SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Hytrin 5 mg Tablets
Hytrin 10 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Hytrin 5 mg tablets contain 5 mg of terazosin as monohydrochloride dihydrate.
Hytrin 10 mg tablets contain 10 mg of terazosin as monohydrochloride dihydrate.

Excipients with known effect:
Hytrin 5 mg tablets: Lactose (123.07 mg).
Hytrin 10 mg tablets: Lactose (117.68 mg)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hytrin 5 mg tablets are: Tan, round, flat, bevelled edge tablets embossed with corporate logo and triangular facets on one face, plain on the other.

Hytrin 10 mg tablets are: Blue, round, flat, bevelled edge tablets embossed with corporate logo and triangular facets on one face, 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

Posology

Hypertension

Adults

Initial dose
Do not start treatment with a new patient if it is not possible to reach a dose of 1 mg and 2 mg.

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

If 1 or 2 mg dose is not optional, the physician should consider alternative therapies for these patients.

BPH

Adults

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

Initial dose
Do not start treatment with a new patient if it is not possible to reach a dose of 1 mg and 2 mg.
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 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.

Transient side effects may occur at each titration step. If any side effects persist, consideration should be given to reducing the dose.

If administration is discontinued for more than several days, therapy should be re-instituted using the initial dose titration regimen. Do not start treatment after discontinuation if it is not possible to reach a dose of 1 mg and 2 mg.

If 1 or 2 mg dose is not optional, the physician should consider alternative therapies for these patients.

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

Renal impairment

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

Paediatric population

Safety and efficacy in children has not been established.

Method of administration
For oral use

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Known sensitivity to other alpha-adrenoceptor blockers.
Patients with a history of micturition syncope.

4.4. Special warnings and precautions for use

Terazosin hydrochloride, like other alpha-adrenoceptor blockers, can cause marked lowering of blood pressure, especially postural hypotension and syncope in association with the first dose or first few doses of therapy. A similar effect can be anticipated if therapy is interrupted for more than a few doses and then re-started. Syncope has also been reported with other alpha-adrenoceptor blockers in association with rapid dosage increases or the introduction of another antihypertensive drug. Syncope is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe supraventricular tachycardia with heart rates of 120 to 160 beats per minute.

In clinical trials, the incidence of postural hypotension was greater in BPH patients than in 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. Do not start treatment after discontinuation if it is not possible to reach a dose of 1 mg and 2 mg.

Before treating the symptoms of benign prostatic hyperplasia (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. Patients with benign prostatic hyperplasia, who simultaneously suffer from congestion of the upper urinary tract, chronic urinary tract infection or bladder stones, should not be treated with terazosin.

Terazosin should not be given to patients with bladder overflow, anuria or advanced renal failure.

Due to the risk of an excessive decrease in blood pressure, caution is advised for the concomitant administration of terazosin and thiazides or other antihypertensive medications. If a thiazide diuretic or another antihypertensive medication is added during treatment with terazosin, the terazosin dose must be reduced or the drug discontinued. A new dose-titration

is essential. When administering terazosin in addition to other antihypertensives, the dose of the other antihypertensives should be reduced before commencement of therapy and adjusted after discontinuation of terazosin.

Due to the vasodilatory effect of terazosin, it should be administered with caution if the following cardiac conditions are present:

- Pulmonary oedema due to aortic or mitral valve stenosis
- High output cardiac insufficiency
- Right-sided cardiac insufficiency due to pulmonary embolism or pericardial effusion
- Left-sided cardiac insufficiency with low filling pressure

In patients with severe coronary heart disease, a very rapid or excessive decrease in blood pressure can lead to an exacerbation of angina pectoris.

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.

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

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-adrenoceptor 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-adrenoceptor 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-adrenoceptor blockers should be made known to the ophthalmic surgeon in advance of surgery.

Hytrin 5 mg and 10 mg Tablets contain lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5. Interaction 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.

Hypotensive effects is enhanced when Terazosin is taken along with adrenergic neurone blockers, alcohol, aldesleukin, alprostadil, anaesthetic (general), angiotensin – II receptor antagonists, antipsychotics, anxiolytics and hypnotics, baclofen, beta-blockers, calcium-channel blockers, clonidine, diazoxide, diuretics, hydralazine, levodopa, monoamine oxidase inhibitors (MAOIs), Methyldopa, Minoxidil, Moxisylyte, Moxonidine, nitrates, sodium nitroprusside, Tizanidine.

Caution should be observed when terazosin is administered with thiazide diuretics or 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.

Hypotensive effects of terazosin are antagonised by the following: corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and oestrogens.

The hypotensive effect is enhanced when terazosin is given with Phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) (see section 4.4). Avoid giving terazosin for 4 hours after Phosphodiesterase-5-inhibitor administration.

4.6. Fertility, pregnancy and lactation

Pregnancy

Terazosin hydrochloride was not teratogenic in either rats or rabbits when administered at oral doses up to 1330 and 165 times, respectively, the maximum recommended human dose. Fetal resorptions occurred in rats dosed with 480mg/kg/day, approximately 1330 times the maximum recommended human dose. Increased fetal resorptions, decreased fetal weight and an increased number of supernumerary ribs were observed in offspring of rabbits dosed with 165 times the maximum recommended human dose. These findings (in both species) were most likely secondary to maternal toxicity.

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

Breast-feeding

It is not known whether terazosin hydrochloride is excreted in breast milk. Because many drugs are excreted in breast milk, caution should be exercised when terazosin hydrochloride is administered to a nursing woman.

Fertility

No data available on human fertility. Animal studies show reduced fertility (see 5.3 Preclinical).

4.7. Effects on ability to drive and use machines

Terazosin tablets have a major influence on the 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 blockers 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.

Adverse drug effects reported with terazosin from multiple sources including clinical trials and spontaneous reports:

System Organ Class	**Frequency**	**Adverse reaction**
Blood and lymphatic system disorder	Not known	Thrombocytopenia
Immune system disorders	Not known	Anaphylactoid reaction
Psychiatric disorders	Not known	Depression, nervousness, anxiety, insomnia
Nervous system disorders	Not known	Dizziness, somnolence, headache, paraesthesia, vertigo
Eye disorders	Not known	Blurred vision, amblyopia, visual impairment, conjunctivitis
Ear and labyrinth disorders	Not known	Tinnitus
Cardiac disorders	Not known	Palpitations, tachycardia, arrhythmia, atrial fibrillation
Vascular disorders	Not known	Postural hypotension, syncope, vasodilatation

Respiratory, thoracic and mediastinal disorders	Not known	Nasal congestion, rhinitis, dyspnoea, sinusitis, bronchitis, epistaxis, flu symptoms, pharyngitis, cold symptoms, cough
Gastrointestinal disorders	Not known	Nausea, abdominal pain, constipation, diarrhoea, dry mouth, dyspepsia, flatulence, vomiting
Skin and subcutaneous tissue disorders	Not known	Pruritus, rash, hyperhidrosis, angioedema
Musculoskeletal and connective tissue disorders	Not known	Back pain, pain in extremity, neck pain, shoulder pain, gout, arthralgia, arthritis, joint disorders, myalgia
Renal and urinary disorders	Not known	Pollakiuria, urinary tract infection and urinary incontinence (primarily reported in post-menopausal women)
Reproductive system and breast disorders	Not known	Libido decreased, erectile dysfunction, priapism
General disorders and administration site conditions	Not known	Asthenia, peripheral oedema, oedema, chest pain, face oedema, pyrexia
Investigations	Not known	Weight increased. Decreased haematocrit, decreased haemoglobin, decreased white blood cell count, decreased total protein and decreased blood albumin (suggestive of haemodilution) Treatment with terazosin for up to 24 months had no significant effect on prostate specific antigen (PSA) levels.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9. Overdose

Symptoms
Acute hypotension

Management
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

Pharmacotherapeutic group: 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.

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.

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 pro static 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. 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.

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 is eliminated in the urine and 60% in the faeces.

Linearity / non-linearity of pharmacokinetics
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

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 $\geq$ 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).
In male rats, terazosin induced benign adrenal medullary tumours at the highest administered dose corresponding to 175 times the maximum human dose.

Carcinogenicity: In male rats, terazosin induced benign adrenal medullary tumours at the highest administered dose corresponding to 175 times the maximum human dose. 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
Dye iron oxide burnt sienna E172 (5 mg tablets)
Dye FD&C No. 2 Al. lake E132 (10 mg tablets)

6.2. Incompatibilities

None known.

6.3. Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store below 25ºC.

6.5. Nature and contents of container

Hytrin 5 mg
Tablets in a blister pack. The 5 mg tablets are supplied in a pack of 28 tablets. Blisters are packaged in a carton with a package insert.

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

6.6. Special precautions for disposal

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

7. Manufacturer:

Amdipharm Sales & Mark. Ltd., England

8. Registration holder:

Biotis Ltd., Hamelacha 22, Rosh Haayin

9. Registration Number

Hytrin 5 mg Tablets: 103 60 28682
Hytrin 10 mg Tablets: 103 61 28683

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