Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Terazosin 2mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 2 mg terazosin (as terazosin monohydrochloride dihydrate).

Excipient with known effect: Each tablet contains 119.93 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet

Yellow coloured, round, flat tablets with bevelled edges and a score line on one side of the tablet.
This tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Terazosin tablets are indicated for:

- The treatment of mild to moderate hypertension
- The symptomatic treatment of urinary obstruction caused by benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Posology
For oral use.

For the different dosage regimens suitable strengths are available.
The dose of terazosin should be adjusted according to the patient's response.

The following is a guide to administration:

Initial dose

The lowest single dose of 1 mg before bedtime for all patients, which should not be exceeded. Strict compliance with this recommendation should be observed to minimise potential acute first-dose hypotensive episodes.

Subsequent doses

Treatment of mild to moderate hypertension:

The single daily dosage may be increased by approximately doubling the dosage at weekly intervals to achieve the desired blood pressure response.

The maintenance dose needs to be adjusted to the patient's response. 2 mg/day may be sufficient with increases up to 10 mg if necessary (clinical studies support the use of 2 – 10 mg as maintenance dose).

The maximum dose is 20 mg of terazosin per day and should not be exceeded.

Use with thiazide diuretics and other antihypertensive agents in the treatment of hypertension:

When adding a thiazide diuretic or another antihypertensive agent to a patient's regimen the dose of terazosin should be reduced or discontinued and retitration carried out if necessary. Caution should be observed when terazosin is administered with thiazides or other antihypertensive agents as hypotension may develop.

Treatment of Benign Prostatic Hyperplasia:

The dose may be increased by approximately doubling at weekly or bi-weekly intervals to achieve the desired reduction in symptoms. The maintenance dose is usually 5 to 10 mg once daily. Improvements in symptoms have been detected as early as two weeks after starting treatment with terazosin.

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

Treatment should be initiated using the 1 mg tablets during seven days, 2 mg tablets during 14 days and 5 mg tablets during 7 days. Response to treatment must be reviewed at four weeks. Transient side effects may occur at each titration step. If any side effects persist, consideration should be given to reducing the dose.

Renal insufficiency

Pharmacokinetic studies indicate that patients with impaired renal function need no alteration in recommended dosage.

Children

Safety and efficacy in children has not been established.

Elderly

Pharmacokinetic studies in the elderly indicate that no major alteration in dosage recommendation is required. However, particular caution should be taken with the titration of the terazosin dose.

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

Use in patients with hepatic insufficiency:

The terazosin dose should be titrated with particular caution in patients with impaired liver function since terazosin undergoes extensive hepatic metabolism and is mainly excreted by the biliary tract. No clinical experience is available in patients with severe hepatic dysfunction.

Method of administration

The first tablet of a defined dose strength should be taken in the evening at bedtime. The following tablets of the same strength may be taken in the morning. The tablets should be taken with a sufficient amount of liquid (i.e. 1 glass of water).

Terazosin therapy of hypertension is a long-term treatment, which should only be interrupted on medical advice. If it is necessary to stop terazosin therapy, the dose should be re-titrated starting with 1 mg terazosin at bedtime.

4.3 Contraindications

Terazosin is contra-indicated:
- in patients with known hypersensitivity to the active substance, to other quinazolines (e.g. prazosin, doxazosin,) or to any of the excipients listed in section 6.1.
- history of micturition syncope.

4.4 Special warnings and precautions for use

In clinical trials, the incidence of postural hypotension was greater in patients who received terazosin for BPH than in patients who received terazosin for hypertension. In this BPH indication, the incidence of postural hypotensive events was greater in patients aged 65 years and over (5.6%) than those aged less than 65 years (2.6%).

Patients should be warned for symptoms of postural hypotension and be advised to sit or lay down in case they occur (see also 4.7 Effects on ability to drive and use machines and 4.8 Undesirable effects).

Before treating the symptoms of BPH with alpha-blockers, other causes of impaired urinary flow or urinary symptoms should be excluded. Also where the diagnosis of BPH has been established, it should be confirmed that there is no concomitant obstruction of the upper urinary tract or any signs of infection before treating with terazosin.

Terazosin therapy requires regular medical monitoring.

In the initial phase of therapy (especially after the first dose or when the terazosin dose is increased) patients may experience a pronounced drop in blood pressure.

Dizziness, light-headedness, weakness, drowsiness and, in rare cases, syncope may occur.

This has also to be assumed in association with missed doses and subsequent re-initiation of terazosin therapy. Patients should be cautioned about these possible adverse events and the circumstances in which they may occur.

To minimise the risk of postural hypotension, patients should be monitored at the start of therapy. As the likelihood of such responses is greater with a higher than recommended starting dose, the recommended dosage regimen should be followed carefully. The patient should take the first dose of terazosin at bedtime and should avoid abrupt changes in position or activities, which could be harmed by dizziness or weariness. This especially applies to the elderly.

Because of its vasodilator action, terazosin should be used with caution in patients with any of the following cardiac conditions:

- pulmonary oedema due to aortic or mitral stenosis
- high output cardiac insufficiency
- right ventricular heart failure caused by pulmonary embolism or pericardial effusion
- left ventricular heart failure with low filling pressure

Caution is also recommended, when terazosin is administered concomitantly with drugs, which may influence hepatic metabolism.

Use in patients with hepatic insufficiency:

As for all medicaments metabolised in the liver, terazosin should be used with particular caution in patients with impaired hepatic function. As there is no data available in patients with severe hepatic dysfunction, use of terazosin in these patients is not recommended.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and terazosin may lead to symptomatic hypotension in some patients. In order to minimise the risk for developing postural hypotension the patient should be stable on the alpha-blocker therapy before initiating use of phospodiesterase-5-inhibitors.

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.

This medicinal product contains lactose; patients with rare hereditary problems of galactose intolerance; the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

4.5 Interaction with other medicinal products and other forms of interactions

In patients receiving terazosin plus ACE inhibitors or diuretics, the proportion reporting dizziness or related side effects was greater than in the total population of terazosin treated patients from clinical trials.

Caution should be observedwhen terazosin is administered with other antihypertensive agents to avoid the possibility ofsignificant hypotension.

When addingterazosin to a diuretic or other antihypertensive agent, dosage reduction and retitration may be necessary.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and terazosin may lead to symptomatic hypotension in some patients (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Although no teratogenic effects were seen in animal testing, the safety during pregnancy and lactation has not yet been established. Furthermore, data from animal studies show that terazosin may increase the duration of pregnancy or inhibit labour. Terazosin should not be used therefore in pregnancy unless the potential benefit out weighs the risk.

Breast-feeding
Breast-feeding should be avoided.

4.7 Effects on ability to drive and use machines

Dizziness, light-headedness or drowsiness may occur with the initial dose or in association with missed doses and subsequent reinitiation of terazosin therapy. Patients should be cautioned about these possible adverse events and the circumstances in which they may occur and advised to avoid driving or hazardous tasks for approximately the first 12 hours after the initial dose or when the dose is increased.

4.8 Undesirable effects

Terazosin, in common with other alpha-adrenoreceptor antagonists, may cause syncope. Syncope episodes may occur within 30-90 minutes of the initial dose of the medicinal product. Occasionally the syncope episode may be preceded by tachycardia with heart rates of 120 to 160 beats per minute. First-dose hypotension might occur which could lead to vertigo and in severe cases syncope. To avoid hypotension, terazosin treatment should be started with a 1 mg dose at bed-time.

The incidence of undesirable effects is based on the following frequencies:

Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)

Blood and the lymphatic system disorders:
Very rare: thromobocytopenia

Immune system disorders:
Very rare: anaphylactic reactions

Nervous system disorders:
Common: nervousness, somnolence, paraesthesia
Uncommon: depression

Ear and labyrinth disorders:
Common: vertigo

Eye disorders:
Common: blurred vision/ amblyopia, colour anomaly

Cardiac disorders:
Common: palpitations, tachycardia, chest pain
Very rare: atrial fibrillation

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea, nasal congestion, sinusitis, epistaxis

Gastrointestinal disorders:
Common: nausea, constipation, diarrhoea, vomiting

Skin and subcutaneous tissue disorders:
Common: pruritus, rash
Uncommon: urticaria

Musculoskeletal and, connective tissue disorders:
Common: back pain

Renal and urinary disorders:
Rare: urinary tract infection and urinary incontinence, (primarily reported in post-menopausal women)

Reproductive system and breast disorders:
Common: impotence
Uncommon: decreased libido
Rare: priapism

General disorders and administration site conditions:
Common: Dizziness, light-headedness, fainting (especially when standing up quickly from a lying or a sitting position - postural hypotension), asthenia, oedema, headache, pain in the extremities.
Uncommon: weight gain, syncope.

Additional adverse events reported in clinical trials or during marketing experience, but which are not clearly associated with the use of terazosin include the following: facial oedema, fever, abdominal, neck and shoulder pain, vasodilation, arrhythmia, dry mouth, dyspepsia, flatulence, gout, arthralgia, arthritis, joint disorders, myalgia, anxiety, insomnia, bronchitis, flu symptoms, pharyngitis, rhinitis, cold symptoms, increased cough, sweating, abnormal vision, conjunctivitis, tinnitus, urinary frequency (increased micturition)

Laboratory tests: laboratory findings suggest the possibility of haemodilution (e.g. decrease in haematocrit, haemoglobin, white blood cells, total protein and albumin) have been observed in controlled clinical trials. No significant effect on prostate specific antigen (PSA) level was reported after terazosin treatment for up to 24 months.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via
HPRA Pharmacovigilance,
Earlsfort Terrace, IRL - Dublin 2;
Tel: +353 1 6764971; Fax: +353 1 6762517.
Website: www.hpra.ie;
E-mail: medsafety@hpra.ie.

4.9 Overdose

Should administration of terazosin lead to acute hypotension; cardiovascular support is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in a 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

Pharmacotherapeutic group: alpha-adrenoreceptor antagonist

ATC code: G04C A03

Use in hypertension:

Although the exact mechanism of the hypotensive action is not established, the relaxation of peripheral blood vessels appears to be produced mainly by competitive antagonism of post-synaptic alpha-1-adrenoceptor. Terazosin usually produces an initial gradual decrease in blood pressure followed by a sustained anti hypertensive action.

Clinical experience indicates that a 2-5% decrease in total cholesterol plasma concentration and a 3-7% decrease in the combined LDLc + VLDLc fraction plasma concentration from pretreatment values are associated with the administration of therapeutic doses of terazosin.

Use in BPH:

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.

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-adrenergicreceptors.

In in-vitro experiments, terazosin has been shown to antagonize 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

Absorption

Terazosin is well absorbed (80-100%). Terazosin has a minimal “first pass” effect and almost the complete dose of terazosin is systematically available. Peak plasma concentrations are reached approximately 1-2 hours after oral dosing in the fasted state. Bioavailability is not significantly affected by food uptake.

Distribution

Approximately 90-94% of terazosin is bound to plasma proteins. Protein binding is independent of total active substance concentrations.

Biotransformation

Main metabolites of terazosin are caused by demethylation and conjugation.

Elimination

Approximately 10% and 20% of orally administered terazosin is excreted as unchanged active substance in urine and in faeces, respectively. Approximately 40% of the administered dose of terazosin is eliminated in urine and 60% in faeces. The total elimination half-life is approximately 8-13 hours.

Linearity / non-linearity

After oral dosing of terazosin AUC and C_{max} increase in proportion with dose over the recommended dose range (2-10 mg).

5.3 Preclinical safety data

Carcinogenicity: terazosin has been shown to produce benign adrenal medullary 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 active substance in man is unknown.

No evidence of a genotoxic effect of terazosin has been reported from in vitro and in vivo investigations of the mutagenic potential of the substance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Talc
Magnesium stearate
Quinoline yellow E104

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Blister of PVC/PVdC and Aluminium
Packs of 14 & 28 tablets.
Not all package sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/040/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th April 2009
Date of last renewal: 30th November 2014

10 DATE OF REVISION OF THE TEXT

January 2019