IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0915/012/003
Case No: 2021543

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

Helsinn Birex Therapeutics Ltd

Damastown, **Mulhuddart**, **Dublin 15**, **Ireland**

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

DOXAZOSIN DISPHAR 4mg 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 **25/06/2007** until **21/04/2010**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Doxazosin Disphar 4mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Doxazosin 4mg (as mesilate).

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Tablet

White, oblong tablets with 'D4' embossed on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Doxazosin is indicated for first-line treatment of hypertension and can be used as monotherapy to control blood pressure in these patients. The drug can also be used in combination with a thiazide diuretic, beta-blocking agent, calcium antagonists or ACE inhibitors when treatment with diuretics or beta-blockers alone has not given the desired effect or is unsuitable.

4.2 Posology and method of administration

Hypertension:
Doxazosin is used in a once daily regimen. The initial dosage is 1 mg, and may be taken in the morning or evening. This dose is maintained for 1 or 2 weeks. The dose can then be increased to 2 mg once a day for another 1 or 2 weeks. If necessary the daily dose can then be gradually increased, observing equal intervals, to 4, 8 and 16 mg once a day, depending on the patient's response. The maximum recommended dose is 16 mg daily. The usual maintenance dose is 2-4mg once daily.

Use in elderly patients:
As with all drugs of this class dosage should be kept as low as possible and increases only under close supervision.

Use in renally impaired patients:
Because the pharmacokinetics of doxazosin remain unchanged in patients with renal insufficiency, and no evidence exists that doxazosin will exacerbate an existing renal insufficiency, the application of the usual dosages is generally advised. As in rare cases an increased sensitivity cannot be ruled out, a more cautious approach with respect to initiating the treatment in such patients may be called for. As doxazosin is highly protein bound, it is not removed by dialysis.

Use in patients with hepatic insufficiency:
The doxazosin dose should be titrated particularly carefully in patients with impaired liver function. No clinical experience is available in patients with serious hepatic dysfunction (cf. 4.4 ‘Warnings and precautions for use’).

Use in children:
As there is insufficient clinical practice experience in children, use of doxazosin in children under the age of 12 is not

recommended.

4.3 Contraindications

- Doxazosin is contra-indicated for patients with a known hypersensitivity to doxazosin, other quinazolines (e.g. prazosin, terazosin) or to any of the excipients used.
- Doxazosin is not recommended for children under the age of 12, since safe conditions for use in children have not been determined.
- Use during lactation: Safety during lactation has not been fully established and therefore is contra-indicated in nursing mothers.

4.4 Special warnings and precautions for use

Patients on a strict low-salt diet or those treated with diuretics appear to be more sensitive to the side effects of an orthostatic nature. The patients should be warned to avoid situations in which they could be injured if dizziness or weakness should occur during the initial phase of the doxazosin treatment. To minimise the risk of blood pressure fall or syncope on postural change, the blood pressure of the patients should be monitored at the initial period of therapy.

Because of its vasodilator action, doxazosin should be used with caution in patients with any of the following cardiac emergencies:
- pulmonary oedema due to aortic or mitral stenosis
- high output cardiac insufficiency
- right ventricular heart failure due to pulmonary embolism or pericardial effusion
- left ventricular heart failure with low filling pressure

In patients with serious coronary suffering a too quick or too distinct lowering of the blood pressure can result in worsening of anginal complaints.

Use in patients with hepatic insufficiency:
Doxazosin should be used with particular caution in patients with liver function impairment. As there is no clinical experience in patients with severe hepatic dysfunction, use in such patients is not recommended.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Caution is also recommended when Doxazosin is administered during pregnancy.

The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with tamulosin. Isolated reports have also been received with other alpha-1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during cataract operation, current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

4.5 Interaction with other medicinal products and other forms of interaction

Doxazosin increases the blood pressure lowering effect of other antihypertensive drugs. The antihypertensive effect may be increased, when doxazosin is administered concomitantly with vasodilators and nitrates.

As for other antihypertensive agents, non-steroidal anti-inflammatory drugs 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 and phenylephrine.

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

4.6 Pregnancy and lactation

Use during pregnancy:
Doxazosin crosses the placenta. No teratogenic effects were seen in animal testing. As there are no adequate or well controlled studies in pregnant women, the safety of doxazosin during pregnancy has not been established. Accordingly, the product should only be used when, in the opinion of the physician, potential benefit outweighs potential risk.

Use during lactation:
Safety during lactation has not been fully established and therefore is contra-indicated in nursing mothers.

4.7 Effects on ability to drive and use machines

The ability to drive and to handle machines can be adversely influenced, especially at the start of the therapy. Patients affected should not drive or operate machinery.

4.8 Undesirable effects

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

Common (>1%)
General: Tiredness/nausea, asthenia, headache, chest pain, somnolence, muscle cramps.
Cardiovascular: Oedema, palpitations.
CNS: Dizziness, vertigo.
GI: Constipation, dyspepsia.
Respiratory: Shortness of breath, nasal congestion.
Psych: Delayed ejaculation, apathy.
Urogenital: Frequent need to urinate, increased urination.
Eyes: Accommodation disturbances.

Less common
General: Facial/general oedema, syncope, facial redness, fever/shivering, paleness.
Cardiovascular: Postural hypotension, arrhythmia, peripheral ischemia, angina pectoris, tachycardia, myocardial infarction.
CNS: Tremor, muscle stiffness.
GI: Anorexia, increased appetite.
Skin: Alopecia.
Respiratory: Epistaxis, bronchospasm, cough, pharyngitis.
Metabolism: Thirst, hypokalaemia, gout.
Musculoskeletal: Muscle pains, joint swelling/aches, muscle weakness.
Psych: Nightmares, memory loss, emotional liability.
Urogenital: Incontinence, urinary disturbances, dysuria.
Eyes: Abnormal tear flow, photophobia.
Ears: Tinnitus.
Miscellaneous: Disturbed sense of taste.

Rare (<0.1%)
Cardiovascular: Cerebrovascular disturbances.
CNS: Depression, agitation, paresthesia.
Haematological: Decrease of leukocytes and thrombocytes.
Respiratory: Laryngeal oedema.

Skin: Rash, itching, purpura.
GI: Stomach pains, diarrhoea, vomiting.
Liver: Icterus, increased liver enzymes, hepatitis.
Metabolism: Hypoglycaemia.
Eyes: Blurred vision.
Miscellaneous: Impotence, priapism, dysgeusia, decreased body temperature in elderly.

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

4.9 Overdose

If an overdosage results in hypotension, the patient should be placed in a lying position immediately, with his head downward. Other supporting measures should be taken if necessary (e.g. administration of plasma expanders and vasopressor agents in case of severe hypotension). Renal function should be monitored and, if necessary, supported. Dialysis is not called for as doxazosin is protein-bound.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: C02CA04
Doxazosin is a selective and competitive antagonist of postsynaptic alpha-1-adrenergic receptors.

Administration of doxazosin will cause a significant reduction in blood pressure due to decreased peripheral vascular resistance. Following once-daily administration a clinically significant reduction in the blood pressure is maintained for up to 24 hours. After administration a gradual reduction in blood pressure will come about; orthostatic effects at the start of the treatment may occur. Maximum reduction in blood pressure will be achieved about 2-6 hours after administration.
In hypertensive patients the blood pressure during the doxazosin therapy is similar in a lying and in a standing position.

Unlike the non-selective alpha adrenergic receptor blocking agents, no tolerance has been observed after a prolonged doxazosin therapy. An increase in the plasma renin activity and tachycardia have only infrequently been observed after a continued therapy.

In clinical studies doxazosin caused a slight reduction in the plasma concentrations of triglycerides, total cholesterol and the LDL fraction. A slight increase in HDL/total cholesterol ratio (approximately 4% to 13% of baseline) has been observed. The clinical significance of these findings remains to be established.

Studies which investigate an effect on cardiovascular morbidity or mortality are ongoing.
Administration of doxazosin to patients with symptomatic BPH results in an improvement of urodynamic symptoms. The effect is reported to be due to selective blockade of the alpha-adrenoreceptors in the smooth muscle of bladder neck, prostate capsule and urethra.

5.2 Pharmacokinetic properties

Following oral administration, doxazosin is absorbed well. Maximum plasma levels are reached after 2 hours and the absolute bioavailability is approximately 63%. Doxazosin is to large extent bound to plasma protein (about 98%). The plasma elimination is biphasic; the terminal half-life is 16-30 hours so that once-daily administration is possible. Doxazosin is metabolised in the liver to a large extent and mainly excreted in the faeces, with less than 5% of the dose excreted as unchanged doxazosin.

Pharmacokinetic tests in the elderly and in patients with renal insufficiency have not shown any important pharmacokinetic differences in comparison with patients with a normal renal function. No tests have been done in

patients with liver function disorders, and neither have the effects been tested of medicines that are known to influence the liver metabolism (such as cimetidine).

5.3 Preclinical safety data

No teratogenic effects were seen in animal testing.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cellulose, Microcrystalline
Lactose, Anhydrous
Sodium Starch Glycolate, Type A
Magnesium Stearate
Silica, Colloidal Anhydrous
Sodium Laurilsulfate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

PVC/PVDC-Aluminium blister strips, 2, 3, 5, 10, 20 or 50 x 10 tablets or 1, 2 or 7 x 14 tablets.

Not all pack sizes may be marketed.

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

Helsinn Birex Therapeutics Ltd
Damastown
Mulhiddart
Dublin 15
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 915/12/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd April 2005

10 DATE OF REVISION OF THE TEXT

June 2007