ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM(S), STRENGTH(S) OF THE MEDICINAL PRODUCT(S), ROUTE(S) OF ADMINISTRATION, APPLICANT(S) MARKETING AUTHORISATION HOLDER(S) IN THE MEMBER STATES

Note: This SPC, labelling and package leaflet is the version that was annexed to the Commission Decision on this Article 29 referral for doxazosin mesilate containing medicinal products. The text was valid at that time.

After the Commission Decision, the Member State competent authorities will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

Member State	Marketing Authorisation Holder	Applicant	Name	Strength	Pharmaceutical Form	Route of administration
Denmark	Winthrop Pharmaceuticals UK Ltd 1 Onslow Street, Guildford, Surrey GU1 4YS United Kingdom Tel: 00 44 (0) 1483 55 4831 Fax: 00 44 (0) 1483 55 4831		Doxazosin 'Winthrop'	4 mg	Prolonged release tablets	Oral
Germany		Winthrop Arzneimittel GmbH Industriestrasse 10 82256 Furstenfeldbruck Germany Tel: 0049 (0) 81 41 3572 324 Fax: 0049 (0) 81 41 3572 329	Doxazosin Winthrop 4 mg Retardtabletten	4 mg	Prolonged release tablets	Oral
Hungary		Chinoin Pharmaceuticals and Chemical Works Co Ltd 1045 Budapest, To utca 1-5 HUNGARY Tel: 0036 1 505 0000 Fax: 0036 1 505 0005	Doxazosin Winthrop 4mg Tablets	4 mg	Prolonged release tablets	Oral
Poland		Winthrop Medicaments 1-13, Bd Romain Rolland, 75014, Paris France Tel: 0033 (0) 1 57 63 33 33 Fax: 0033 (0) 1 57 63 33 30	DOXAWIN XL	4 mg	Prolonged release tablets	Oral

Member State	Marketing Authorisation Holder	Applicant	Name	Strength	Pharmaceutical Form	Route of administration
Slovakia		Winthrop Medicaments 1-13, Bd Romain Rolland, 75014, Paris France Tel: 0033 (0) 1 57 63 33 33 Fax: 0033 (0) 1 57 63 33 30	Doxazosin Winthrop XL 4 mg	4 mg	Prolonged release tablets	Oral
Spain		Winthrop Pharmaceuticals UK Ltd 1 Onslow Street, Guildford, Surrey GU1 4YS United Kingdom Tel: 00 44 (0) 1483 55 4831 Fax: 00 44 (0) 1483 55 4831	Doxazosina WINTHROP 4 mg comprimidos de liberación prolongada EFG	4 mg	Prolonged release tablets	Oral
United Kingdom		Winthrop Pharmaceuticals UK Ltd 1 Onslow Street, Guildford, Surrey GU1 4YS United Kingdom	Slocinx XL 4mg Tablets	4 mg	Prolonged release tablets	Oral

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF Doxazosin "Winthrop" 4 mg prolonged release tablets and associated names (see Annex I)

CHMP was of the opinion that the bioequivalence was sufficiently established after single dose administration in two different bioequivalence studies (study 463/04 and 1995/04-05) and after multiple dose administration (study5208/02-3) according to the CHMP guidelines. The observed differences in T_{max} are modest and the C_{max} of the test tablet is not higher than the innovator tablet. It is unlikely that these differences will result in clinically relevant adverse events. The test product has shown consistent single dose performance across the studies and sufficient reassurance has been provided that the steady state results submitted are representative of other batches. The food-interaction study was not performed according to the CHMP guidelines. However, results of this study indicated that when administered with food no clinical significant differences exist between both products. Since 2002 more than 44,000,000 generic tablets of this formulation have been supplied to the market and that thousands of subjects have been switched from the originator product to the generic product. Up to now there were no adverse events potentially related to a faster release of doxazosin reported. The company made additionally a commitment for post-marketing surveillance.
In conclusion essential similarity has been sufficiently demonstrated. Any additional doubts regarding essential similarity are overcome by a commitment for post-marketing surveillance of the applicant. The CHMP is of the opinion the product does not differ significantly from the originator in terms of efficacy and safety.

GROUNDS FOR AMENDMENT OF THE SUMMARY(IES) OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Whereas

- The scope of the referral was to agree whether Doxazosin "Winthrop" 4mg prolonged release tablets differ significantly with regards to the release profile from the originator product with potential for increased incidence of adverse events such as dizziness and hypotension, whether there were significant differences in performance of test batches in the single dose phase of studies 5208 and 1995 and whether the applicant has deviated from CHMP guidelines on the design of the bioequivalence studies, particularly in relation to the effect of food with concern regarding the adequate sensitivity of to detect a difference between products,
- It is unlikely that the potential differences observed between the reference product and the generic versions influence the information in the Summary of Product Characteristics (SPC).
- The SPC, labelling and package leaflet proposed by the applicant has been assessed based on the documentation submitted, the scientific discussion within the Committee and the new wording proposed in the updated Guideline on SPC dated October 2005 and the latest QRD template,

the CHMP has recommended the granting of the Marketing Authorisation(s) for which the Summary of Product Characteristics, labelling and package leaflet are set out in Annex III for Doxazosin "Winthrop" 4 mg prolonged release tablets and associated names (see Annex I).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]

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 “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

Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]can be taken with or without food. The tablets must be swallowed whole with a sufficient amount of liquid. The prolonged-release 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. If necessary, the dosage may be increased to 8 mg doxazosin once daily.

Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]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 Winthrop 4 mg prolonged release tablets and associated names [See Annex I]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 prolonged release tablets aggravates existing renal impairment, the usual dose can be used in these patients.

Patients with hepatic impairment: Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]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 prolonged release tablets is not recommended (see section 4.4).

Children and adolescents: Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]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 oesophageal or gastrointestinal obstruction or decreased lumen diameter of the gastrointestinal tract
- Lactation.

4.4 Special warnings and precautions for use

Patients with acute heart diseases:
Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]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 prolonged release tablets 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 prolonged release tablets 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 Winthrop 4 mg prolonged release tablets and associated names [See Annex I]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 insufficiency exists, use in these patients is not recommended. Caution is also recommended when doxazosin prolonged release tablets is administered concomitantly with medicinal products which may influence hepatic metabolism (e.g. cimetidine).

Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]should be used with care in patients with Diabetic Autonomic Neuropathy.

Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]may influence plasma renin activity and urinary excretion of vanillylmandelic acid. This should be considered when interpreting laboratory data.

4.5 Interactions 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 prolonged release tablets in pregnant women. Animal studies have shown reduced foetal survival at high doses (see section 5.3). Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]should not be used during pregnancy unless clearly needed.

Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]is contraindicated during lactation as the medicinal product accumulates in the milk of lactating rats (see section 5.3) and there is no information about the excretion of the medicinal product into human breast milk. Alternatively, breast-feeding must be stopped, if treatment with Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]is unavoidable.

4.7 Effects on ability to drive and use machines

Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]has moderate influence on the ability to drive and use machines, especially at the beginning of therapy.

4.8 Undesirable effects

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

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

The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as very common (≥1/10); common (>1/100 to <1/10); uncommon (>1/1000 to <1/100); rare (>1/10 000 to <1/1000); very rare (<1/10 000).

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, broncho spasms, 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.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 Winthrop 4 mg prolonged release tablets and associated names [See Annex I]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 {Invented name}. In patients with hypertension, the decrease in blood pressure during treatment with Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]was similar in both the sitting and standing position.

Patients treated with immediate release doxazosin tablets against hypertension can be transferred to Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]prolonged release tablets 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 Winthrop 4 mg prolonged release tablets and associated names [See Annex I]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 Winthrop 4 mg prolonged release tablets and associated names [See Annex I]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 Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]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 in Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]prolonged release tablets lead to a minor variation in plasma levels. Peak/trough ratio of Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]prolonged release tablets is less than half that of immediate release doxazosin tablets.
At steady-state, the relative bioavailability of doxazosin from Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]prolonged release tablets 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

Polyethylene oxide
Microcrystalline cellulose
Povidone
α-tocopherol
Butylhydroxytoluene (E321)
Colloidal anhydrous silica
Sodium stearyl fumarate
Methacrylic acid copolymer (Eudragir L30 D-55)
Macrogol 1300-1600
Titanium dioxide (E171)

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/aluminium blister pack.
Pack sizes: 28, 30 & 100 tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8 MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

[To be completed nationally]

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

[See Annex I - To be completed nationally]
Doxazosin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 Prolonged-release tablets
30 Prolonged-release tablets
100 Prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

[See Annex I - To be completed nationally]
Doxazosin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

[See Annex I - To be completed nationally]
(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.

In this leaflet:

1 WHAT DOXAZOSIN WINTHROP 4 MG PROLONGED RELEASE TABLETS AND ASSOCIATED NAMES [SEE ANNEX I]IS AND WHAT IT IS USED FOR

Doxazosin is one of a group of medicines called alpha-blockers and can be used to treat high blood pressure, or the symptoms caused by the enlargement of the prostate in men.

In patients taking Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]to treat high blood pressure (hypertension), the doxazosin works by relaxing the blood vessels so that the blood passes through them more easily and this helps to lower your blood pressure.

In patients with an enlargement to the prostate gland, a common side effect is poor and/or frequent passing of urine. Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]work by relaxing the muscle around the bladder exit and prostate gland, which allows the urine to pass more easily.

2 BEFORE YOU TAKE DOXAZOSIN WINTHROP 4 MG PROLONGED RELEASE TABLETS AND ASSOCIATED NAMES [SEE ANNEX I]

Do not take Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]
- if you have ever suffered an allergic reaction (e.g. itching, reddening of the skin or difficulty breathing) to the active ingredient, doxazosin, or any of the other ingredients of {Invented name}
- if you know that you are sensitive to quinazolines (e.g. prazosin, terazosin) which is the chemical family of medicines to which doxazosin belongs
- if you are breast feeding.

- If you have any kind of congestion or blockage in your urinary tract, an infection of the urinary tract or have bladder stones
- if you suffer from kidney problems, overflow incontinence (you do not feel the urge to urinate) or anuria (your body is not producing any urine)
- if you have or have had in the past any form of obstruction of the digestive tract.

Take special care with Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]
- if you are suffering from heart disease
- if you are suffering from liver disease
- if you suffer from diabetic autonomic neuropathy, a disease associated with diabetes which affects your nervous system.

Before surgery or anaesthesia even at the dentist, you should tell the doctor or the dentist that you are taking {Invented name}.

Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]is not recommended for use in children and adolescents due to a lack of clinical experience.

Taking other medicines
Tell your doctor if you are already taking any of the following:
- other medicine to lower blood pressure
- painkillers called non-steroidal anti-inflammatory medicine (NSAIDs) eg. Ibuprofen
- medicine containing Estrogen
- medicine containing Dopamine, Metaraminol, Methoxamine, Adrenaline (Epinephrine) cough and cold remedies as they may contain Ephedrine, Phenylephrine.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]with food and drink
Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]can be taken with or after food.

Pregnancy and breast-feeding
Do not take Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]if you are pregnant or breast-feeding. Speak to your doctor first.

Driving and using machines
Your Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]may affect your ability to drive or operate machinery, especially when you first start to take your tablets.

3 HOW TO TAKE DOXAZOSIN WINTHROP 4 MG PROLONGED RELEASE TABLETS AND ASSOCIATED NAMES [SEE ANNEX I]

Always take Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual dose of Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]is one tablet taken as a single dose each day. Your doctor may wish to increase your dose to 8mg. This is the maximum dose of Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I].

Your tablets should be swallowed whole. Do not chew or crush them.
Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]can be taken at any time of day, during or after meals. Choose a time that is convenient and take your tablet at this time each day. Do not change the dose or stop taking your tablets unless you have spoken to your doctor.

If you take more Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]than you should:
Taking too many tablets at once can make you feel unwell. If you take too many tablets, tell your doctor immediately or go to the nearest hospital casualty department.

If you forget to take {Invented name}:
Do not worry. If you forget to take your tablet, leave the dose out completely. Then go on as before.

If you stop taking {Invented name}:
Keep taking your tablets until your doctor tells you to stop.

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

4 POSSIBLE SIDE EFFECTS

Like all medicines, Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]can cause side effects, although not everybody gets them.

The following side effects have been reported:

Common side effects, seen in more than 1 in 100 patients but less than 1in 10, include apathia muscle cramps, tiredness, a general feeling of being unwell or weakness, headache, sleepiness, problems with focussing your eyes, palpitations, chest pain, giddiness, dizziness, swelling, faintness or dizziness when standing up from a sitting or lying position (orthostatic dysregulation), shortness of breath, runny nose (rhinitis), constipation, indigestion, an increased desire or need to urinate and delayed ejaculation weakness (asthenia).

Uncommon effects, seen in more than 1 out of 1,000 patients but less than 1 in 100 patients, include low levels of potassium in the blood, gout, increased thirst, nightmares, forgetfulness (amnesia), emotional instability, tremor, muscle stiffness, increased tear production, abnormal intolerance to light, ringing in the ears (tinnitus), heart flutters, angina pectoris, an increase or slowing of the heart rate, heart attack, low blood pressure especially on getting up from a sitting or lying position, reduced blood supply to the limbs, dizziness on standing (syncope), nose bleeds, tightening of the chest, cough, throat inflammation, lack of appetite or increased appetite, taste disturbances, hair loss, swelling of the face and joints, muscle pain, swelling of joint and pain (arthralgia), muscle weakness, incontinence, difficulty with or pain on urinating, flushing, fever (shivers) and loss of colour.

Rare side effects, seen in more than 1 in 10,000 patients but less than 1 out of 1,000, include low blood sugar levels, depression, feeling restless (agitation), pins and needles, blurred vision, stroke (cerebrovascular disturbance), swelling of the voice box, abdominal pain, diarrhoea, vomiting, jaundice, increased liver enzymes in the blood, rash, itching or reddening of the skin, impotence, painful, persistent erection of the penis and low body temperature (especially in the elderly).

Very rare effects seen in less than 1 in 10,000 patients include a reduction in red and white cells and platelets in the blood and an increase in urea and creatinine levels in the blood.

You may feel faint or dizzy when standing up from a sitting or lying position especially at the beginning of your treatment or if you restart your treatment after a break. If this happens do not worry but make sure that you do not drive, operate machinery or carry out any activity which might be dangerous should you feel faint. If these symptoms persist or become a problem please contact your doctor.

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

5 HOW TO STORE {INVENTED NAME}:

Keep out of the reach and sight of children.

Do not use after the expiry date which is stated on the carton.

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 Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]contains:

- ***The active substance is doxazosin mesilate. Each tablet contains the active ingredient doxazosin mesilate equivalent to 4mg of doxazosin.***
- ***The other ingredients are: blends of polyethylene oxide preparations containing butylhydroxytoluene (E321), microcrystalline cellulose, povidone, α- tocopherol, colloidal anhydrous silica and sodium stearyl fumarate. The tablet coating contains methacrylic acid copolymer, colloidal anhydrous silica, macrogol and titanium dioxide (E171).***

What Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]looks like and contents of the pack:
Your medicine is in the form of a round biconvex white prolonged release tablet.
Doxazosin Winthrop 4 mg prolonged release tablets and associated names [See Annex I]are available in blister packs of 28, 30 and 100 tablets.

Marketing Authorisation Holder and Manufacturer:
Marketing Authorisation Holder:
[To be completed nationally]

Manufacturer:

Chapeltown Distribution Centre

51 Cart Road, Chapeltown, Sheffield, S35 2PF

United Kingdom

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

[To be completed on finalisation of the procedure]

This leaflet was last approved in [To be completed nationally].