

IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0966/009/002

Case No: 2027193

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

Ergha Healthcare Ltd

Damastown, Mulhuddart, Dublin 15

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

Hyrax 5 mg 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 **28/06/2007** until **28/07/2010**.

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

Hiraz 5 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg Terazosin (as terazosin hydrochloride dihydrate).

For excipients see 6.1

3 PHARMACEUTICAL FORM

Tablet.

Mottled tan round, flat tablet with beveled edges, embossed with '93' on one side and '762' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Terazosin is a selective blocker of post-junctional alpha-1-adrenoreceptors, well absorbed after oral dosing, metabolised in the liver and with an elimination $T_{1/2}$ of 10-12 hours and excretion through the intestinal tract and urine.

Terazosin is indicated as:

a peripheral vasodilator for use in the management of hypertension either alone or in conjunction with other antihypertensive agents such as thiazide diuretics or betaadrenoreceptor blockers.

an alpha-1-adrenoreceptor blocker for use in the symptomatic treatment of benign prostatic hyperplasia.

4.2 Posology and method of administration

Adults Only

Hypertension

An initial dose of 1.0mg should be given in the evening, one to two hours before retiring. If no untoward effect has occurred a dose of 2.0mg daily may be given after 7 to 14 days. Subsequent increments should be tailored to the individual patient's response and requirements, bearing in mind the delay in complete response.

The usual procedure thereafter is to increase the dose by gradual increments to the level of optimum response usually 5-10mg daily. Doses over 20mg rarely improve efficacy and doses over 40mg have not been studied.

If additional anti-hypertensive therapy is to be introduced, the dose of terazosin should be reduced and re-titration carried out if necessary.

In the elderly dosage should be kept as low as possible, and increments made under close supervision.

Benign Prostatic Hyperplasia

An initial dose of 1.0mg daily should be given in the evening. This dose may be increased by approximately doubling the dose at weekly intervals to achieve the desired reduction in symptoms. The maintenance dose is usually 5 to 10 mg

once daily. At present there are insufficient data to suggest symptomatic relief with doses above 10mg.

4.3 Contraindications

Use in patients hypersensitive to quinazolines. Use in the presence of congestive heart failure, due to mechanical obstruction (e.g. aortic valve or mitral valve stenosis, pulmonary embolism, restrictive pericarditis).

4.4 Special warnings and precautions for use

Pharmacokinetic studies indicate that patients with impaired renal function need no alteration in recommended dosage. There is no evidence that terazosin aggravates renal dysfunction.

There is as yet insufficient experience of use of terazosin in children under the age of 12 years.

An excessive hypotensive effect may occur in some patients following soon after the initial doses. This is usually self limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration. Please also see Section 4.7 “Effects on Ability to Drive and Use Machines”.

The usual half-life of terazosin is 10-12 hours. This may be significantly prolonged in patients with congestive cardiac failure (by up to 7-8 hours), usually with reduction on clinical improvement.

In certain patients with left ventricular failure, the decrease in left ventricular filling consequent to vigorous therapy may result in a significant fall in cardiac output and systemic blood pressure after administration of terazosin. These effects should be kept in mind when introducing therapy and continuous titration of dose used.

Since the drug is metabolised in the liver it should only be used with care in patients with existing hepatic dysfunction.

As with other alpha-1-adrenoreceptor antagonists, terazosin is not recommended in patients with history of micturition syncope.

Laboratory Tests: Small but statistically significant decreases in haematocrit, haemoglobin, white blood cells, total protein and albumin were observed in controlled clinical trials. These laboratory findings suggest the possibility of haemodilution.

Treatment with terazosin for up to 24 months had no significant effect on Prostate Specific Antigen (PSA) levels.

In clinical trials, the incidence of postural hypotension was greater in BPH patients than those with hypertension.

If administration is discontinued for more than several days, therapy should be re-instituted using the initial dosing regimen.

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

4.5 Interaction with other medicinal products and other forms of interaction

Terazosin is highly protein bound. There is a theoretical potential for interaction with such drugs as anticoagulants and nonsteroidal anti-inflammatory drugs leading to higher plasma levels of drug.

Except for angiotensin converting enzyme (ACE) inhibitors and diuretics, no clinically significant interactions have been observed with Terazosin in BPH. In BPH patients the adverse events profile of patients treated concurrently with non-steroidal anti-inflammatory drugs (NSAIDs), theophylline, antianginal agents, oral hypoglycaemic agents, ACE inhibitors or diuretics was compared to the profile in the general treated population.

In the small subset of patients who were treated with Terazosin and ACE inhibitors or diuretics, the percent reporting dizziness or other dizziness-related adverse events appears to be greater than in the total population of terazosin patients from double-blind placebo-controlled studies.

Caution should be observed when Terazosin is administered concomitantly with other antihypertensive agents (e.g. calcium antagonists) to avoid the possibility of significant hypotension. When adding Terazosin to a diuretic or other antihypertensive agent, dosing reduction and retitration of these agents may be necessary.

4.6 Pregnancy and lactation

Terazosin should not be used in pregnancy unless the potential benefit outweighs the risk. Although no teratogenic effects were noted in animal studies, safety during pregnancy or lactation has not been established.

4.7 Effects on ability to drive and use machines

It is recommended that the initial doses should be given when the patient is not required to undertake any activity such as travelling or working machinery. The drug may also induce drowsiness. Patients should not drive or operate machinery unless it has been shown not to effect physical or mental capacity.

4.8 Undesirable effects

Adverse Events:

Terazosin in common with other alpha-adrenoceptor antagonists may cause syncope. Syncopal episodes have occurred within 30 to 90 minutes of the initial dose of the drug. Syncope has occasionally occurred in association with rapid dosage increases or in the introduction of another antihypertensive agent.

In clinical trials in hypertension, the incidence of syncopal episodes was approximately one percent. In most cases this was believed to be due to an excessive postural hypotensive effect although occasionally the syncopal episode has been preceded by a bout of tachycardia with heart rates of 120 to 160 beats per minute.

If syncope occurs the patient should be placed in a recumbent position and supportive treatment applied as necessary. This adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Dizziness, light-headedness or fainting may occur when standing up quickly from a lying or sitting position. Patients should be advised of this possibility and instructed to lie down if these symptoms appear and then sit for a few minutes before standing to prevent their recurrence. These adverse effects are self-limiting and in most cases do not recur after the initial period of therapy or during subsequent re-titration.

The most common side effects were asthenia, palpitations, nausea, dizziness, peripheral oedema, somnolence, nasal congestion/rhinitis and blurred vision/amblyopia.

In addition, the following have been reported: back pain, headache, tachycardia, postural hypotension, syncope, oedema, weight gain, pain in extremities, depression, decreased libido, nervousness, paraesthesia, vertigo, dyspnoea, sinusitis and impotence.

Additional adverse reactions reported in clinical trials or reported during marketing experience but not clearly associated with the use of terazosin included the following: chest pain, facial oedema; fever; abdominal pain; neck pain; shoulder pain; arrhythmia; vasodilation; constipation; diarrhoea; dry mouth; dyspepsia; flatulence; vomiting; gout; arthralgia; arthritis; stiffness; joint disorder; myalgia; anxiety; insomnia; bronchitis; epistaxis; flu symptoms; pharyngitis; rhinitis; cold symptoms; pruritis; rash; increased cough; sweating; abnormal vision; conjunctivitis; tinnitus; urinary frequency; urinary tract infection and urinary incontinence primarily reported in post-menopausal women.

Anaphylaxis has rarely been reported.

Increases in hepatic enzyme levels have been reported.

Post marketing experience:

Thrombocytopenia and priapism have been reported. Atrial fibrillation has been reported: however, a cause and effect relationship has not been established.

Laboratory tests:

Small but statistically significant decreases in haematocrit, haemoglobin, white blood cells, total protein and albumin were observed in controlled clinical trials. These laboratory findings suggest the possibility of haemodilution. Treatment with terazosin for up to 24 months had no significant effect on prostate specific antigen (PSA) levels.

4.9 Overdose

Should administration of Terazosin lead to acute hypotension, cardiovascular support is of first importance. Restoration of blood pressure and normalisation of heart rate may be accomplished by keeping the patient in supine position. If this measure is inadequate, shock should first be treated with volume expanders and if necessary, vasopressors could then be used. Renal function should be monitored and general supportive measures applied as required. Dialysis may not be of benefit since laboratory data indicate that terazosin is highly protein bound.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties***Hypertension*

Although the exact mechanism of hypotensive action is not established, the relaxation of peripheral blood vessels appears to be produced mainly by competitive antagonism of post-synaptic alpha-adrenoceptors.

Terazosin usually produces an initial gradual decrease in blood pressure followed by a sustained antihypertensive action.

Unlike other antihypertensives, Terazosin does not show adverse effects on the blood profile. The clinical implications of these findings have yet to be established.

Benign Prostatic Hyperplasia

Studies suggest that alpha-1-adrenoreceptor antagonism is useful in improving the urodynamics in patients with chronic bladder obstruction such as in benign prostatic hyperplasia (BPH).

The symptoms of BPH are caused mainly by the presence of an enlarged prostate and by the increased smooth muscle tone of the bladder outlet and prostate, which is regulated by alpha-1-adrenergic receptors.

In *in-vitro* experiments, terazosin has been shown to antagonise phenylephrine-induced contractions of human prostatic tissue. In clinical trials terazosin has been shown to improve the urodynamics and symptomatology in patients with BPH.

5.2 Pharmacokinetic properties

The plasma concentration of the parent drug is a maximum about 1 hour post administration and declines with a half-life of approximately 12 hours. The drug is highly bound to plasma proteins.

5.3 Preclinical safety data

Carcinogenicity: Terazosin has been shown to produce tumours in male rats when administered at a high dose over a long period of time. No such occurrences were seen in female rats or in a similar study in mice. The relevance of these findings with respect to the clinical use of the drug in man is unknown.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Dye (Iron oxide yellow E172, Iron Oxide Red E172)
Crospovidone
Povidone (PVP-K30)
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

5mg tablet – blister packs containing 14, 20 (including samples), 28 (including samples), 30 (including 3 X 10), 50, 84, 100.*

The blister packs are composed of PVC/PVDC, heat sealed with an aluminium foil backing.

* Not all pack sizes will 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

Ergha Healthcare Ltd
Damastown
Mulhuddart
Dublin 15
Republic of Ireland

8 MARKETING AUTHORISATION NUMBER

PA 966/9/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29/07/2005

10 DATE OF REVISION OF THE TEXT

June 2007