic impairment. Since no clinical experience from patients with severe hepatic insufficiency exists, use in these patients is not recommended (see section 4.4).

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

Method of administration
Doxadura XL 4 mg prolonged release tablets can be taken with or without food. The tablets should be swallowed whole with a sufficient amount of liquid. The patient should not chew, divide or crush the tablet.

4.3 Contraindications

Doxazosin is contraindicated in
- in patients with hypersensitivity to the active substance, other types of quinazolines (e.g. prazosin, terazosin) or to any of the excipients listed in section 6.1
- in patients with a history of orthostatic hypotension
- in patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infection or bladder stones
- in patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract
- in during lactation (see section 4.6) (for the hypertension indication only)
- in 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

Information to be given to the patient:
Patients should be informed that doxazosin tablets should be swallowed whole. Patients should not chew, divide or crush the tablets.

For some prolonged-release formulations the active compound is surrounded by an inert, non-absorbable coating that is designed to control the release of the drug over a prolonged period. After transit through the gastrointestinal tract, the empty tablet shell is excreted. Patients should be advised not to be concerned if they occasionally observe remains in their stools that look like a tablet.

Abnormally short transit times through the gastrointestinal tract (e.g. following surgical resection) could result in incomplete absorption. In view of the long half-life of doxazosin the clinical significance of this is unclear.

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 minimise 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.

Patients with acute cardiac conditions:
As with any other vasodilatory anti-hypertensive agent it is prudent medical practice to advise caution 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

Hepatically impaired patients:
As with any drug wholly metabolised 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 haemodynamically 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.

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.

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

Excipients
This medicinal product contains less than 1mmol sodium (23mg) per tablet, that is to say essentially 'sodium-free'.

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). 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 indometacin.

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, 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.

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.

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

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 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).

Breastfeeding
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 (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

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).

MedDRA ***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	Anorexia, gout, increased appetite

Psychiatric disorders	Uncommon Very rare	Anxiety, depression, insomnia Agitation, nervousness
Nervous system disorders	Common Uncommon Very rare	Dizziness, headache, somnolence Cerebrovascular accident, hypoesthesia, syncope, tremor Dizziness postural, paraesthesia
Eye disorders	Very rare Not known	Blurred vision Intraoperative floppy iris syndrome (see section 4.4)
Ear and labyrinth disorders	Common Uncommon	Vertigo Tinnitus
Cardiac disorders	Common Uncommon Very rare	Palpitation, tachycardia Angina pectoris, myocardial infarction Bradycardia, cardiac arrhythmias
Vascular disorders	Common Very rare	Hypotension, postural hypotension Flush
Respiratory, thoracic and mediastinal disorders	Common Uncommon Very rare	Bronchitis, cough, dyspnoea, rhinitis Epistaxis Bronchospasm
Gastrointestinal disorders	Common Uncommon Not known	Abdominal pain, dyspepsia, dry mouth, nausea Constipation, diarrhoea, flatulence, vomiting, gastroenteritis Taste disturbances
Hepatobiliary disorders	Uncommon Very rare	Abnormal liver function tests Cholestasis, hepatitis, jaundice
Skin and subcutaneous tissue disorders	Common Uncommon Very rare	Pruritus Skin rash Alopecia, purpura, urticaria
Musculoskeletal and connective tissue disorders	Common Uncommon Very rare	Back pain, myalgia Arthralgia Muscle cramps, muscle weakness
Renal and urinary disorders	Common Uncommon Very rare	Cystitis, urinary incontinence Dysuria, haematuria, micturition frequency Micturition disorder, nocturia, polyuria, increased diuresis
Reproductive system and breast disorders	Uncommon	Impotence

	Very rare Not known	Gynaecomastia, priapism Retrograde ejaculation
General disorders and administration site conditions	Common Uncommon Very rare	Asthenia, chest pain, influenza-like symptoms, peripheral oedema Pain, facial oedema 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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' in the Google Play or Apple App Store.

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.

Toxicity
There is limited data on the effect of overdoses. Syncope occurred in a fasting adult who had taken doxazosin 16 mg. A 13-year-old experienced moderate intoxication following a maximum dose of doxazosin 40 mg.

Symptoms:
Headache, dizziness, unconsciousness, syncope, dyspnoea, hypotension, palpitations, tachycardia, arrhythmia. Nausea, vomiting. Possibly hypoglycaemia, hypokalaemia.

Treatment:
Ventricle emptying and charcoal if required. In cases of hypotension: lower the head position, provide intravenous fluids and if needed vasopressors (for instance noradrenaline or ephedrine). Provide symptomatic treatment as needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists

ATC code: C02CA04

The generic name for the active substance in Doxadura™ XL 4mg is doxazosin, which is a quinazoline derivative. Doxazosin has a vasodilating effect through selective and competitive blocking of postsynaptic alpha-1-receptors.

With once daily dosing, clinically significant reductions in blood pressure are present throughout the day and at 24-hours post dose.

Habituation has not been observed during long-term treatment with doxazosin immediate release tablets. Increase in plasma renin activity and tachycardia have rarely been seen during long-term treatment.

Doxazosin has a beneficial effect on blood lipids with significant increase of HDL/total cholesterol ratio (app. 4-13% of base line values). The clinical relevance of these findings is still unknown.

Doxazosin improves insulin sensitivity in patients with impaired sensitivity to insulin. Treatment with doxazosin immediate release tablets has been shown to result in regression of left ventricular hypertrophy. Studies on morbidity and mortality have not yet been terminated.

Hypertension:

Analysis of two dose-effect studies (including a total of 630 patients treated with doxazosin) have shown that patients treated with immediate release tablets in dosages of 1mg, 2mg or 4mg are equally controlled on doxazosin prolonged-release tablets containing 4mg.

Interim analysis of the study “Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial” (ALLHAT) shows that patients with hypertension and at least one other clinical risk factor for coronary heart disease treated with doxazosin are exposed to a doubled risk for chronic heart failure compared to patients treated with chlortalidone. Furthermore, they had 25% higher risk of developing clinically significant cardiovascular disorders. The doxazosin arm of ALLHAT was discontinued as a result of these findings. There was no difference in mortality.

The results are difficult to interpret due to various reasons such as differences in effect on systolic blood pressure and discontinuation of diuretics in the doxazosin-treated group prior to commencement of the treatment.

Benign Prostatic hyperplasia:

Doxazosin has been shown to inhibit phenylephrine induced contraction in the prostate. High levels of alpha-1-adrenoreceptors have been observed in the prostatic muscular stroma, the proximal part of the urethra and base of the urinary bladder, which medicates smooth muscle tonus in the prostatic part of the urethra. Blocking alpha-1-adrenoreceptors through doxazosin reduces the tonus of the smooth muscle in the prostatic part of the urethra which facilitates the urinary flow. This is the

pharmacological basis for clinical use of doxazosin in treatment for benign prostatic hyperplasia.

Effect and safety studies (with a total of 1,317 patients treated with doxazosin) have only been performed in patients with a baseline of ≥ 12 on the International Prostate Symptom Score and a maximum urinary flow of <15 ml/sec. Data from these studies indicate that patients well controlled on immediate release tablets of doxazosin in doses of 1 mg, 2 mg or 4 mg are equally controlled on doxazosin 4 mg prolonged-release tablets.

5.2 Pharmacokinetic properties

Absorption
After oral administration of therapeutic doses, doxazosin prolonged-release tablets are well absorbed with peak blood levels gradually reached at 6 to 8 hours after dosing. Peak plasma levels are approximately one third of the level obtained after administration of immediate release doxazosin tablets. Trough levels at 24 hours are, however, similar for both formulations.

The pharmacokinetic properties of doxazosin in prolonged-release tablets lead to a minor variation in plasma levels.

Peak/trough ratio of doxazosin prolonged-release tablets is less than half that of immediate release doxazosin tablets.

At steady-state, the relative bioavailability of doxazosin from prolonged-release tablets compared to that of immediate release form was 54 % at the 4 mg dose and 59 % at the 8 mg dose.
Concomitant intake of food results in a somewhat higher degree of absorption, AUC is 14 % higher and C_{max} 23 % higher compared with intake when fasting. C_{min} is unaffected by concomitant food intake.

Distribution
Approximately 98 % of doxazosin is protein-bound in plasma. Volume of distribution: 1 litre/kg.

Biotransformation
Doxazosin is primarily metabolised by O-demethylation and hydroxylation. Doxazosin is extensively metabolised with < 5 % excreted as unchanged product.

Elimination
Clearance of doxazosin is 1.3 ml/min/kg.
The plasma elimination is biphasic with the terminal elimination half-life being 22 hours and hence this provides the basic for once daily dosing.

Special populations
Elderly

Pharmacokinetic studies with doxazosin prolonged-release tablets in the elderly have shown no significant alterations compared to younger patients.

Renal impairment
Pharmacokinetic studies with doxazosin immediate release tablets in patients with renal impairment did not show any significant alterations compared to that of patients with normal renal function.

Liver impairment
There are only limited data concerning patients with liver impairment and on the effects of medicinal products known to influence hepatic metabolism (e.g. cimetidine). In a clinical study of 12 subjects with moderate hepatic impairment, single dose administration of doxazosin resulted in an increase of AUC of 43 % and a decrease in oral clearance of approximately 30 %.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Tablet core:

Polyethylene oxide

Microcrystalline cellulose

Povidone

All-rac-α-Tocopherol

Colloidal anhydrous silica

Sodium stearyl fumarate

Butylhydroxytoluene (E321)

Tablet coat:

Methacrylic acid - ethyl acrylate copolymer (1:1)

Colloidal anhydrous silica

Macrogol

Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable

6.3 Shelf life

Blister (PVC/PVDC/Al): 5 years.

Plastic bottle: 36 months, after first opening of bottle: 8 weeks.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (PVC/PVDC/aluminium)

Cartons with 10, 20, 28, 30, 50, 56, 60, 90, 98, 100, 140 (10x14) prolonged-release tablets

Calendar packs of 28 and 98 prolonged-release tablets

Unit dose pack of 50 x 1 prolonged-release tablets

Plastic bottle (PP container with LDPE lid and space filler (LDPE)).

Plastic bottle with 500 prolonged-release tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Genus Pharmaceuticals Limited
T/A Genus Pharmaceuticals
Linthwaite
Huddersfield
HD7 5QH
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 06831/0171

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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