SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Terazostad 1 mg tablets
Terazostad 2 mg tablets
Terazostad 5 mg tablets
Terazostad 10 mg tablets
Terazostad 1 mg + 2 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains terazosin 1 mg, 2 mg, 5 mg or 10 mg (as terazosin hydrochloride dihydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

1 mg tablet: white, round tablet
2 mg tablet: orange, round tablet, with a break mark on one side. The tablet can be divided into equal halves.
5 mg tablet: red, round tablet
10 mg tablet: blue, round tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Terazostad tablets are indicated for:
- the treatment of mild to moderate hypertension
- symptomatic treatment of urinary obstruction caused by benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Adults:
For the treatment of hypertension:
The dose of terazosin should be managed according to each patients response.
The starting dose for all patients is 1 mg before bedtime and this should not be exceeded during the first week of treatment. Patients should be advised to comply in order to avoid first-dose hypotensive effect. The dose can be increased by approximately doubling the dose at weekly intervals until effective control of blood pressure is established.

The usual maintenance dose is 2 mg daily. However, for certain patients, an increased dose may become necessary. A maximum dose of 20 mg should not be exceeded.
Reduction of dose should be undertaken when adding other antihypertensive medication followed by re-titration if required.

For the treatment of Benign Prostatic Hyperplasia (BPH):
The dose of terazosin should be managed according to each patients response.

The starting dose for all patients is 1 mg at night-time for 7 days and this should not be exceeded during the first week of treatment. The dose can then be increased to 2 mg daily for 14 days, followed -if necessary- by 5 mg daily for 7 days. Response to treatment must be reviewed at four weeks. Transient undesirable effects may occur at each titration step. If any undesirable effects persist, consideration should be given to reducing the dose.

The usual recommended dose is 5 mg once daily. The maximum daily dose is 10 mg.

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

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

Use in patients with impaired renal function or the elderly

In general terazosin should not be used in patients with a reduced urinary outflow or anuria or an advanced renal impairment.

No dosage adjustments are required in the elderly.

Use in patients with hepatic impairment

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. As no clinical experience is available in patients with severe hepatic impairment, the use of terazosin is not recommended in these patients.

Use in children and adolescents

There are no reports regarding the efficacy and safety of the medicinal product in children and adolescents under the age of 18 years. Therefore, the use of terazosin is not recommended for this group.

Method of administration

Terazostad tablets should be swallowed whole and not chewed and can be taken with or without food.

4.3 Contraindications

Hypersensitivity to terazosin, or to a structurally similar alpha-adrenergic antagonist or to any of the excipients.
History of micturition syncope.

4.4 Special warnings and precautions for use

"First dose" effect might occur after the first terazosin dose or during the initial period of treatment. This consists of marked reduction of blood pressure mainly as orthostatic hypotension (vertigo, unsteadiness, syncope). Volume depletion, restricted salt-intake and advance age (i.e. 65 years or over) increase the risk of postural hypotension. It should be born in mind that this is also likely to happen when terazosin treatment is restarted after a few days break. In such case, the 1 mg initial dose should be prescribed.

Syncope has been seen in one percent of patients in hypertension trials. Rapid dose increase as well as combining terazosin with a diuretic and/or another antihypertensive might result in syncope. Syncope is related to marked postural hypotension, and in some cases it is preceded by tachycardia (120-160/min). Postural hypotension is most pronounced within a short time of terazosin intake, while the risk of syncope is the greatest 30-90 minutes following terazosin administration.

Terazosin should be given cautiously to individuals with known susceptibility to developing hypotension.

Before starting terazosin therapy for BPH, carcinoma of the prostate should be excluded. The blood pressure of patients with BPH should be measured at baseline and monitored thereafter particularly at times of dose adjustment. Possible antihypertensive treatment should also be taken into consideration. Effectiveness of terazosin in the management of BPH should be evaluated after allowing a period of 4-6 weeks of treatment with the maintenance dose.

The patient should take the first dose of terazosin at bedtime and should avoid abrupt changes in position or activities, which could cause 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 aeortic or mitral stenosis.
- high output cardiac insufficiency.
- right ventricular heart failure caused by pulmonary embolism or pericardial effusion.
- left ventricular heart failure with low filing pressure.

Use in patients with hepatic impairment: Since terazosin is primarily metabolised in the liver, it should be used with particular caution in patients with impaired hepatic function. As there is no data available in patients with severe hepatic impairment, use of terazosin in these patients is not recommended.

Patients with benign prostatic hyperplasia and having a simultaneous obstruction of the upper urinary tract, chronic infection of the urinary tract or bladder stone should not be treated with terazosin.
In general, terazosin should not be used in patients with a reduced urinary outflow or anuria or an advanced renal deficiency.

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

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

For 2 mg tablets:
Sunset Yellow (E110) can cause allergic-type reactions including asthma. Allergy is more common in those people who are allergic to aspirin.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is required when prescribing terazosin with other antihypertensive agents as significant hypotension has been observed. Dose re-titration may be required when diuretics or antihypertensives are added to the medication regimen.

Combination of terazosin with other alpha-receptor blockers is not recommended.

Furthermore, the antihypertensive effect may be increased, when terazosin is administered concomitantly with vasodilators and nitrates.

As for other antihypertensive agents, non-steroidal antirheumatics or estrogens may reduce the antihypertensive effect of terazosin.

Sympathomimetics may reduce the antihypertensive effect of terazosin.

Terazosin may reduce blood pressure and vasculare reactions to dopamine, ephedrine, epinephrine, metaraminol, methoxamine and phenylephrine.

Terazosin may reduce the anti-hypertensive effect of intravenously administered clonidine.

Terazosin may influence plasma renin activity and urinary excretion of vanillymandelic acid. This should be considered when interpreting laboratory data.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil or vardenafil) and terazosin may lead to symptomatic hypotension in some patients (see section4.4).

4.6 Pregnancy and lactation

There are no adequate data from the use of terazosin in pregnant women. Studies in animals have not shown any teratogenic effects of terazosin, but other reproductive effects were observed at very high dosages (see 5.3 Preclinical Safety Data). Terazosin should not be used during pregnancy unless the potential benefit outweighs the possible risk.

Data from animal studies show that terazosin may increase the duration of pregnancy or inhibit labour. Terazostad tablets should not be used shortly before birth.

It is not known whether terazosin is excreted in breast milk. Caution should be exercised when terazosin is administered to a breast-feeding woman.

4.7 Effects on ability to drive and use machines

Terazostad tablets have a major influence on the ability to drive and use machines.

Due to the risk of dizziness, light-headedness or drowsiness, patients should be advised not to drive a vehicle, operate machinery or perform activities with increased risk of accidents for 12 hours after starting terazosin treatment and when increasing the dose or when there is concomitant alcohol ingestion.

4.8 Undesirable effects

As with other alpha-adrenoceptor blocking antagonists, terazosin 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 minutes. 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% to < 10%
Uncommon: ≥0.1% to < 1%
Rare: ≥0.01% to < 0.1%
Very rare: ≤ 0.01 % including isolated reports

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
Eye disorders:
Common: blurred vision, 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, connective tissue and bone 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, dyspapsia, 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) levels was reported after terazosin treatment for up to 24 months.

4.9 Overdose

Toxicity: The experience from overdose is limited.
Symptoms: The effects on circulation are most important. Likely symptoms are dizziness, confusion, syncope, dyspnoea, fall in blood pressure, palpitations, tachycardia, nausea. Possibly hypoglycaemia and hypokalaemia. Possibly muscular spasm.
Treatment: Gastric lavage if justified, active charcoal. In case of fall in blood pressure lowered headrest is recommended, intravenous fluid therapy, vasopressors (preferably dopamine 4 –5 microgram/kg/minute initially, later possibly increase of dose or noradrenaline) if necessary. Symptomatic therapy in other cases. Because of the high degree of protein binding for terazosin, dialysis is unlikely to be beneficial. Renal function should be monitored and general supportive measures applied as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacoptherapeutic Group - Alpha-adrenoreceptor antagonist

ATC Code: C02CA, G04CA03

Terazosin, the active substance of Terazostad tablets, is a selective peripheral α_1-adrenergic blocking agent. Its antihypertensive effects may result from postsynaptic α_1-adrenergic blockade, leading to vasodilatation, decreased total peripheral resistance and venous return. Terazosin is a long-acting oral agent that is useful when given once daily to hypertensives. Long-term treatment with terazosin does not usually cause reflex tachycardia; while cardiac output, renal perfusion and glomerular filtration rate hardly become affected.

Although it has no effect on the underlying pathophysiologic mechanism involved in BPH, terazosin has been shown to significantly increase urinary flow rates and decrease outflow obstruction. It is also effective in easing BPH-related symptoms by preventing stimulation of α_1-adrenergic receptors and consequent smooth muscle contractions in the bladder and prostatic uretha. Urodynamic improvement

may help reduce urinary tract infection. The medicinal product, however, does not affect the size of the prostate.

A significant antihypertensive effect has been observed 3 hours following oral administration of terazosin. The medicinal product`s antihypertensive effect has been reported to persist for 24 hours after oral administration.

Effects of terazosin on cardiovascular morbidity and mortality have not been investigated.

5.2 Pharmacokinetic properties

The bioavailability is 90%. Concomitant intake of food does not affect the degree of absorption. Peak plasma concentration occurs after 1–2 hours. The plasma protein binding degree is 90 – 94%. Terazosin is to a high degree metabolised in the liver through hydrolysis and demethylation. Approximately a third of the given dose is, however, excreted in unchanged form, 10% in the urine, and 20% in the faeces. Plasma clearance has been estimated to be 80 ml/minute.
Half-life for terazosin is 12 hours. The elimination of terazosin does not seem to be dependent on renal function.

5.3 Preclinical safety data

Preclinical data reveal no special hazards for humans based on conventional studies of safety pharmacology.

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.

Decreased fertility and testicular atrophy were seen in rats at repeated administration of doses ≥ 20-30 times higher than the maximum recommended human dose. Foetal resorptions, decreased foetal weights, increased number of supernumerary ribs and decreased post-natal survival were noted in reproductive toxicity studies in rats and rabbits at maternally toxic doses (60 – 280 times the maximum recommended human dose).

No carcinogenic effect of terazosin was seen in studies in mice or female rats. In male rats, terazosin induced benign adrenal medullary tumours at the highest administered dose corresponding to 175 times the maximum human dose. The clinical relevance of this finding is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1 mg: Lactose monohydrate
cellulose powdered
croscarmellose sodium
magnesium stearate

2 mg: Lactose monohydrate
cellulose powdered
croscarmellose sodium
magnesium stearate
sunset yellow FCF E110

5 mg: Lactose monohydrate

cellulose powdered
croscarmellose sodium
magnesium stearate
iron oxide red E172

10 mg: Lactose monohydrate
cellulose powdered
croscarmellose sodium
magnesium stearate
indigotine lake E132

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blister PVC/Al

1 mg: 10, 28
2 mg: 10, 14, 20, 28, 30, 50, 84, 98, 100
5 mg: 14, 20, 28, 30, 50, 84, 98, 100
10 mg: 28, 30, 84, 98, 100
7x1 mg + 7x2 mg
7x1 mg +14x2 mg
7x1 mg + 21x2 mg
3x1 mg + 11x2 mg

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Stada Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel
Germany

8. MARKETING AUTHORISATION NUMBER(S)

1 mg: 17702

2 mg: 17703
5 mg: 17704
10 mg: 17705
1 mg + 2 mg: 19080

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 November 2002
Date of last renewal: 29 November 2007

10. DATE OF REVISION OF THE TEXT

14 January 2010