IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1035/001/001
Case No: 1025972

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Jacobsen Pharma

Vemmingbund Strandvej 111, **DK-6310, Broadger**, **Denmark**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Duraglan 4 mg Prolonged Release Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **23/11/2007** until **22/11/2012**.

Signed on behalf of the Irish Medicines Board this

_____

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Duraglan 4mg Prolonged Release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains doxazosin 4mg (as mesilate)

For a full list of excipients, see 6.1

3 PHARMACEUTICAL FORM

Prolonged release tablets

White round, biconvex tablets with 'DL' embossed on one side

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Duraglan XL is indicated for the treatment of hypertension and can be used as a sole agent to control blood pressure in hypertensive patients.

In patients inadequately controlled on single antihypertensive therapy, Duraglan XL tablets may be used in combination with a thiazide diuretic, beta-adrenoceptor blocking agent, calcium antagonist or an antiotensin-converting enzyme inhibitor.

4.2 Posology and method of administration

The initial dose of Duraglan XL is 4mg once daily. A significant number of patients will be controlled on this dose. If necessary, the dosage may be increased to 8mg once daily according to patient response.

The maximum recommended dose is 8mg once daily.

Duraglan XL can be taken with or without food.

The tablets should be swallowed whole with a sufficient amount of liquid.

Elderly: In common with other drugs of this class, the dosage should be kept a low as possible and increments made under close supervision.

Use in Renally Impaired Patients: Since the pharmacokinetics of doxazosin are unchanged in patients with renal insufficiency, and there is no evidence that doxazosin aggravates existing renal dysfunction, the usual dosage may be used in these patients. Duraglan XL is not dialysable.

Use in Hepatically Impaired Patients. Duraglan XL should be used with care in patients with significant existing hepatic dysfunction. (See section 4.4 Special warnings and special precautions for use.)

Use in Children: There is insufficient experience to recommend the use of Duraglan XL in Children under 12 years of age.

4.3 Contraindications

Duraglan XL is contra-indicated in patients with a known hypersensitivity to quinazolines (e.g.doxazosin, prazosin, terazosin) or any constituents of Duraglan XL 4mg Tablets.

Duraglan XL is contra-indicated in patients with a history of gastro-intestinal obstruction, oesophageal obstruction, or any degree of decreased lumen diameter of the gastro-intestinal tract.

Use during lactation: Animal studies have shown that doxazosin accumulates in breast milk. The clinical safety of doxazosin during lactation has not been established, consequently Duraglan XL is contra-indicated in nursing mothers.

4.4 Special warnings and precautions for use

Information for the Patient: Patients would be informed that Duraglan XL should be swallowed whole. Patients should not chew, divide or crush the tablets.

In Duraglan XL 4mg Tablets the medications is contained within a non-absorbable shell that has been specially designed to slowly release the drug. When this process is completed the empty tablet is eliminated from the body. Patients should be advised that they should not be concerned if they occasionally observe in the stools something that looks like a tablet.

Use with PDE-5 Inhibitors*:* Concomitant administration of an alpha blocker with a PDE-5 inhibitor should be used with caution as it may lead to symptomatic hypotension in some patients. No studies have been conducted with Cardura XL.

Impaired Renal Function: There is no evidence that doxazosin aggravates renal dysfunction. However, Duraglan XL dosage introduction and adjustment should be carried out with great care.

Impaired Liver function: As with any drug wholly metabolised by the liver, Duraglan XL should be administered with caution in patients with evidence of impaired hepatic function (see 5.2 Pharmacokinetic Properties)

An excessive hypotensive effect may occur in some patients following soon after initial treatment often in persons who have shown evidence of over reaction with other antihypertensives and usually with the initial dose. If is recommended that the initial dosage should be given when the patient is not required to undertake any activity such as driving or operating machinery.

4.5 Interaction with other medicinal products and other forms of interaction

Dozasosin is highly bound to plasma proteins (98%). *In vitro* data in human plasma indicates that doxazosin has no effect on protein binding of the drugs tested (digoxin, phenytoin, warfarin or indomethacin) however, the theoretical potential for interaction with other protein bound drugs should be borne in mind. No adverse interactions have been observed with thiazide diuretics, frusemide, beta-blocking agents, non-steroidal anti-inflammatory drugs, antibiotics, oral hypoglycaemic drugs, uricosuric agents, or anticoagulants.

Concomitant administration of an alpha blocker with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients (see section 4.4 Special Warnings and Special Precautions for Use). No studies have been conducted with Duraglan XL.

In an open-label, randomized, placebo-controlled trial in 22 healthy male volunteers, the administration of a single 1 mg dose of doxazosin on day 1 of a four-day regimen of oral cimetidine (400 mg twice daily) resulted in a 10% increase in mean AUC of doxazosin, and no statistically significant changes in mean Cmax and mean half-life of doxazosin. The 10% increase in the mean AUC for doxazosin with cimetidine is within intersubject variation (27%) of the mean AUC for doxazosin with placebo.

Doxazosin can potentiate the blood pressure lowering activity of other antihypertensives.

4.6 Pregnancy and lactation

***Use during pregnancy*:** Doxazosin crosses the placenta. Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at extremely high doses. These doses were approximately 300 times the maximum recommended human dose. As there are no adequate and well controlled studies in pregnant women, the safety of doxazosin use during pregnancy has not yet been established. Accordingly, Duraglan XL should be used only when, in the opinion of the physician, potential benefit outweighs potential risk.

Use during lactation: Contra-indicated. See 4.3 above.

4.7 Effects on ability to drive and use machines

The ability to drive or use machinery may be impaired, especially when initiating therapy. The drug may also induce drowsiness. Patients should not drive or operate machinery unless it has been shown not to affect their alertness or dexterity.

4.8 Undesirable effects

In clinical trials, the most common reactions associated with doxazosin modified-release formulations were of a postural type (rarely associated with fainting) or non-specific and included:

Cardiac disorders: palpitation, tachycardia

Ear and Labyrinth Disorders: vertigo

Gastrointestinal Disorders: abdominal pain, dry mouth,nausea

General Disorders and Administration Site Conditions: asthenia, chest pain,
peripheral oedema

Musculoskeletal and Connective Tissue Disorders: back pain, myalgia

Nervous System Disorders: dizziness, headache

Respiratory, Thoracic and Mediastinal Disorders: coughing, bronchitis

Skin and Subcutaneous Tissue Disorders: pruritis

Renal and Urinary Disorders: urinary incontinence, cystitis

Vascular Disorders: postural hypotension

In post-marketing experience with immediate release doxazosin formulations, the following additional adverse events have been reported:

Blood and Lymphatic Disorders: leucopenia, thrombocytopenia

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: blurred vision
Gastrointestinal Disorders: constipation, diarrhoea, dyspepsia, flatulence, vomiting, dry mouth

General Disorders and Administration Site Conditions: fatigue, malaise, pain

Hepatobiliary Disorders: cholestasis, hepatitis, jaundice

Immune System Disorders: allergic reaction

Investigations: abnormal liver function tests, weight increase

Metabolism and Nutrition: anorexia
Musculoskeletal and Connective Tissue Disorders: arthralgia, muscle cramps, muscle weakness

Nervous System Disorders: postural dizziness, hypoaesthesia, paraesthesia, syncope, tremor

Psychiatric Disorders: agitation, anxiety, depression, insomnia, nervousness
Renal and Urinary Disorders: dysuria, haematuria, micturition disorder, micturition frequency, nocturia, polyuria, urinary incontinence

Reproductive System and Breast Disorders: gynaecomastia, impotence, priapism

Respiratory, Thoracic and Mediastinal Disorders: aggravated bronchospasm, dyspnoea, epistaxis, coughing

Skin and Subcutaneous Tissue Disorders: alopecia, purpura, skin rash, urticaria, pruritus

Vascular Disorders: hot flushes, hypotension

Analysis of haematologic data from hypertensive patients receiving doxazosin in controlled hypertension clinical trials showed that the mean WBC and mean neutrophil counts were decreased by 2.4% and 1.0% respectively, compared to placebo, a phenomenon seen with other alpha blocking drugs.

The following additional adverse events have been reported in marketing experience among patients treated for hypertension with immediate release doxazosin tablets. In general, these are not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin: tachycardia, palpitations, chest pain, angina pectoris, myocardial infarction, cerebrovascular accidents, cardiac arrhythmias and blurred vision.

The undesirable effects for doxazosin modified-release formulations are similar to those with immediate release Doxazosin tablets.

4.9 Overdose

Should overdosage lead to hypotension, the patient should be immediately placed in a supine, head down position. Other supportive measures may be appropriate in individual cases. Since doxazosin is highly protein bound, dialysis is not indicated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Doxazosin is a potent and selective post-junctional alpha 1-adrenoceptor antagonist,
ATC Code C02CA04.

Administration of doxazosin modified-release formulations to 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-adrenoreceptors 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. In patients with hypertension, blood pressure during treatment with doxazosin modified-release formulations was similar in both the supine and standing position.

Responder data from the 2 primary hypertension efficacy studies (including a total of 630 doxazosin treated patients) indicate that those patients controlled on 1mg, 2mg, or 4mg doxazosin immediate release tablets would be equally well controlled on doxazosin modified-release formulations.

Doxazosin has been shown to be free of adverse metabolic effects and is suitable for use in patients with coexistent diabetes mellitus, gout and insulin resistance.

Doxazosin is suitable for use in patients with coexistent asthma, left ventricular hypertrophy and in elderly patients. Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation and enhanced activity of tissue plasminogen activator.

Additionally, doxazosin improves insulin sensitivity in patients with impairment. Doxazosin produces favourable effects on blood lipids, with a significant increase in the HDL/total cholesterol ratio and trends to a favourable reduction in total triglycerides.

It therefore confers an advantage over diuretics and beta adrenoceptor blocking agents
Which adversely affect these parameters.

Based on the established association of hypertension and blood lipids with coronary heart disease, the favourable effects of doxazosin therapy on both blood pressure and lipids indicate a reduction in risk of developing coronary heart disease.

5.2 Pharmacokinetic properties

Absorption

After oral administration of therapeutic doses, doxazosin modified-release formulations are well absorbed with peak blood levels gradually reached at 8 to 9 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 characteristics of doxazosin modified-release formulations will lead to a smoother plasma profile.

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

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

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

Biotransformation/Elimination

The plasma elimination is biphasic with the terminal elimination half-life being 22 hours and hence this provides the basis for once daily dosing. Doxazosin is extensively metabolised with <5% excreated as unchanged drug.

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

There are only limited data in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). In a clinical study in 12 patients with moderate hepatic impairment, single dose administration of doxazosin resulted in an increase in AUC of 43% and a decrease in apparent oral clearance of 30% (see also 4.4 Special Warnings and Special precautions for Use)

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

Doxazosin is primarily metabolised by O-demethylation and hydroxylation.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional animal studies in safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity. For further information see section 4.6 Pregnancy and lactation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
Polyethylene oxide,
Microcrystalline cellulose (E460(i)),
Povidone,
α-Tocopherol (E307),
Silica, colloidal anhydrous
Sodium stearyl fumarate
Butylhydroxytoluene (E321)

Coating
Methacrylic acid copolymer
Macrogol
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 precautions

6.5 Nature and contents of container

Duraglan prolonged release tablets are available in packs of 28, 30 and 100 tablets.

Aluminium/PVdC/PVC blister strips with aluminium foil.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Jacobsen Pharma,
Vemmingbund,
Strandvej 111, DK 6310, Broadger,
Denmark.

8 MARKETING AUTHORISATION NUMBER

PA 1035/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 23rd November 2007

10 DATE OF REVISION OF THE TEXT