Public Assessment Report

Decentralised

Doxand XL 4mg Prolonged-release Tablets
Doxamid XL 4mg Prolonged-release Tablets
Dosano XL 4mg Prolonged-release Tablets

UK/H/874/001/DC
UK/H/875/001/DC
UK/H/877/001/DC

Sandoz GMBH

TABLE OF CONTENTS

Module 1

Product Name	Doxand XL 4 mg Prolonged-release Tablets Doxamid XL 4 mg Prolonged-release Tablets Dosano XL 4 mg Prolonged-release Tablets
Type of Application	Doxazosin mesilate
Active Substance (INN)	Alpha-adrenoceptor antagonists
Pharmacotherapeutic Classification (ATC)	C02 CA04
Pharmaceuctical Form and Strength	4 mg Prolonged-release Tablets
Procedure Numbers	UK/H/874/001/DC UK/H/875/001/DC UK/H/877/001/DC
RMS	UK
CMS	Doxand : DK, EE, ES, PHU, LT, LV, PL Doxamid : CZ, DE, EE, ES, HU, LT, LV, SK Dosano : IE
Start Date	07/02/2006
End Date	22/05/2007
MA Number	PL 04520/0101 PL 04520/0102 PL 04520/0103
Name and address of MA holder	Sandoz GMBH Biochemiestrasse 10 A-6250 Kundl Austria

Module 2

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxand XL 4mg Prolonged-release Tablets

Doxazosin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round, biconvex tablets marked with “DL”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Essential hypertension
- Symptomatic treatment of benign prostatic hyperplasia.

4.2 Posology and method of administration

The tablets can be taken with or without food. The tablets must be swallowed whole with a sufficient amount of liquid. The tablets should not be chewed, divided or crushed.

The maximum recommended dose is 8 mg doxazosin once daily.

Essential hypertension:

Adults: Usually 4 mg doxazosin once daily. It may take up to four weeks to reach optimal effect. If necessary, the dosage may be increased to 8 mg doxazosin once daily.

Doxazosin can be used as sole agent or in combination with another medicinal product e.g. a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an ACE-inhibitor.

Symptomatic treatment of prostatic hyperplasia:

Adults: Usually 4 mg doxazosin once daily. If necessary, the dosage may be increased to 8 mg doxazosin once daily.

Doxazosin may be used in benign prostatic hyperplasia (BPH) patients who are either hypertensive or normotensive, as the blood pressure changes in normotensive patients are clinically insignificant. In hypertensive patients both conditions are treated concomitantly.

Elderly: Same dosage as for adults.

Patients with 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, the usual dose can be used in these patients (see section 4.4).

Patients with hepatic impairment: Doxazosin should be given with particular caution to patients with evidence of impaired liver function. In patients with severe hepatic impairment clinical experience is lacking and therefore the use of doxazosin is not recommended. (see section 4.4).

Children and adolescents: Doxazosin is not recommended for use in children and adolescents due to a lack of clinical experience.

4.3 Contraindications

- Hypersensitivity to the active substance, other quinazolines (e.g. prazosin, terazosin), or to any of the excipients
- Benign hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infections or bladder stones
- 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.

4.4 Special warnings and precautions for use

Doxazosin is not considered appropriate as first-line treatment, this does not exclude the second- or third-line use in combination with other types of antihypertensives.

Simultaneous administration of sildenafil or other phosphodiesterase type 5 (PDE-5) inhibitors to patients taking alpha-blocker therapy may lead to symptomatic hypotension in some patients (see section 4.5).

Patients with acute heart diseases:

Doxazosin should be administered with caution in patients with the following acute heart diseases: Pulmonary oedema as a result of aortic or mitral stenosis, heart failure at high

output, right sided heart failure as a result of pulmonary embolism or pericardiac effusion and left sided ventricular heart insufficiency 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.

On initiation of therapy or increasing of dose the patient should be monitored to minimise the potential for postural effects, e.g. hypotension and syncope. 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. Special care should be taken with hypotensive patients or patients with known orthostatic dysregulation taking doxazosin to treat benign prostatic hyperplasia (BPH). They should be informed about the potential risk for injuries and measures of precaution to minimise orthostatic symptoms.

Patients with hepatic impairment:

Doxazosin should be administered with caution in patients with signs of mild to moderate hepatic impairment (see section 5.2). Since no clinical experience from patients with severe hepatic impairment exists, use in these patients is not recommended. Caution is also recommended when doxazosin is administered concomitantly with medicinal products which may influence hepatic metabolism (e.g. cimetidine).

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

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 indicate that doxazosin has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. Doxazosin has been administered together with thiazide diuretics, furosemide, beta-blocking agents, antibiotics, oral hypoglycaemic agents, uricosuric agents, or anticoagulants without adverse drug interactions. Doxazosin potentiates the blood pressure lowering effect of other antihypertensives. Non-steroidal antirheumatics or estrogens 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 concerning interactions with agents influencing hepatic metabolism.

Simultaneous administration of sildenafil or other PDE-5 inhibitors to patients taking alpha-blocker therapy may lead to symptomatic hypotension in some patients. Therefore, sildenafil doses above 25 mg should not be taken within 4 hours of taking an alpha-blocker (see section 4.4).

4.6 Pregnancy and lactation

There are no adequate data from the use of doxazosin in pregnant women. Although no teratogenic effects were noted in animal studies, doxazosin should not be used during pregnancy unless clearly needed (see section 5.3).

Animal studies have shown that doxazosin is accumulated in the milk (see section 5.3). There is no information available on accumulation of doxazosin in human breast milk. Doxazosin should therefore not be administered to breastfeeding women. Interruption of breast-feed should be considered in cases of required continuation of doxazosin.

4.7 Effects on ability to drive and use machines

Doxazosin has a minor or moderate influence on the ability to drive and use machines, especially at the beginning of therapy. Some patients may experience impaired ability to react.

4.8 Undesirable effects

The occurrence of adverse reactions are mainly due to the pharmacological properties of the medicinal product.

The adverse reaction profile in clinical trials with patients with benign prostatic hyperplasia corresponded to the one seen in hypertension.

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, <1/1, 000); very rare (<1/10, 000), including isolated reports

Blood and the lymphatic system disorders:

Very rare : Reduction of erythrocytes, leucocytes and thrombocytes

Metabolism and nutrition disorders:

Uncommon : thirst, hypokalaemia, gout

Rare : hypoglycaemia

Very rare : increase in serum urea.

Psychiatric disorders:

Common : apathia

Uncommon : nightmares, amnesia, emotional instability

Rare : depression, agitation

Nervous system disorders:

Common : muscle cramps, fatigue, malaise, headache, somnolence

Uncommon : tremor, muscular stiffness
Rare : paraesthesia

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

Ear and labyrinth disorders:
Uncommon : tinnitus

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
Uncommon : anorexia, increased appetite, taste disturbances
Rare : abdominal discomfort, diarrhoea, vomiting

Hepato-biliary disorders:
Rare : icterus, increased liver values

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

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

Renal and urinary disorders:

Common : frequent desire to micturate, increased micturation, delayed ejaculation

Uncommon : incontinence, micturation disturbances, dysuria

Rare : impotence, priapism

Very rare : increase of serum creatinine.

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 recommenced after a break.

4.9 Overdose

Symptoms:

Headache, dizziness, unconsciousness, syncope, dyspnoea, hypotension, palpitation, tachycardia, arrhythmia. Nausea, vomiting. Possibly hypoglycaemia, hypokalaemia.

Treatment:

Symptomatic treatment. Close control of blood pressure. Since doxazosin is strongly bound to plasma proteins dialysis is not indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoceptor antagonists

ATC code: C02CA04

Hypertension:

Administration of doxazosin in hypertensive patients causes a clinically significant reduction in blood pressure as a result of a reduction in systemic vascular resistance. This effect is thought to result from selective blockade of the alpha-1-adrenoceptors located in the vasculature. With once daily dosing, clinically significant reductions in blood pressure are present throughout the day and at 24-hours post dose. The majority of patients are controlled on the initial dose of 4 mg doxazosin. In patients with hypertension, the decrease in blood pressure during treatment with doxazosin was similar in both the sitting and standing position.

Patients treated with immediate release doxazosin tablets against hypertension can be transferred to doxazosin prolonged-release and the dose titrated upwards as needed, while maintaining effect and tolerability.

Habituation has not been observed during long-term treatment with doxazosin. 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), and significant reduction in total glycerides and total cholesterol. The clinical relevance of these findings is still unknown.

Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation as well as enhanced capacity of tissue plasminogen-activator. The clinical relevance of these findings is still uncertain.

Additionally, doxazosin improves insulin sensitivity in patients with impaired sensitivity to insulin, but also concerning this finding the clinical relevance is still uncertain.

Doxazosin has shown to be free of metabolic adverse effects and is suitable for treatment of patients with coexistent asthma, diabetes, left ventricular dysfunction or gout.

Prostatic hyperplasia:

Administration of doxazosin to patients with prostatic hyperplasia results in a significant improvement in urodynamics and symptoms as a result of a selective blockade of alpha-adrenoceptors located in the prostatic muscular stroma, capsule and bladder neck.

Most of the patients with prostatic hyperplasia are controlled with the initial dose.

Doxazosin has shown to be an effective blocker of 1A subtype of alpha-adrenoceptors which make up more than 70% of the adrenergic subtypes in prostate.

Throughout the recommended dosage range, doxazosin has only a minor or no effect on blood pressure in normotensive benign prostatic hyperplasia (BPH) patients.

5.2 Pharmacokinetic properties

Absorption:

After oral administration of therapeutic doses, doxazosin in Doxand XL 4mg Prolonged-release Tablets is well absorbed with peak blood levels gradually reached at 6 to 8 hours after dosing. Peak plasma levels are approximately one third of those of the same dose of immediate release doxazosin tablets. Trough levels at 24 hours are, however, similar. The pharmacokinetic properties of doxazosin lead to a minor variation in plasma levels. Peak/trough ratio of doxazosin prolonged-release is less than half that of immediate release doxazosin tablets.

At steady-state, the relative bioavailability of doxazosin from doxazosin prolonged-release compared to immediate release form was 54% at the 4 mg dose and 59% at the 8 mg dose.

Distribution:

App. 98% of doxazosin is protein-bound in plasma.

Biotransformation:

Doxazosin is extensively metabolised with <5% excreted as unchanged product.

Doxazosin is primarily metabolised by O-demethylation and hydroxylation.

Elimination:

The plasma elimination is biphasic with the terminal elimination half-life being 22 hours and hence this provides the basic for once daily dosing

Elderly:

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

Renal impairment:

Pharmacokinetic studies with doxazosin in patients with renal impairment also showed no significant alterations compared to patients with normal renal function.

Liver impairment:

There are only limited data in patients with liver impairment and on the effects of medicinal products 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 of AUC of 43% and a decrease in oral clearance of app. 40%. Doxazosin therapy in patients with hepatic impairment should be performed with caution (see section 4.4.).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity. 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 foetus. A dosage regime of 82 mg/kg/day (8 times the human exposure) was associated with reduced foetal survival.

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

Core

Macrogol 200

Macrogol 900,

Butylhydroxytoluene (E321)

Cellulose microcrystalline,

Povidone K 30,

α-Tocopherol (E307),

Colloidal anhydrous silica,

Sodium stearyl fumarate

Coating

Methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30%

Silica colloidal anhydrous

Macrogol 1300-1600

Titanium dioxide (E 171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC//Al blister: 14, 28, 30, 56 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz GmbH

Biochemiestrasse 10

6250 Kundl

Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 04520/0101

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/05/2007

10 DATE OF REVISION OF THE TEXT

22/05/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxamid XL 4mg Prolonged-release Tablets

Doxazosin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round, biconvex tablets marked with “DL”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Essential hypertension
- Symptomatic treatment of benign prostatic hyperplasia.

4.2 Posology and method of administration

The tablets can be taken with or without food. The tablets must be swallowed whole with a sufficient amount of liquid. The tablets should not be chewed, divided or crushed.

The maximum recommended dose is 8 mg doxazosin once daily.

Essential hypertension:

Adults: Usually 4 mg doxazosin once daily. It may take up to four weeks to reach optimal effect. If necessary, the dosage may be increased to 8 mg doxazosin once daily.

Doxazosin can be used as sole agent or in combination with another medicinal product e.g. a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an ACE-inhibitor.

Symptomatic treatment of prostatic hyperplasia:

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Doxazosin may be used in benign prostatic hyperplasia (BPH) patients who are either hypertensive or normotensive, as the blood pressure changes in normotensive patients are clinically insignificant. In hypertensive patients both conditions are treated concomitantly.

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Children and adolescents: Doxazosin is not recommended for use in children and adolescents due to a lack of clinical experience.

4.3 Contraindications

- Hypersensitivity to the active substance, other quinazolines (e.g. prazosin, terazosin), or to any of the excipients
- Benign hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infections or bladder stones
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Doxazosin should be administered with caution in patients with the following acute heart diseases: Pulmonary oedema as a result of aortic or mitral stenosis, heart failure at high output, right sided heart failure as a result of pulmonary embolism or pericardiac effusion and left sided ventricular heart insufficiency with low filling pressure.

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4.6 Pregnancy and lactation

There are no adequate data from the use of doxazosin in pregnant women. Although no teratogenic effects were noted in animal studies, doxazosin should not be used during pregnancy unless clearly needed (see section 5.3).

Animal studies have shown that doxazosin is accumulated in the milk (see section 5.3). There is no information available on accumulation of doxazosin in human breast milk. Doxazosin should therefore not be administered to breastfeeding women. Interruption of breast-feed should be considered in cases of required continuation of doxazosin.

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Doxazosin has a minor or moderate influence on the ability to drive and use machines, especially at the beginning of therapy. Some patients may experience impaired ability to react.

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The occurrence of adverse reactions are mainly due to the pharmacological properties of the medicinal product.

The adverse reaction profile in clinical trials with patients with benign prostatic hyperplasia corresponded to the one seen in hypertension.

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, <1/1, 000); very rare (<1/10, 000), including isolated reports

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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 recommenced after a break.

4.9 Overdose

Symptoms:

Headache, dizziness, unconsciousness, syncope, dyspnoea, hypotension, palpitation, tachycardia, arrhythmia. Nausea, vomiting. Possibly hypoglycaemia, hypokalaemia.

Treatment:

Symptomatic treatment. Close control of blood pressure. Since doxazosin is strongly bound to plasma proteins dialysis is not indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoceptor antagonists

ATC code: C02CA04

Hypertension:

Administration of doxazosin in hypertensive patients causes a clinically significant reduction in blood pressure as a result of a reduction in systemic vascular resistance. This effect is thought to result from selective blockade of the alpha-1-adrenoceptors located in the vasculature. With once daily dosing, clinically significant reductions in blood pressure are present throughout the day and at 24-hours post dose. The majority of patients are controlled on the initial dose of 4 mg doxazosin. In patients with hypertension, the decrease in blood pressure during treatment with doxazosin was similar in both the sitting and standing position.

Patients treated with immediate release doxazosin tablets against hypertension can be transferred to doxazosin prolonged-release and the dose titrated upwards as needed, while maintaining effect and tolerability.

Habituation has not been observed during long-term treatment with doxazosin. 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), and significant reduction in total glycerides and total cholesterol. The clinical relevance of these findings is still unknown.

Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation as well as enhanced capacity of tissue plasminogen-activator. The clinical relevance of these findings is still uncertain.

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Prostatic hyperplasia:

Administration of doxazosin to patients with prostatic hyperplasia results in a significant improvement in urodynamics and symptoms as a result of a selective blockade of alpha-adrenoceptors located in the prostatic muscular stroma, capsule and bladder neck.

Most of the patients with prostatic hyperplasia are controlled with the initial dose.

Doxazosin has shown to be an effective blocker of 1A subtype of alpha-adrenoceptors which make up more than 70% of the adrenergic subtypes in prostate.

Throughout the recommended dosage range, doxazosin has only a minor or no effect on blood pressure in normotensive benign prostatic hyperplasia (BPH) patients.

5.2 Pharmacokinetic properties

Absorption:

After oral administration of therapeutic doses, doxazosin in **[To be completed nationally]** 4mg Prolonged-release Tablets is well absorbed with peak blood levels gradually reached at 6 to 8 hours after dosing. Peak plasma levels are approximately one third of those of the same dose of immediate release doxazosin tablets. Trough levels at 24 hours are, however, similar. The pharmacokinetic properties of doxazosin lead to a minor variation in plasma levels. Peak/trough ratio of doxazosin prolonged-release is less than half that of immediate release doxazosin tablets.

At steady-state, the relative bioavailability of doxazosin from doxazosin prolonged-release compared to immediate release form was 54% at the 4 mg dose and 59% at the 8 mg dose.

Distribution:

App. 98% of doxazosin is protein-bound in plasma.

Biotransformation:

Doxazosin is extensively metabolised with <5% excreted as unchanged product.

Doxazosin is primarily metabolised by O-demethylation and hydroxylation.

Elimination:

The plasma elimination is biphasic with the terminal elimination half-life being 22 hours and hence this provides the basic for once daily dosing

Elderly:

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

Renal impairment:

Pharmacokinetic studies with doxazosin in patients with renal impairment also showed no significant alterations compared to patients with normal renal function.

Liver impairment:

There are only limited data in patients with liver impairment and on the effects of medicinal products 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 of AUC of 43% and a decrease in oral clearance of app. 40%. Doxazosin therapy in patients with hepatic impairment should be performed with caution (see section 4.4.).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity. 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 foetus. A dosage regime of 82 mg/kg/day (8 times the human exposure) was associated with reduced foetal survival.

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

Core

Macrogol 200

Macrogol 900,

Butylhydroxytoluene (E321)

Cellulose microcrystalline,

Povidone K 30,

α-Tocopherol (E307),

Colloidal anhydrous silica,

Sodium stearyl fumarate

Coating

Methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30%

Silica colloidal anhydrous

Macrogol 1300-1600

Titanium dioxide (E 171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC//Al blister: 14, 28, 30, 56 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz GmbH

Biochemiestrasse 10

6250 Kundl

Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 04520/0102

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/05/2007

10 DATE OF REVISION OF THE TEXT

22/05/2007

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Dosano XL 4 mg Prolonged-release Tablets

Doxazosin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Prolonged-release tablet.

White, round, biconvex tablets marked with “DL”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Essential hypertension
- Symptomatic treatment of benign prostatic hyperplasia.

4.2 Posology and method of administration

The tablets can be taken with or without food. The tablets must be swallowed whole with a sufficient amount of liquid. The tablets should not be chewed, divided or crushed.

The maximum recommended dose is 8 mg doxazosin once daily.

Essential hypertension:

Adults: Usually 4 mg doxazosin once daily. It may take up to four weeks to reach optimal effect. If necessary, the dosage may be increased to 8 mg doxazosin once daily.

Doxazosin can be used as sole agent or in combination with another medicinal product e.g. a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an ACE-inhibitor.

Symptomatic treatment of prostatic hyperplasia:

Adults: Usually 4 mg doxazosin once daily. If necessary, the dosage may be increased to

8 mg doxazosin once daily.

Doxazosin may be used in benign prostatic hyperplasia (BPH) patients who are either hypertensive or normotensive, as the blood pressure changes in normotensive patients are clinically insignificant. In hypertensive patients both conditions are treated concomitantly.

Elderly: Same dosage as for adults.

Patients with 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, the usual dose can be used in these patients (see section 4.4).

Patients with hepatic impairment: Doxazosin should be given with particular caution to patients with evidence of impaired liver function. In patients with severe hepatic impairment clinical experience is lacking and therefore the use of doxazosin is not recommended. (see section 4.4).

Children and adolescents: Doxazosin is not recommended for use in children and adolescents due to a lack of clinical experience.

4.3 Contraindications

- Hypersensitivity to the active substance, other quinazolines (e.g. prazosin, terazosin), or to any of the excipients
- Benign hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infections or bladder stones
- 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.

4.4 Special warnings and precautions for use

Doxazosin is not considered appropriate as first-line treatment, this does not exclude the second- or third-line use in combination with other types of antihypertensives.

Patients with acute heart diseases:

Doxazosin should be administered with caution in patients with the following acute heart diseases: Pulmonary oedema as a result of aortic or mitral stenosis, heart failure at high output, right sided heart failure as a result of pulmonary embolism or pericardiac effusion and left sided ventricular heart insufficiency 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.

On initiation of therapy or increasing of dose the patient should be monitored to minimise the potential for postural effects, e.g. hypotension and syncope. 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. Special care should be taken with hypotensive patients or patients with known orthostatic dysregulation taking doxazosin to treat benign prostatic hyperplasia (BPH). They should be informed about the potential risk for injuries and measures of precaution to minimise orthostatic symptoms.

Patients with hepatic impairment:

Doxazosin should be administered with caution in patients with signs of mild to moderate hepatic impairment (see section 5.2). Since no clinical experience from patients with severe hepatic impairment exists, use in these patients is not recommended. Caution is also recommended when doxazosin is administered concomitantly with medicinal products which may influence hepatic metabolism (e.g. cimetidine).

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

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 indicate that doxazosin has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin. Doxazosin has been administered together with thiazide diuretics, furosemide, beta-blocking agents, antibiotics, oral hypoglycaemic agents, uricosuric agents, or anticoagulants without adverse drug interactions. Doxazosin potentiates the blood pressure lowering effect of other antihypertensives. Non-steroidal antirheumatics or estrogens 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 concerning interactions with agents influencing hepatic metabolism.

4.6 Pregnancy and lactation

There are no adequate data from the use of doxazosin in pregnant women. Although no teratogenic effects were noted in animal studies, doxazosin should not be used during pregnancy unless clearly needed (see section 5.3).

Animal studies have shown that doxazosin is accumulated in the milk (see section 5.3). There is no information available on accumulation of doxazosin in human breast milk. Doxazosin should therefore not be administered to breastfeeding women. Interruption of breast-feed should be considered in cases of required continuation of doxazosin.

4.7 Effects on ability to drive and use machines

Doxazosin has a minor or moderate influence on the ability to drive and use machines, especially at the beginning of therapy. Some patients may experience impaired ability to react.

4.8 Undesirable effects

The occurrence of adverse reactions are mainly due to the pharmacological properties of the medicinal product.

The adverse reaction profile in clinical trials with patients with benign prostatic hyperplasia corresponded to the one seen in hypertension.

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, <1/1, 000); very rare (<1/10, 000), including isolated reports

Blood and the lymphatic system disorders:

Very rare : Reduction of erythrocytes, leucocytes and thrombocytes

Metabolism and nutrition disorders:

Uncommon : thirst, hypokalaemia, gout

Rare : hypoglycaemia

Very rare : increase in serum urea.

Psychiatric disorders:

Common : apathia

Uncommon : nightmares, amnesia, emotional instability

Rare : depression, agitation

Nervous system disorders:

Common : muscle cramps, fatigue, malaise, headache, somnolence

Uncommon : tremor, muscular stiffness

Rare : paraesthesia

Eye disorders:

Common : accomodation disturbances

Uncommon : lacrimation, photophobia

Rare : blurred vision

Ear and labyrinth disorders:

Uncommon : tinnitus

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

Uncommon : anorexia, increased appetite, taste disturbances

Rare : abdominal discomfort, diarrhoea, vomiting

Hepato-biliary disorders:

Rare : icterus, increased liver values

Skin and subcutaneous tissue disorders:

Uncommon : alopecia, oedema of the face/general oedema

Rare : rash, pruritus, purpura

Musculoskeletal, connective tissue and bone disorders:

Uncommon : muscular pain, swelling of joints/arthralgia, muscle weakness

Renal and urinary disorders:

Common : frequent desire to micturate, increased micturation, delayed ejaculation

Uncommon : incontinence, micturation disturbances, dysuria

Rare : impotence, priapism

Very rare : increase of serum creatinine.

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 recommenced after a break.

4.9 Overdose

Symptoms:

Headache, dizziness, unconsciousness, syncope, dyspnoea, hypotension, palpitation, tachycardia, arrhythmia. Nausea, vomiting. Possibly hypoglycaemia, hypokalaemia.

Treatment:

Symptomatic treatment. Close control of blood pressure. Since doxazosin is strongly bound to plasma proteins dialysis is not indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Alpha-adrenoceptor antagonists

ATC code: C02CA04

Hypertension:

Administration of doxazosin in hypertensive patients causes a clinically significant reduction in blood pressure as a result of a reduction in systemic vascular resistance. This effect is thought to result from selective blockade of the alpha-1-adrenoceptors located in the vasculature. With once daily dosing, clinically significant reductions in blood pressure are present throughout the day and at 24-hours post dose. The majority of patients are controlled on the initial dose of 4 mg doxazosin. In patients with hypertension, the decrease in blood pressure during treatment with doxazosin was similar in both the sitting and standing position.

Patients treated with immediate release doxazosin tablets against hypertension can be transferred to doxazosin prolonged-release and the dose titrated upwards as needed, while maintaining effect and tolerability.

Habituation has not been observed during long-term treatment with doxazosin. 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), and significant reduction in total glycerides and total cholesterol. The clinical relevance of these findings is still unknown.

Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation as well as enhanced capacity of tissue plasminogen-activator. The clinical relevance of these findings is still uncertain.

Additionally, doxazosin improves insulin sensitivity in patients with impaired sensitivity to insulin, but also concerning this finding the clinical relevance is still uncertain.

Doxazosin has shown to be free of metabolic adverse effects and is suitable for treatment of patients with coexistent asthma, diabetes, left ventricular dysfunction or gout.

Prostatic hyperplasia:

Administration of doxazosin to patients with prostatic hyperplasia results in a significant improvement in urodynamics and symptoms as a result of a selective blockade of alpha-adrenoceptors located in the prostatic muscular stroma, capsule and bladder neck.

Most of the patients with prostatic hyperplasia are controlled with the initial dose.

Doxazosin has shown to be an effective blocker of 1A subtype of alpha-adrenoceptors which make up more than 70% of the adrenergic subtypes in prostate.

Throughout the recommended dosage range, doxazosin has only a minor or no effect on blood pressure in normotensive benign prostatic hyperplasia (BPH) patients.

5.2 Pharmacokinetic properties

Absorption:

After oral administration of therapeutic doses, doxazosin in Dosano XL 4mg Prolonged-release Tablets and associated names is well absorbed with peak blood levels gradually reached at 6 to 8 hours after dosing. Peak plasma levels are approximately one third of those of the same dose of immediate release doxazosin tablets. Trough levels at 24 hours are, however, similar. The pharmacokinetic properties of doxazosin lead to a minor variation in plasma levels. Peak/trough ratio of doxazosin prolonged-release is less than half that of immediate release doxazosin tablets.

At steady-state, the relative bioavailability of doxazosin from doxazosin prolonged-release compared to immediate release form was 54% at the 4 mg dose and 59% at the 8 mg dose.

Distribution:

App. 98% of doxazosin is protein-bound in plasma.

Biotransformation:

Doxazosin is extensively metabolised with <5% excreted as unchanged product.

Doxazosin is primarily metabolised by O-demethylation and hydroxylation.

Elimination:

The plasma elimination is biphasic with the terminal elimination half-life being 22 hours and hence this provides the basic for once daily dosing

Elderly:

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

Renal impairment:

Pharmacokinetic studies with doxazosin in patients with renal impairment also showed no significant alterations compared to patients with normal renal function.

Liver impairment:

There are only limited data in patients with liver impairment and on the effects of medicinal products 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 of AUC of 43% and a decrease in oral clearance of app. 40%. Doxazosin therapy in patients with hepatic impairment should be performed with caution (see section 4.4.).

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity. 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 foetus. A dosage regime of 82 mg/kg/day (8 times the human exposure) was associated with reduced foetal survival.

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

Core

Macrogol 200

Macrogol 900,

Butylhydroxytoluene (E321)

Cellulose microcrystalline,

Povidone K 30,

α-Tocopherol (E307),

Colloidal anhydrous silica,

Sodium stearyl fumarate

Coating

Methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30%

Silica colloidal anhydrous

Macrogol 1300-1600

Titanium dioxide (E 171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVDC//Al blister: 14, 28, 30, 56 or 98 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sandoz GmbH

Biochemiestrasse 10

6250 Kundl

Austria

8 MARKETING AUTHORISATION NUMBER(S)

PL 04520/0103

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/05/2007

10 DATE OF REVISION OF THE TEXT

22/05/2007

Module 3

Product Information Leaflet

SANDOZ

PACKAGE LEAFLET: INFORMATION FOR THE USER

SZ0000000000

Doxand XL 4 mg Prolonged-release Tablets

Doxazosin

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. WHAT DOXAND XL 4 MG PROLONGED-RELEASE TABLETS ARE AND WHAT THEY ARE USED FOR

Doxand XL 4 mg Prolonged-release Tablets are one of a group of medicines called alpha-blockers.

They are used to treat:
- high blood pressure
- symptoms caused by enlargement of the prostate gland in men.

In patients taking this medicine to treat high blood pressure (hypertension), it works by relaxing blood vessels so that blood passes through them more easily. This helps to lower blood pressure.

In patients with enlargement of the prostate gland, this medicine is taken to treat poor and/or frequent passing of urine. This is common in patients with enlargement of the prostate gland (benign prostatic hyperplasia). This medicine works by relaxing muscle around the bladder exit and prostate gland so urine is passed more easily.

2. BEFORE YOU TAKE DOXAND XL 4 MG PROLONGED-RELEASE TABLETS

Do not take this medicine
- if you are allergic (hypersensitive) to doxazosin, related quinazolines e.g. prazosin or terazosin, or any of the other ingredients of this medicine (see section 6)
- if you have had any form of obstruction of the digestive tract
- if you have an enlarged prostate gland together with congestion of the upper urinary tract, chronic urinary tract infections or bladder stones
- if you have an overflow bladder, an inability to urinate, or kidney failure.

Take special care with this medicine
Talk to your doctor before taking this medicine:
- if you have liver disease
- if you have heart disease
- if you have risk factors for cardiovascular disease, e.g. smoking, high blood cholesterol, diabetes
- if you have a low blood pressure
- if you have a fall in blood pressure on standing up, causing dizziness, light-headedness or fainting.

Dizziness, weakness and in rare cases fainting may occur, especially when you first start taking this medicine. You should therefore be careful at the beginning of treatment, and avoid situations that could lead to injury if these symptoms occur.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is especially important to mention the following before taking this medicine:
- medicines used to treat difficulties in getting an erection (e.g. sildenafil, tradalafil or vardenafil); together with Doxand XL 4 mg Prolonged-release Tablets they may lower your blood pressure
- medicines for high blood pressure (called anti-hypertensives)
- aspirin or similar medicines (non-steroidal anti-inflammatories)
- medicines that contain oestrogen (e.g. oral contraceptives)
- medicines usually used to treat asthma, heart conditions, eye problems, or blocked noses (called sympathomimetics).

Pregnancy and breast-feeding
- If you are pregnant do not take this medicine without consulting your doctor first. The safety of this medicine in pregnancy is not sufficiently established.
- You should not take this medicine if you are breast-feeding.

Driving and using machines
Take care if you drive or operate machinery. Your tablets may affect your ability to drive or operate machinery safely, particularly when you first start to take them. They may make you feel weak or dizzy. If affected, do not drive or operate machinery and contact your doctor immediately.

3. HOW TO TAKE DOXAND XL 4 MG PROLONGED-RELEASE TABLETS

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose of Doxand XL 4 mg Prolonged-release Tablets is 4 mg taken as a single daily dose.
Your doctor may wish to increase your dose to 8 mg once daily. This is the maximum dose of Doxand XL 4 mg Prolonged-release Tablets.

Method of administration:
- Do not chew, divide or crush the tablets.
- Swallow the tablets whole with a drink of water.
- You can take these tablets with or without food.

Children and adolescents:
This medicine is not recommended for patients under the age of 18 years.

If you take more of this medicine than you should
Too many tablets at once may make you unwell. If several tablets are taken it may be dangerous. Tell your doctor immediately or go to your nearest hospital casualty department.

If you forget to take this medicine
Do not worry. If you forget to take a tablet, leave that dose out completely. Then go back to your usual schedule.

If you stop taking this medicine
It is important to keep taking your tablets. Do not change the dose or stop taking the tablets without first checking with your doctor.
Do not wait until your tablets are finished before seeing your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious:
If any of the following happens, stop taking this medicine and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Allergic reactions such as wheezing, shortness of breath, extreme dizziness or collapse, swelling of the face or throat, or a serious skin rash with red spots or blisters.
- Chest pain, increased or irregular heart beat, heart attack or stroke.
- Yellowing of the skin or whites of the eyes, caused by liver problems.

- Unusual bruising or bleeding caused by low blood platelets.

These side effects are uncommon (affects less than 1 in 100 patients) or rare (affects less than 1 in 1000 patients).
Other side effects:

Common (affects less than 1 in 10 patients):
- apathy, headache, sleepiness
- vision disturbances
- abnormal heartbeat
- giddiness, dizziness
- swelling of the skin
- shortness of breath, nasal stuffiness or runny nose (rhinitis)
- constipation, indigestion
- muscle cramps
- frequent need to urinate, increased urination
- difficulty to reach a climax (delayed ejaculation)
- weakness, fatigue, generally feeling unwell

Uncommon (affects less than 1 in 100 patients):
- loss of appetite, increased appetite, thirst, taste disturbances
- low blood levels of potassium which can cause muscle weakness, twitching or abnormal heart rhythm
- nightmares, emotional instability
- shaking (tremor), memory loss
- increased production of tears, excessive sensitivity to light
- ringing or noise in the ears
- slowing of the heart rate
- fall in blood pressure on standing up which may cause dizziness, light-headedness or fainting
- reduced blood supply to the hands and feet
- flushing
- nose bleeds
- cough, difficulty in breathing or wheezing
- sore throat
- hair loss
- gout, painful joints
- painful muscles, muscle weakness, muscle stiffness
- inability to control urination (urinary incontinence), difficulty or pain on passing urine
- fever/shivering, paleness
- swelling of feet or lower legs

Rare (affects less than 1 in 1000 patients):
- agitation, depression
- tingling or altered sensitivity of the hands and feet
- blurred vision
- stomach/abdominal pains, diarrhoea, feeling/being sick
- skin rash, itching
- painful persistent erection of the penis or failure/inability to achieve penile erection
- decreased body temperature in elderly
- low blood sugar level, liver enzyme increases

Very rare (affects less than 1 in 10,000 patients):
- low numbers of white and red blood cells
- increased blood levels of urea and creatin

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DOXAND XL 4 MG PROLONGED-RELEASE TABLETS

Keep out of the reach and sight of children.

Do not use Doxand XL 4 mg Prolonged-release Tablets after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Doxand XL 4 mg Prolonged-release Tablets contain
- The active substance is doxazosin. Each tablet contains 4 mg doxazosin (as mesilate).
- Other ingredients are:

Core:
Macrogol 200,
Macrogol 900,
Butylhydroxytoluene (E321),
Cellulose microcrystalline,
Povidone K 30,
α-Tocopherol (E307),
Colloidal anhydrous silica,
Sodium stearyl fumarate;
Coating:
Methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30%,
Colloidal anhydrous silica,
Macrogol (1300-1600),
Titanium dioxide (E171).

What Doxand XL 4 mg Prolonged-release Tablets look like and contents of the pack
Doxand XL 4 mg Prolonged-release Tablets are white round biconvex tablets marked with "DL"
Doxand XL 4 mg Prolonged-release Tablets are packed in blisters.
The blisters are packed in a carton box containing 14, 28, 30, 56 or 98 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Sandoz GmbH, Biochemiestrasse 10, A-6250 Kundl, Austria

Manufacturer:
Sandoz A/S C.F. Tietgens Boulevard 40, 5220 Odense SØ, Denmark. **or**
Salutas Pharma GmbH, Otto-von-Guericke-Allee 1, 39179 Barleben, Germany. **or**
HEXAL® POLSKA Sp. z o.o., ul. Domaniewska 50 C, 02-672 Warszawa, Poland.

This medicinal product is authorised in the Member States of the EEA under the following names:

Country	Product name of generic product
United Kingdom	Doxand XL 4mg Prolonged-release Tablets
Denmark	Doxazosin Hexal
Estonia	Doxazosin HEXAL
Spain	Doxazosina Neo Bexal 4 mg comprimidos de liberación prolongada EFG
Hungary	Doxazosin Sandoz URO 4 mg retard filmtabletta
Lithuania	Doxazosin HEXAL 4mg pailginto atpalaidavimo tabletės
Latvia	Doxazosin HEXAL® 4 mg ilgstošās darbības tabletes
Poland	Doxazosin-1A Pharma

This leaflet is last approved in 06/2007 (to be amended after approval).

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SANDOZ

PACKAGE LEAFLET: INFORMATION FOR THE USER
Doxamid XL 4 mg Prolonged-release Tablets
Doxazosin

SZ0000000000

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
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1. WHAT DOXAMID XL 4 MG PROLONGED-RELEASE TABLETS ARE AND WHAT THEY ARE USED FOR

Doxamid XL 4 mg Prolonged-release Tablets are one of a group of medicines called alpha-blockers.

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- high blood pressure
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In patients with enlargement of the prostate gland, this medicine is taken to treat poor and/or frequent passing of urine. This is common in patients with enlargement of the prostate gland (benign prostatic hyperplasia). This medicine works by relaxing muscle around the bladder exit and prostate gland so urine is passed more easily.

2. BEFORE YOU TAKE DOXAMID XL 4 MG PROLONGED-RELEASE TABLETS

Do not take this medicine
- if you are allergic (hypersensitive) to doxazosin, related quinazolines e.g. prazosin or terazosin, or any of the other ingredients of this medicine (see section 6)
- if you have had any form of obstruction of the digestive tract
- if you have an enlarged prostate gland together with congestion of the upper urinary tract, chronic urinary tract infections or bladder stones
- if you have an overflow bladder, an inability to urinate, or kidney failure.

Take special care with this medicine
Talk to your doctor before taking this medicine:
- if you have liver disease
- if you have heart disease
- if you have risk factors for cardiovascular disease, e.g. smoking, high blood cholesterol, diabetes
- if you have a low blood pressure
- if you have a fall in blood pressure on standing up, causing dizziness, light-headedness or fainting.

Dizziness, weakness and in rare cases fainting may occur, especially when you first start taking this medicine. You should therefore be careful at the beginning of treatment, and avoid situations that could lead to injury if these symptoms occur.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is especially important to mention the following before taking this medicine:
- medicines used to treat difficulties in getting an erection (e.g. sildenafil, tradalafil or vardenafil); together with Doxamid XL 4 mg Prolonged-release Tablets they may lower your blood pressure
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Your doctor may wish to increase your dose to 8 mg once daily. This is the maximum dose of Doxamid XL 4 mg Prolonged-release Tablets.

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- Swallow the tablets whole with a drink of water.
- You can take these tablets with or without food.

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This medicine is not recommended for patients under the age of 18 years.

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Too many tablets at once may make you unwell. If several tablets are taken it may be dangerous. Tell your doctor immediately or go to your nearest hospital casualty department.

If you forget to take this medicine
Do not worry. If you forget to take a tablet, leave that dose out completely. Then go back to your usual schedule.

If you stop taking this medicine
It is important to keep taking your tablets. Do not change the dose or stop taking the tablets without first checking with your doctor.
Do not wait until your tablets are finished before seeing your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious:
If any of the following happens, stop taking this medicine and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Allergic reactions such as wheezing, shortness of breath, extreme dizziness or collapse, swelling of the face or throat, or a serious skin rash with red spots or blisters.
- Chest pain, increased or irregular heart beat, heart attack or stroke.
- Yellowing of the skin or whites of the eyes, caused by liver problems.

- Unusual bruising or bleeding caused by low blood platelets.

These side effects are uncommon (affects less than 1 in 100 patients) or rare (affects less than 1 in 1000 patients).
Other side effects:

Common (affects less than 1 in 10 patients):
- apathy, headache, sleepiness
- vision disturbances
- abnormal heartbeat
- giddiness, dizziness
- swelling of the skin
- shortness of breath, nasal stuffiness or runny nose (rhinitis)
- constipation, indigestion
- muscle cramps
- frequent need to urinate, increased urination
- difficulty to reach a climax (delayed ejaculation)
- weakness, fatigue, generally feeling unwell

Uncommon (affects less than 1 in 100 patients):
- loss of appetite, increased appetite, thirst, taste disturbances
- low blood levels of potassium which can cause muscle weakness, twitching or abnormal heart rhythm
- nightmares, emotional instability
- shaking (tremor), memory loss
- increased production of tears, excessive sensitivity to light
- ringing or noise in the ears
- slowing of the heart rate
- fall in blood pressure on standing up which may cause dizziness, light-headedness or fainting
- reduced blood supply to the hands and feet
- flushing
- nose bleeds
- cough, difficulty in breathing or wheezing
- sore throat
- hair loss
- gout, painful joints
- painful muscles, muscle weakness, muscle stiffness
- inability to control urination (urinary incontinence), difficulty or pain on passing urine
- fever/shivering, paleness
- swelling of feet or lower legs

Rare (affects less than 1 in 1000 patients):
- agitation, depression
- tingling or altered sensitivity of the hands and feet
- blurred vision
- stomach/abdominal pains, diarrhoea, feeling/being sick
- skin rash, itching
- painful persistent erection of the penis or failure/inability to achieve penile erection
- decreased body temperature in elderly
- low blood sugar level, liver enzyme increases

Very rare (affects less than 1 in 10,000 patients):
- low numbers of white and red blood cells
- increased blood levels of urea and creatin

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DOXAMID XL 4 MG PROLONGED-RELEASE TABLETS

Keep out of the reach and sight of children.

Do not use Doxamid XL 4 mg Prolonged-release Tablets after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Doxamid XL 4 mg Prolonged-release Tablets contain
- The active substance is doxazosin. Each tablet contains 4 mg doxazosin (as mesilate).
- Other ingredients are:

Core:
Macrogol 200,
Macrogol 900,
Butylhydroxytoluene (E321),
Cellulose microcrystalline,
Povidone K 30,
α-Tocopherol (E307),
Colloidal anhydrous silica,
Sodium stearyl fumarate;
Coating:
Methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30%,
Colloidal anhydrous silica,
Macrogol (1300-1600),
Titanium dioxide (E171).

What Doxamid XL 4 mg Prolonged-release Tablets look like and contents of the pack
Doxamid XL 4 mg Prolonged-release Tablets are white round biconvex tablets marked with "DL"
Doxamid XL 4 mg Prolonged-release Tablets are packed in blisters.
The blisters are packed in a carton box containing 14, 28, 30, 50, 56, 98 or 100 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Sandoz GmbH, Biochemiestrasse 10, A-6250 Kundl, Austria.

Manufacturer:
Sandoz A/S C.F. Tietgens Boulevard 40, 5220 Odense SØ, Denmark. **or**
Salutas Pharma GmbH, Otto-von-Guericke-Allee 1, 39179 Barleben, Germany. **or**
HEXAL® POLSKA Sp. z o.o., ul. Domaniewska 50 C, 02-672 Warszawa, Poland.

This medicinal product is authorised in the Member States of the EEA under the following names:

Country	Product name of generic product
United Kingdom	Doxamid XL 4mg Prolonged-release Tablets
Czech Republic	Doxazosin Retard 4 mg 1APharma
Germany	Doxazosin - 1A Pharma 4 mg Retardtabletten
Estonia	Doxazosin 1A Pharma
Spain	Doxazosina Neo Acost 4 mg comprimidos de liberación prolongada EFG
Hungary	Doxazosin URO 1a Pharma 4 mg retard tablets
Lithuania	Doxazosin 1A Pharma 4 mg pailginto atpalaidavimo tabletės
Latvia	Doxazosin 1A Pharma® 4 mg ilgstošās darbības tabletes
Slovak Republic	Doxazosin 1A Pharma 4 mg tablety s predĺženým uvoľňovaním

This leaflet is last approved in 05/2007 (to be amended after approval).

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SANDOZ

PACKAGE LEAFLET: INFORMATION FOR THE USER
Dosano XL 4 mg Prolonged-release Tablets
Doxazosin

SZ0000000000

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

1. WHAT DOSANO XL 4 MG PROLONGED-RELEASE TABLETS ARE AND WHAT THEY ARE USED FOR

Dosano XL 4 mg Prolonged-release Tablets are one of a group of medicines called alpha-blockers.

They are used to treat:
- high blood pressure
- symptoms caused by enlargement of the prostate gland in men.

In patients taking this medicine to treat high blood pressure (hypertension), it works by relaxing blood vessels so that blood passes through them more easily. This helps to lower blood pressure.

In patients with enlargement of the prostate gland, this medicine is taken to treat poor and/or frequent passing of urine. This is common in patients with enlargement of the prostate gland (benign prostatic hyperplasia). This medicine works by relaxing muscle around the bladder exit and prostate gland so urine is passed more easily.

2. BEFORE YOU TAKE DOSANO XL 4 MG PROLONGED-RELEASE TABLETS

Do not take this medicine
- if you are allergic (hypersensitive) to doxazosin, related quinazolines e.g. prazosin or terazosin, or any of the other ingredients of this medicine (see section 6)
- if you have had any form of obstruction of the digestive tract
- if you have an enlarged prostate gland together with congestion of the upper urinary tract, chronic urinary tract infections or bladder stones
- if you have an overflow bladder, an inability to urinate, or kidney failure.

Take special care with this medicine
Talk to your doctor before taking this medicine:
- if you have liver disease
- if you have heart disease
- if you have risk factors for cardiovascular disease, e.g. smoking, high blood cholesterol, diabetes
- if you have a low blood pressure
- if you have a fall in blood pressure on standing up, causing dizziness, light-headedness or fainting.

Dizziness, weakness and in rare cases fainting may occur, especially when you first start taking this medicine. You should therefore be careful at the beginning of treatment, and avoid situations that could lead to injury if these symptoms occur.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is especially important to mention the following before taking this medicine:
- medicines used to treat difficulties in getting an erection (e.g. sildenafil, tradalafil or vardenafil); together with Dosano XL 4 mg Prolonged-release Tablets they may lower your blood pressure
- medicines for high blood pressure (called anti-hypertensives)
- aspirin or similar medicines (non-steroidal anti-inflammatories)
- medicines that contain oestrogen (e.g. oral contraceptives)
- medicines usually used to treat asthma, heart conditions, eye problems, or blocked noses (called sympathomimetics).

Pregnancy and breast-feeding
- If you are pregnant do not take this medicine without consulting your doctor first. The safety of this medicine in pregnancy is not sufficiently established.
- You should not take this medicine if you are breast-feeding.

Driving and using machines
Take care if you drive or operate machinery. Your tablets may affect your ability to drive or operate machinery safely, particularly when you first start to take them. They may make you feel weak or dizzy. If affected, do not drive or operate machinery and contact your doctor immediately.

3. HOW TO TAKE DOSANO XL 4 MG PROLONGED-RELEASE TABLETS

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual dose of Dosano XL 4 mg Prolonged-release Tablets is 4 mg taken as a single daily dose.
Your doctor may wish to increase your dose to 8 mg once daily. This is the maximum dose of Dosano XL 4 mg Prolonged-release Tablets.

Method of administration:
- Do not chew, divide or crush the tablets.
- Swallow the tablets whole with a drink of water.
- You can take these tablets with or without food.

Children and adolescents:
This medicine is not recommended for patients under the age of 18 years.

If you take more of this medicine than you should
Too many tablets at once may make you unwell. If several tablets are taken it may be dangerous. Tell your doctor immediately or go to your nearest hospital casualty department.

If you forget to take this medicine
Do not worry. If you forget to take a tablet, leave that dose out completely. Then go back to your usual schedule.

If you stop taking this medicine
It is important to keep taking your tablets. Do not change the dose or stop taking the tablets without first checking with your doctor.
Do not wait until your tablets are finished before seeing your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects could be serious:
If any of the following happens, stop taking this medicine and tell your doctor immediately or go to the casualty department at your nearest hospital:
- Allergic reactions such as wheezing, shortness of breath, extreme dizziness or collapse, swelling of the face or throat, or a serious skin rash with red spots or blisters.
- Chest pain, increased or irregular heart beat, heart attack or stroke.
- Yellowing of the skin or whites of the eyes, caused by liver problems.

- Unusual bruising or bleeding caused by low blood platelets.

These side effects are uncommon (affects less than 1 in 100 patients) or rare (affects less than 1 in 1000 patients).

Other side effects:

Common (affects less than 1 in 10 patients):
- apathy, headache, sleepiness
- vision disturbances
- abnormal heartbeat
- giddiness, dizziness
- swelling of the skin
- shortness of breath, nasal stuffiness or runny nose (rhinitis)
- constipation, indigestion
- muscle cramps
- frequent need to urinate, increased urination
- difficulty to reach a climax (delayed ejaculation)
- weakness, fatigue, generally feeling unwell

Uncommon (affects less than 1 in 100 patients):
- loss of appetite, increased appetite, thirst, taste disturbances
- low blood levels of potassium which can cause muscle weakness, twitching or abnormal heart rhythm
- nightmares, emotional instability
- shaking (tremor), memory loss
- increased production of tears, excessive sensitivity to light
- ringing or noise in the ears
- slowing of the heart rate
- fall in blood pressure on standing up which may cause dizziness, light-headedness or fainting
- reduced blood supply to the hands and feet
- flushing
- nose bleeds
- cough, difficulty in breathing or wheezing
- sore throat
- hair loss
- gout, painful joints
- painful muscles, muscle weakness, muscle stiffness
- inability to control urination (urinary incontinence), difficulty or pain on passing urine
- fever/shivering, paleness
- swelling of feet or lower legs

Rare (affects less than 1 in 1000 patients):
- agitation, depression
- tingling or altered sensitivity of the hands and feet
- blurred vision
- stomach/abdominal pains, diarrhoea, feeling/being sick
- skin rash, itching
- painful persistent erection of the penis or failure/inability to achieve penile erection
- decreased body temperature in elderly
- low blood sugar level, liver enzyme increases

Very rare (affects less than 1 in 10,000 patients):
- low numbers of white and red blood cells
- increased blood levels of urea and creatin

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DOSANO XL 4 MG PROLONGED-RELEASE TABLETS

Keep out of the reach and sight of children.

Do not use Dosano XL 4 mg Prolonged-release Tablets after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Dosano XL 4 mg Prolonged-release Tablets contain
- The active substance is doxazosin. Each tablet contains 4 mg doxazosin (as mesilate).
- Other ingredients are:

Core:
Macrogol 200,
Macrogol 900,
Butylhydroxytoluene (E321),
Cellulose microcrystalline,
Povidone K 30,
α-Tocopherol (E307),
Colloidal anhydrous silica,
Sodium stearyl fumarate;
Coating:
Methacrylic acid ethyl acrylate copolymer (1:1) dispersion 30%,
Colloidal anhydrous silica,
Macrogol (1300-1600),
Titanium dioxide (E171).

What Dosano XL 4 mg Prolonged-release Tablets look like and contents of the pack
Dosano XL 4 mg Prolonged-release Tablets are white round biconvex tablets marked with "DL"
Dosano XL 4 mg Prolonged-release Tablets are packed in blisters.
The blisters are packed in a carton box containing 14, 28, 30, 56 or 98 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder:
Sandoz GmbH, Biochemiestrasse 10, A-6250 Kundl, Austria.

Manufacturer:
Sandoz A/S C.F. Tietgens Boulevard 40, 5220 Odense SØ, Denmark. **or**
Salutas Pharma GmbH, Otto-von-Guericke-Allee 1, 39179 Barleben, Germany. **or**
HEXAL® POLSKA Sp. z o.o., ul. Domaniewska 50 C, 02-672 Warszawa, Poland.

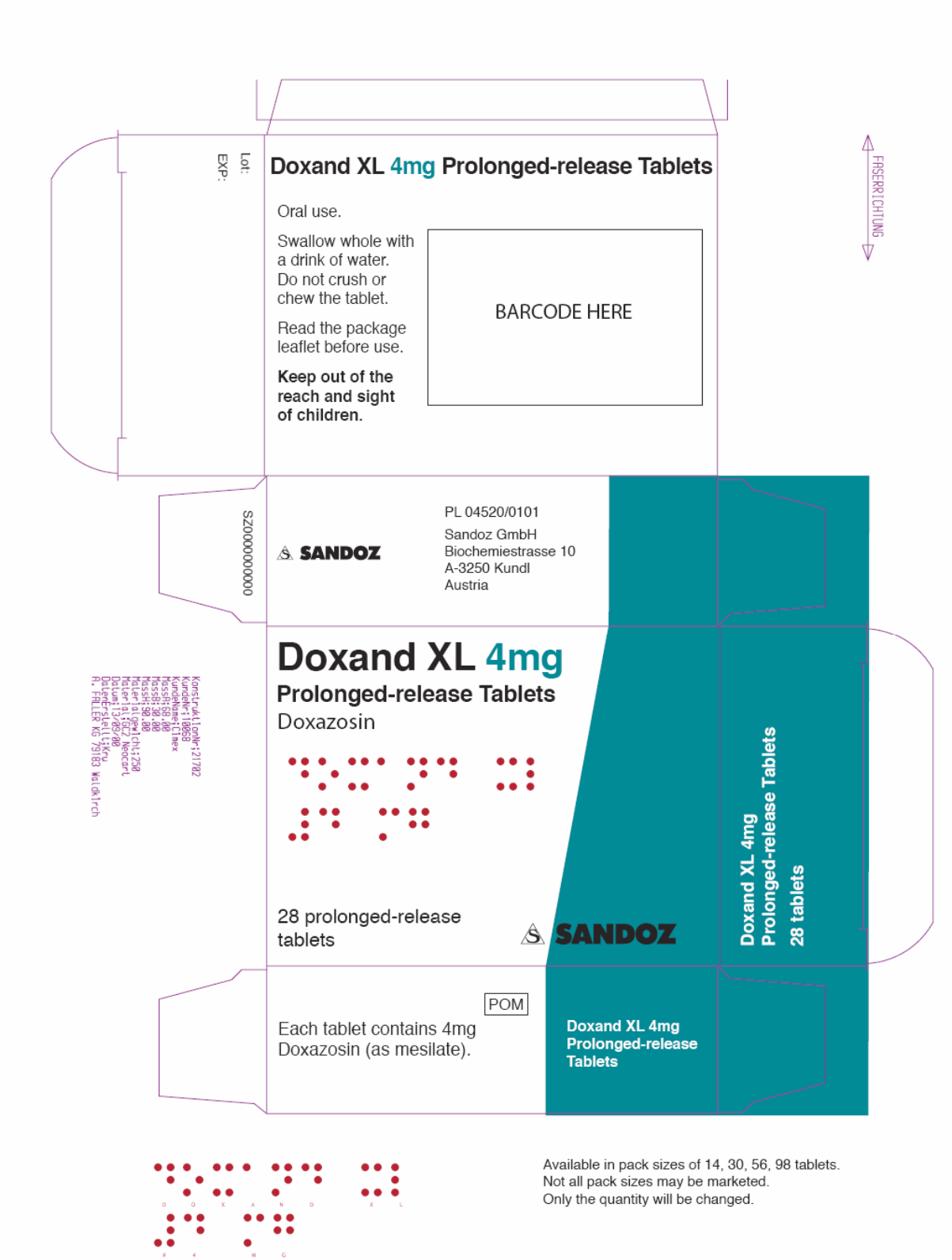
This medicinal product is authorised in the Member States of the EEA under the following names:

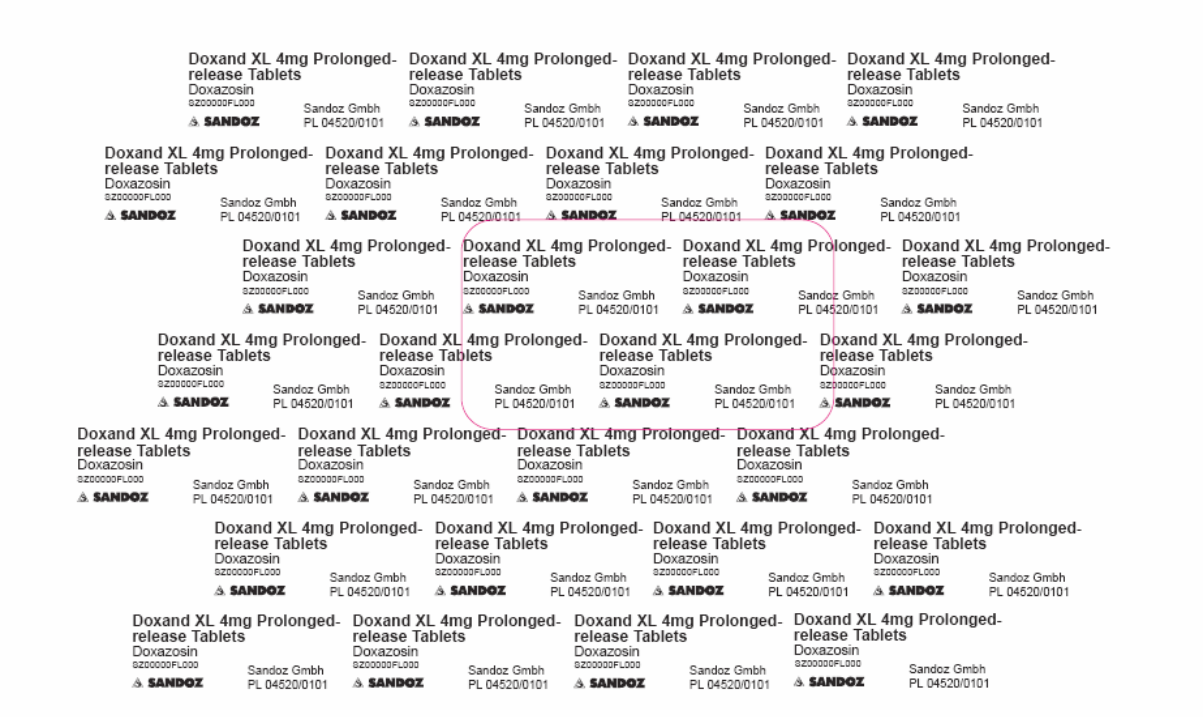
Country	Product name of generic product
United Kingdom	Dosano XL 4mg Prolonged-release Tablets
Ireland	Doxane XL 4 mg Prolonged Release Tablets

This leaflet is last approved in: 12/2006 (to be amended after approval). SZ0000000000

Module 4

Labelling

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Doxazosin
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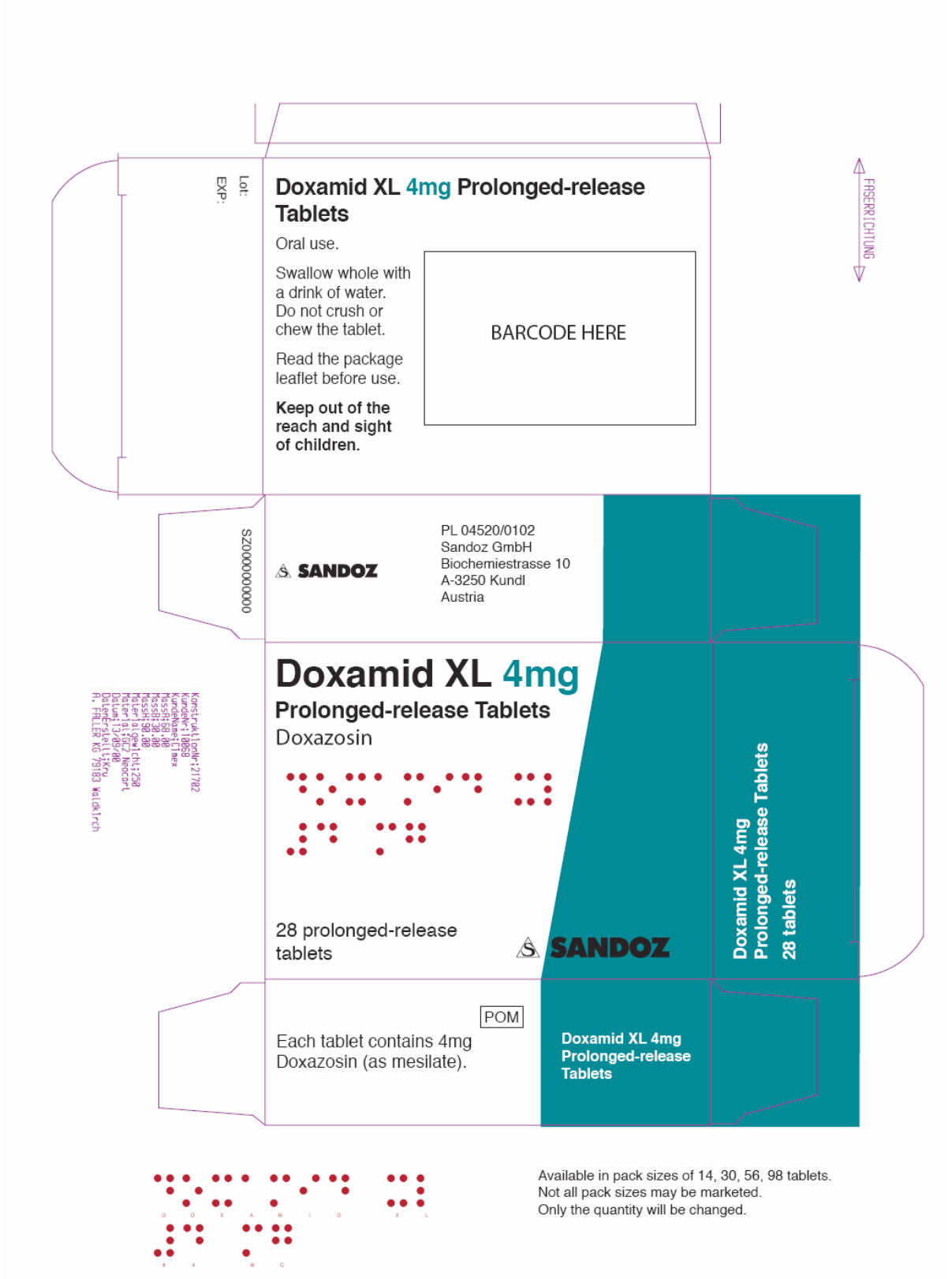
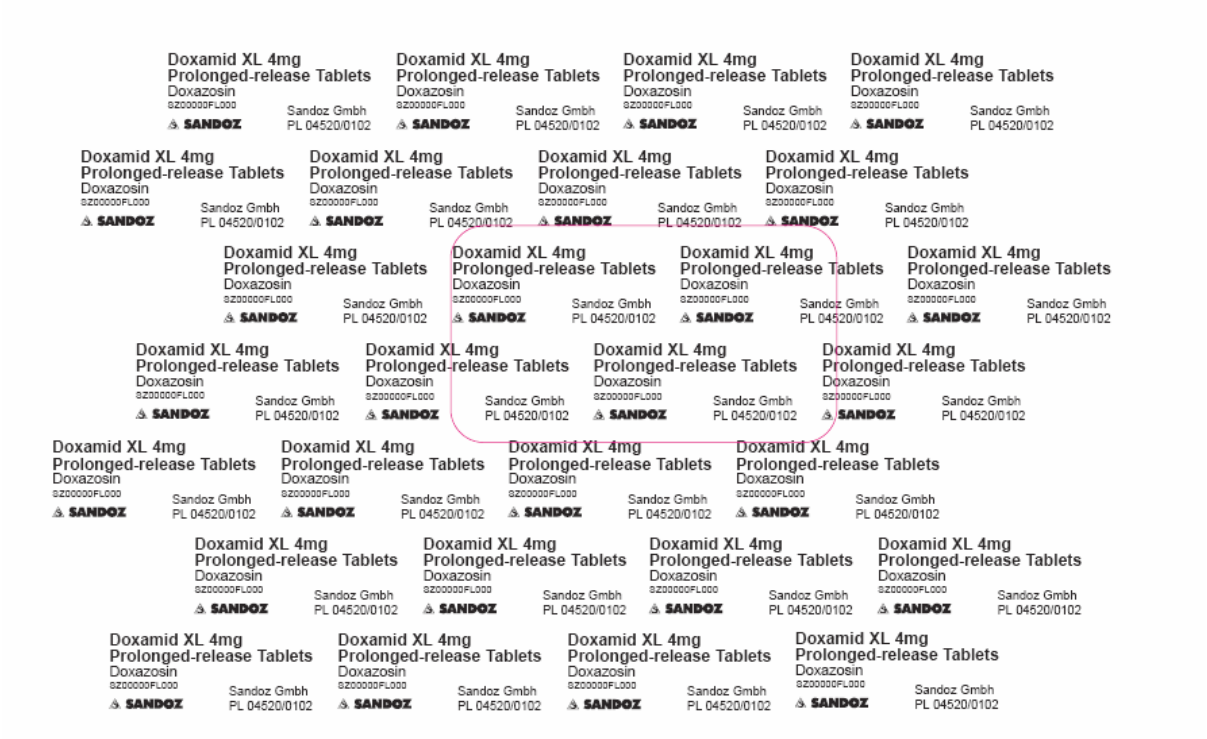
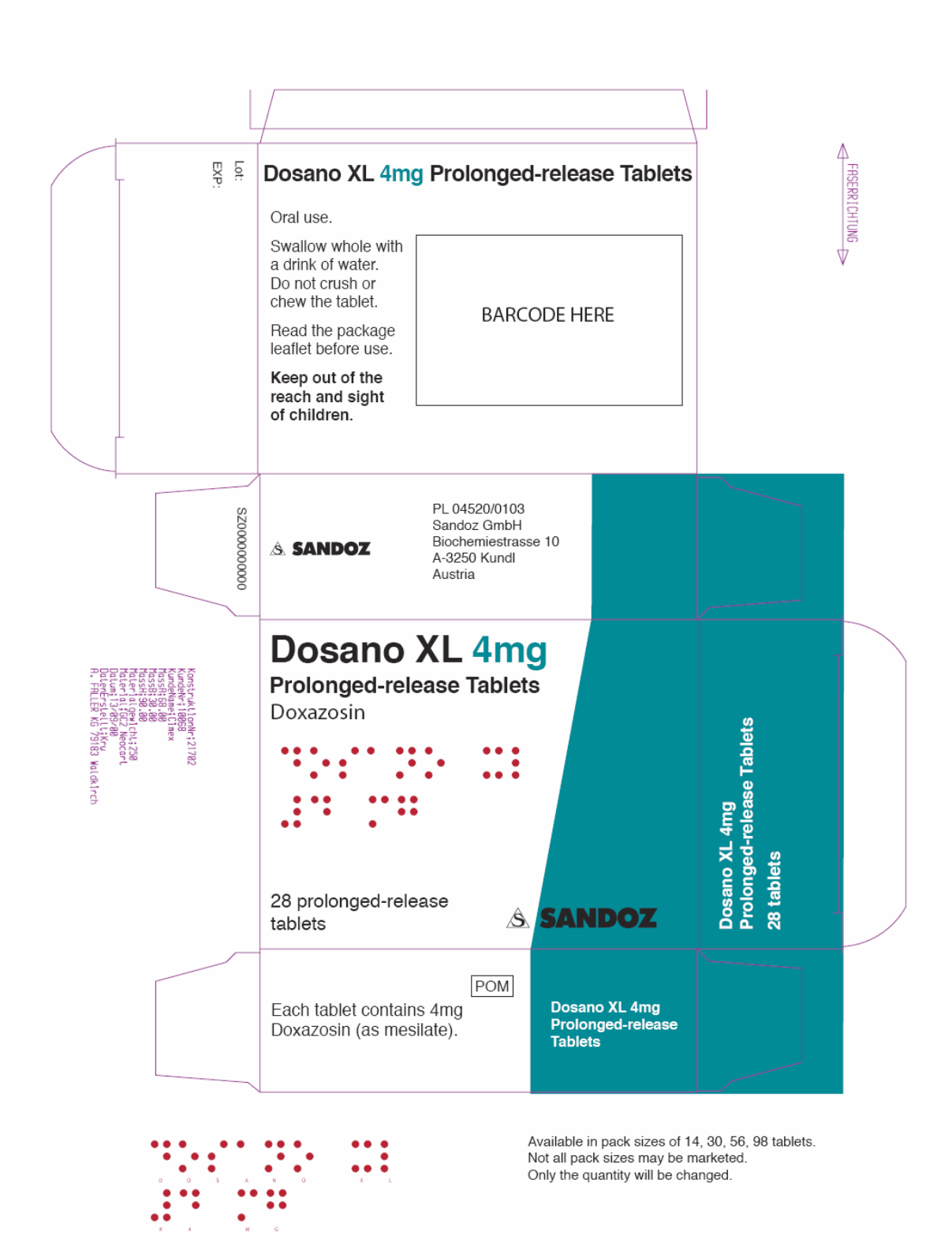
SANDOZ
Sandoz Gmbh
PL 04520/0101


Lot:
EXP:
Doxamid XL 4mg Prolonged-release Tablets
Oral use.
Swallow whole with a drink of water. Do not crush or chew the tablet.
Read the package leaflet before use.
Keep out of the reach and sight of children.
BARCODE HERE
FASERRICHTUNG
SZ0000000000
SANDOZ
PL 04520/0102
Sandoz GmbH
Biochemiestrasse 10
A-3250 Kundl
Austria
Doxamid XL 4mg
Prolonged-release Tablets
Doxazosin
28 prolonged-release tablets
SANDOZ
Doxamid XL 4mg Prolonged-release Tablets 28 tablets
POM
Each tablet contains 4mg Doxazosin (as mesilate).
Doxamid XL 4mg Prolonged-release Tablets
Available in pack sizes of 14, 30, 56, 98 tablets.
Not all pack sizes may be marketed.
Only the quantity will be changed.


Doxamid XL 4mg
Prolonged-release Tablets
Doxazosin
SZ00000FL000
SANDOZ
Sandoz Gmbh
PL 04520/0102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Oral use.
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Keep out of the reach and sight of children.
BARCODE HERE
FASERRICHTUNG
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A-3250 Kundl
Austria
Dosano XL 4mg
Prolonged-release Tablets
Doxazosin
28 prolonged-release tablets
SANDOZ
Dosano XL 4mg Prolonged-release Tablets 28 tablets
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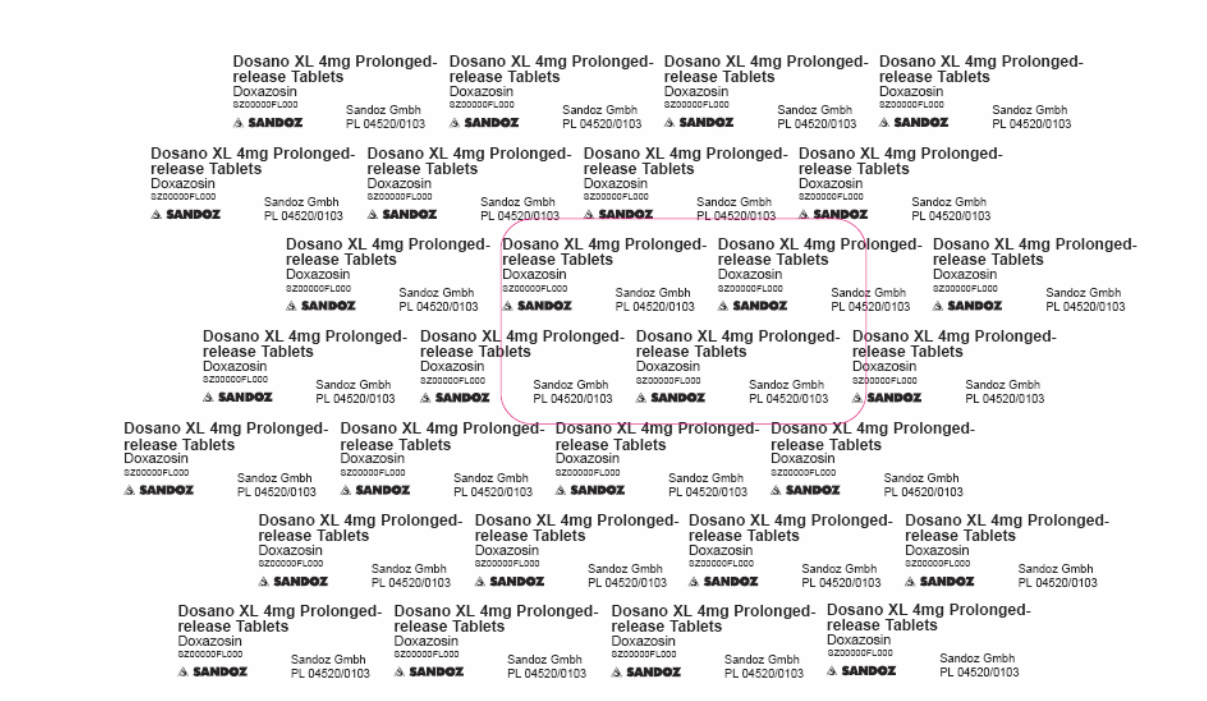
Each tablet contains 4mg Doxazosin (as mesilate).
Dosano XL 4mg Prolonged-release Tablets
Available in pack sizes of 14, 30, 56, 98 tablets.
Not all pack sizes may be marketed.
Only the quantity will be changed.


Dosano XL 4mg Prolonged-release Tablets
Doxazosin
SZ00000FL000
SANDOZ
Sandoz Gmbh
PL 04520/0103

Module 5

Scientific discussion during initial procedure

RECOMMENDATION

Based on the review of the data and the Applicant's response to the questions raised by RMS and CMSs on quality, safety and efficacy, the RMS considers that the application for Doxazosin XL 4mg Prolonged-release tablets in the treatment of hypertension and benign prostatic hyperplasia, is approvable.

This is based on the fact that during the recently completed CHMP arbitration procedures (A-29/718-20 & A-29/729-30), the overall opinion was that these products could be considered bioequivalent based on the three studies provided and the data are identical to this dossier. (The RMS recommends this while retaining its divergent opinion within the arbitration procedure along with other member states).

The proposed SmPC and PIL are along the lines of arbitration procedure decisions and are considered acceptable.

EXECUTIVE SUMMARY

Problem statement

The treatment of Hypertension and Benign prostatic hyperplasia are indeed complex. A number of agents have been used in the treatment of Essential hypertension including alpha blockers, beta-blockers, ACE inhibitors, Angiotensin receptor blockers, diuretics and others. Of these, alpha blockers are a specific group of drugs that are prone to excessive first dose response and postural hypotension when administered as immediate release formulations. In order to reduce this first dose phenomenon, a long (~4 week titration phase starting with the smallest dose possible has been advocated and practiced. Modified release formulations with slower release characteristics have addressed some of the issues by reducing the titration period and also to an extent the postural hypotension associated with administration of immediate release formulations of alpha blockers. The crux of the benefit of the modified release formulations hinges on this aspect i.e., reduction of adverse events by slower release of the active agent. The prolonged release formulations have been previously authorised (brand leader, Cardura from Pfizer, Diblocin from Astra-Zeneca etc). In this MAA/Dossier, the applicant claims essential similarity to the brand leader and has submitted bioequivalence studies to establish this similarity.

About the product

Doxazosin, an imidazoline alpha blocker was first authorised in the EU in 1987 for treatment of hypertension as an immediate release formulation of the following strengths; 1mg, 2mg and 4 mg. Subsequently, the indication of benign prostatic hyperplasia was authorised based on its alpha blocking action on the bladder neck muscle to reduce urinary retention and in some member states as a substitute until surgical relief of bladder neck obstruction. The utility of doxazosin in treatment of these two indications is accepted although more recently

questions have been raised about the adverse events in hypertensives after long term use based on the ALLHAT trial results. Doxazosin, similar to prazosin and terazosin, is limited in its use by the occurrence of first dose and postural hypotension as described above. The introduction of the modified release formulation was expected to reduce the frequency of these adverse events but true comparative data are not available.

The current formulation under discussion is a modified release formulation at 4mg strength and the applicant seeks to demonstrate bioequivalence with the reference formulation as a proof of essential similarity in accordance with the article 10(1) of the Directive 2001/83/EC as amended.

General comments on the submitted dossier

The preclinical part of the dossier is limited as the active has been in clinical use for a number of years; the immediate release formulation has been authorised in EU since 1987 and the modified release formulation since 1998. Therefore there are no new preclinical studies or data included in the dossier.

The clinical part contains two bioequivalence studies. The first is a triphasic study with single dose, steady state and food effect phases. The second is a single dose study as repeat of replacement for the single dose part of the first study. The applicant has also included the required Clinical overview and Expert report that provides satisfactory review of the literature of the pharmacodynamics, efficacy and safety of Doxazosin in the claimed indications.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GCP aspects

The RMS has been assured that design and conduct of the submitted bioequivalence studies were in compliance with GCP. There is however reference in the Dossier and the expert report to another study conducted by Avoxova, Poland as being non-compliant with GCP. This study is not however part of this dossier at the present point in time.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance

The synthesis of doxazosin mesilate is well controlled. The control tests and specifications for drug substance are adequately drawn up in line with the recent publication of a Ph. Eur. monograph for doxazosin mesilate. Additional testing for residual solvents, particle size distribution and polymorphism are also performed.

Stability studies have been performed using the drug substance. No significant changes in any parameters were observed. The proposed retest period of 2 years is justified.

Drug Product

The development of the product has been described, the choice of excipients is justified and their functions explained.
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on pilot and commercial scale batches. The batch analysis results show that the finished products meet the specifications proposed.
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
The proposed shelf-life of 36 months with no special storage requirements for the drug product is considered acceptable.

Non-clinical aspects

No new non-clinical data were provided in support of this application. The pharmacodynamic, pharmacokinetic and toxicological properties of doxazosin mesilate are well known, and were satisfactorily reviewed in the applicant's non-clinical overview.

Clinical aspects

Pharmacokinetics

The applicant has provided 3 bioequivalence studies; a phased study, a single dose study and the pilot study submitted during the responses phase.

The phased study consisted of 3 phases; a single dose study, a steady state study and a fed state study. Of these, the single dose study failed to show bioequivalence with the reference product. The steady state phase results were within the acceptability limits (as per CHMP guideline 1401/98). The fed state results showed that the test product showed a greater change than the reference product (28% increase in Cmax vs 8% for reference product). This was within the acceptability criteria of bioequivalence although the design of the study may have underestimated the effect of food marginally (~6% as per applicant's calculations).

The single dose study results were within the 80-125% acceptability criteria for Cmax , AUCt and AUCinf. There were some differences in the release profiles between products but

the applicant argues that these were not of clinical relevance. There was no steady state phase in this study.

The pilot study was in 11 subjects and tested bioequivalence of 3 test formulations with a reference product. Off these 1 proved bioequivalent while the other two did not. The batch proved bioequivalent has been confirmed as the biobatch for subsequent processing and the commercial production. Of note, in this biostudy there 3 reports of dizziness and syncope overall. The release profiles in this study were similar to that noted in the other two studies.

Identical data set was the subject of several aFCHMP arbitration procedures (EMEA/A-29/718-72-0, and A-29/729-730) that ended in Jun 28th. Based on the discussions during the arbitration procedures, the CHMP concluded that these formulations could be considered bioequivalent, by majority with several MS expressing divergent opinion.

Pharmacodynamics

The applicant has not provided any new pharmacodynamic data for these applications. The following is a summary from published information.

The expert report has reviewed the available literature and discusses the role of Doxazosin in the indication proposed. Significant parts of the discussion is around projected/ simulated BP reduction with Doxazosin although there are several small studies that included BP monitoring, both individual recordings and ambulatory recordings. The sample size of the studies do not have an impact on the current application as these were with the originator that is still currently authorised.

The ALLHAT trial had important implications on current use of doxazosin. In this study the doxazosin compared with chlorthalidone, lisinopril and amlodipine. The Doxazosin arm was terminated early as there was increased incidence of stroke (RR 1.19; 95% CI 1.10 to 1.40), combined cardiovascular risk (RR 1.25 at 4 yrs, 95% CI 1.17 to 1.33). The risk of CHF was doubled in the doxazosin group (RR 2.04, 95% CI 1.79 to 2.32) in comparison to chlorthalidone. This may have an impact on whether doxazosin is used as first line or second line agent. This study used the standard immediate release formulation of doxazosin.

Clinical efficacy and safety

There are no new data of efficacy or safety provided with this application.

BENEFIT RISK ASSESSMENT

Based on the review of the data, the responses, and the recent CHMP opinion on the arbitration procedures (A-29/718-20 & A-29/729-30), it is considered that bioequivalent between the formulations has been shown despite the limitations of the study. Therefore, grant of marketing authorisation could be recommended.

Module 6

Steps taken after procedure

Doxand	Type	Purpose
22/05/2007	1B	Name change in Poland Doxahexal to Doxazosin-A
11/07/2007	1B	Name Change in Spain

Doxazosina Hexal 4 mg Comprimidos de liberación prolongada EFG to
Doxazosina Neo Bexal 4 mg Comprimidos de liberación prolongada EFG

Doxamid	Type	Purpose
04/07/2007	1B	Add pack size
11/07/2007	1B	Name change in Spain

Doxazosina 1A Pharma 4 mg compromidos de liberación prolongada EFG to
Doxazosina Neo Acost 4 mg compromidos de liberación prolongada EFG

Dosano – Not applicable