Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Hytrin 5mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect
Contains lactose monohydrate 123.07 mg per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet
A tan round flat, bevel edged tablet embossed with company logo ' ' and triangular facets on one face and plain on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hytrin is a selective blocker of post-junctional alpha-1-adrenoreceptors.

Hytrin is indicated as:

- A peripheral vasodilator for use in the management of hypertension either alone or in conjunction with other anti-hypertensive agents such as thiazide diuretics or beta-adrenoreceptor blockers.
- An alpha-1-adrenoreceptor blocker for use in the symptomatic treatment of benign prostatic hyperplasia.

4.2 Posology and method of administration

Posology

Hypertension
Adults

An initial dose of 1.0 mg should be given in the evening, one to two hours before retiring. If no untoward effect has occurred a dose of 2.0 mg 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 - 10 mg daily. Doses over 20 mg rarely improve efficacy and doses over 40 mg 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.

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

Benign Prostatic Hyperplasia
Adults

An initial dose of 1.0 mg 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 10 mg.

Paediatric population
Hytrin should not be used in children.

Method of administration

For oral use only

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with a history of micturition syncope.
- History of postural hypotension (in benign prostatic hyperplasia).

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.

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

As with all alpha-1 receptor blockers, terazosin should be used with caution in patients with congestive heart failure.

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 (see section 4.7).

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 metabolized 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.

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

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. An 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.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and terazosinmay 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 phosphodiesterase-5-inhibitors.

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 non-steroidal 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 Hytrin in BPH. In BPH patients the adverse events profile of patients treated concurrently with non-steroidal anti-inflammatory drugs (NSAIDs), theophylline, anti-anginal 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 Hytrin 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 Hytrin is administered concomitantly with other antihypertensive agents (e.g. calcium antagonists) to avoid the possibility of significant hypotension. When adding Hytrin to a diuretic or other antihypertensive agent, dosing reduction and re-titration of these agents may be necessary.

Phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy and breast feeding
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.

Fertility
No Data available

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

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 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.

The most commonly reported adverse effect is dizziness affecting about 10%-15% of patients.

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 undesirable effects are listed below by organ class and the following frequency convention:

The incidence of adverse effects is based on the following frequencies:
Very common (≥1/10);
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);
Not known (cannot be estimated from the available data)

System organ class	Common	Uncommon	Rare	Not Known
Blood and lymphatic system disorders			Thrombocytopenia	
Metabolism and nutrition disorders				Gout
Psychiatric disorders				Nervousness, depression, anxiety, insomnia, decreased libido
Nervous system disorders	Somnolence, dizziness, syncope, paraesthesia, headache			
Eye disorders	Blurred vision/ amblyopia			Conjunctivitis, abnormal vision
Ear and labyrinth disorders	Vertigo			Tinnitus
Cardiac disorders	Palpitations, tachycardia		Atrial fibrillation	Arrhythmia
Vascular disorders	Orthostatic hypotension			Vasodilation e.g flushing
Respiratory, thoracic and mediastinal disorders	Nasal congestion/ rhinitis, dyspnoea			Bronchitis, cough, epistaxis, pharyngitis, sinusitis
Gastrointestinal disorders	Nausea, diarrhoea			Abdominal pain, dyspepsia, vomiting, constipation, flatulence, dry mouth
Skin and subcutaneous tissue disorders	Skin rash, pruritus,			Angioedema, hyperhidrosis, urticaria
Musculoskeletal and connective tissue disorders				Back pain, neck pain, shoulder pain, pain in extremities, arthralgia, arthritis, joint stiffness, musculoskeletal stiffness, joint disorder, myalgia
Renal and urinary disorders			Incontinence (mainly in postmenopausal	Increased urinary frequency, urinary tract infection

			women)	
Reproductive system and breast disorders	Erectile dysfunction		Priapism	
General disorders and/or administration site conditions	Asthenia, oedema, peripheral oedema, chest pain			Face oedema, influenza like illness, cold symptoms, fever
Investigations	Weight increased			

At least two cases of severe anaphylaxis were reported to be associated with the administration of terazosin in hypertension.

Increases in hepatic enzyme levels have been reported.

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
Website: www.hpra.ie.

4.9 Overdose

Symptoms
Administration of Hytrin lead to acute hypotension, cardiovascular support is of first importance.

Management
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

Pharmacotherapeutic group: Drug for benign prostatic hyperplasia, alpha-adrenoreceptor antagonists, ATC Code: G04CA03

Mechanism of action and Pharmacodynamic effects
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-adrenoceptors. Hytrin usually produces an initial gradual decrease in blood pressure followed by a sustained antihypertensive action.

Unlike other anti-hypertensives, Hytrin 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.

Clinical efficacy and safety
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

Absorption
Terazosin is rapidly and almost completely absorbed from the gastrointestinal tract after oral doses. The bioavailability of oral terazosin is approximately 90%. The plasma concentration of the parent drug is a maximum about 1hour post administration and declines with a half-life of approximately 12 hours. Food has little or no effect on bioavailability.

Distribution
The drug is highly bound to plasma proteins. Approximately 90-94% of terazosin is bound to plasma proteins.

Biotransformation
It is metabolised in the liver. Hepatic metabolism is extensive with major biliary elimination

Elimination
Approximately 40% of the administered dose is eliminated in the urine and 60% in the faeces.

5.3 Preclinical 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. 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
Pregelatinised Maize Starch
Purified talc
Magnesium stearate
Iron oxide burnt sienna (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

5mg tablet - blister packs containing 28 tablets.
The blister packs are composed of PVC/PvDC, heat sealed with an aluminium foil backing.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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