יש להוסיף: "פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר"
אושר 1.12.2011

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hytrin starter pack (7 tablets of 1 mg and 7 tablets of 2 mg)
Hytrin 2 mg tablets
Hytrin 5 mg tablets
Hytrin 10 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Terazosin as monohydrochloride dihydrate

3. PHARMACEUTICAL FORM

Blue, round, flat bevelled tablets embossed with logo and triangular facets on one face and plain on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

For symptomatic treatment of urinary obstruction caused by benign prostatic hypertrophy (BPH).
For mild to moderate hypertension.

4.2. Posology and method of administration

Hypertension.

Adults

Initial dose

1 mg before bedtime is the starting dose for all patients and should not be exceeded. Compliance with this initial dosage recommendation should be strictly observed to minimise potential for acute first-dose hypotensive episodes.

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

The usual maintenance dose is 2mg to 10mg once daily. Doses over 20mg rarely improve efficacy and doses over 40mg have not been studied.

BPH

Adults Only:

The dose of terazosin should be adjusted according to the patient's response. The following is a guide to administration:

Initial dose
1 mg before bedtime is the starting dose for all patients and should not be exceeded. Strict compliance with this recommendation should be observed to minimise acute first-dose hypotensive episodes.

Subsequent dose
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 10mg 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 10mg once daily.

Treatment should be initiated using the BPH Starter Pack and response to treatment 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.

Use in renal insufficiency

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

Use in Children

Safety and efficacy in children has not been established.

Use in the Elderly

Pharmacokinetic studies in the elderly indicate that no alteration in dosage recommendation is required.

Postural Hypotension

Postural hypotension has been reported to occur in patients receiving terazosin for the symptomatic treatment of urinary obstruction caused by BPH. In these cases, 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%)

Use with thiazide diuretics and other antihypertensive agents

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

4.3. Contraindications

Known sensitivity to alpha-adrenoceptor antagonists.

4.4. Special warnings and precautions for use

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

In clinical trials, the incidence of postural hypotension was greater in BPH patients than those with hypertension. In these cases, the incidence of postural hypotension events was greater in patients aged 65 years and over (5.6%) than those aged less than 65 years (2.6%).

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

There have been reports of hypotension following the use of a phosphodiesterase-5 (PDE-5) inhibitor and terazosin. Concomitant treatment with tadalafil is not recommended and caution is advised when sildenafil or vardenafil is administered with terazosin (see section 4.5)

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 cataract operation current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

4.5. Interactions with other medicinal products and other forms of interaction

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 observed when terazosin is administered with other antihypertensive agents, to avoid the possibility of significant hypotension. When adding terazosin to a diuretic or other antihypertensive agent, dosage reduction and retitration may be necessary.

Terazosin has been given without interaction with analgesics/anti-inflammatories, cardiac glycosides, hypoglycemics, antiarrhythmics, anxiolytics/sedatives, antibacterials, hormones/steroids and drugs used for gout.

Hypotension has been reported when terazosin has been used with phosphodiesterase-5 (PDE-5) inhibitors. Concomitant treatment with terazosin and sildenafil or vardenafil should only be initiated if the patient is stabilised on terazosin. In addition, vardenafil should not be administered within 6 hours of terazosin, and sildenafil should not be initiated within 4 hours of terazosin therapy.

4.6. Pregnancy and lactation

Although no teratogenic effects were seen in animal testing, the safety of Hytrin use during pregnancy or during lactation has not yet been established. Hytrin should not be used therefore in pregnancy unless the potential benefit outweighs the risk.

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 Hytrin therapy. Patients should be cautioned about these possible adverse effects and the circumstances in which they may occur and advised to avoid driving or hazardous tasks for approximately 12 hours after initial dose or when the dose is increased.

4.8. Undesirable effects

Hytrin 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 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.

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.

<u>Adverse events reported with terazosin</u>

The most common events were asthenia, palpitations, nausea, peripheral oedema, dizziness, 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; decreased libido; depression; 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 include the following:
chest pain; facial oedema; fever; abdominal pain; neck pain; shoulder pain; vasodilation; arrhythmia; constipation; diarrhoea; dry mouth; dyspepsia; flatulence; vomiting; gout; arthralgia; arthritis; joint disorders; 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.

At least two cases of anaphylactoid reactions have been reported with the administration of terazosin.

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 Hytrin 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 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

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

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

In clinical trials, plasma concentrates of total cholesterol and combined low density and very low density lipoproteins were found to be slightly reduced following Hytrin administration.

Additionally, the increase in total cholesterol seen with other hypertensive agents did not occur when these were used in combination with Hytrin.

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 pro static 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. Food has little or no effect on bioavailability. Approximately 40% of the administered dose is eliminated in the urine and 60% in the faeces. The drug is highly bound to plasma proteins.

5.3. Pre-clinical safety data

Carcinogenicity: Hytrin 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
Maize starch
Pregelatinised starch
Purified talc
Magnesium stearate
Purified water
Dye quuinoline yellw aluminium E104 lake (2 mg tablets)
Dye iron oxide burnt sienna E172 (5 mg tablets)
Dye FD & blue No. 2 lake (10 mg tablets)

6.2. Incompatibilities

None known.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store in a cool place, not above 25ºC.

6.5. Nature and contents of container

Tablets in a blister original pack. Blisters are packaged in a carton with a package insert. The 10 mg tablets are supplied in packs of 28 tablets.

6.6. Instructions for use/handling

Not applicable.

7. Manufacturer:

Aesica Queenborough LTD., UK

7.1 MARKETING AUTHORISATION HOLDER

Biotis L.t.d. , Hamelacha 22, Rosh Haayin, Israel

8. MARKETING AUTHORISATION NUMBER

Hytrin starter pack:103 58 28680 :
Hytrin 2 mg tablets 103 59 28681
Hytrin 5 mg tablets 103 60 28682
Hytrin 10 mg tablets 103 61 28683