Proprietary name:	UROTAL
Dosage form:	Capsules
Active Ingredient:	Tamsulosin hydrochloride
Strength per dosage unit:	0,4 mg per capsule

1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

Urotal 0,4 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0,4 mg of tamsulosin hydrochloride.

Excipients with known effect:

Sugar-free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to off white pellets filled in hard gelatin capsule size "1" Olive green opaque cap & orange opaque body imprinted with "TAM" on cap and "0.4 mg" on body in black ink.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Urotal is indicated for the treatment of functional symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Posology:

One capsule daily to be taken after breakfast or the first meal of the day.

Special populations

Renal Impairment:

No dose adjustment is warranted in renal impairment.

Hepatic impairment:

No dose adjustment is warranted in patients with mild to moderate hepatic insufficiency (see section 4.3).

Method of administration:

For oral use.

The capsule should be swallowed whole and should not be crunched or chewed, as this will interfere with the sustained release property of the active ingredient.

4.3 Contraindications

Urotal is contraindicated in:

- known hypersensitivity to tamsulosin hydrochloride, or to any of the excipients listed in section 6.1.
- a history of orthostatic hypotension.
- severe hepatic insufficiency.
- combination with strong inhibitors of CYP3A4, e.g. ketoconazole (see section 4.5)

4.4 Special warnings and precautions for use

Orthostatis:

A reduction in blood pressure can occur during treatment with **Urotal,** as a result of which, orthostatic hypotension and syncope can occur. At the first signs of orthostatic hypotension (dizziness, weakness), the patient should sit or lie down until the symptoms have disappeared.

Before therapy with **Urotal** is initiated, the patient should be examined to exclude the presence of other conditions which can cause the same symptoms as benign prostatic hyperplasia.
Digital rectal examination and when necessary, determination of prostate specific antigen (PSA) should be performed before treatment and at regular intervals afterwards.
The treatment of patients with severe renal impairment (creatinine clearances of < 10 mL/ min) should be approached with caution, as these patients have not been studied.

Intraoperative Floppy Iris Syndrome (IFIS):
The “Intraoperative Floppy Iris Syndrome” (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients previously treated with tamsulosin. IFIS may increase the risk of eye complications during and after the operation. Discontinuing tamsulosin 1 to 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not yet been established. IFIS has also been reported in patients who had discontinued tamsulosin as in **Urotal** for a longer period prior to cataract surgery.

The initiation of therapy with tamsulosin in patients for whom cataract surgery is scheduled is not recommended.
During pre-operative assessment cataract surgeons and ophthalmic teams should be consider whether patients scheduled for cataract surgery are being or have been treated with tamsulosin in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

Medicine interactions:

Urotal should not be given in combination with strong inhibitors of CYP3A4 (e.g. ketoconazole) in patients with poor metaboliser CYP2D6 phenotype.

Urotal should be used with caution in combination with moderate inhibitors of CYP3A4 (e.g. erythromycin).

Urotal should be used with caution in combination with cimetidine, particularly at a dose higher than 0,4 mg.

Urotal should not be used in combination with other alpha adrenergic blockers.

Caution is advised when alpha adrenergic blockers including **Urotal** are co-administered with PDE5 inhibitors. Alpha adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two medicine classes can potentially cause symptomatic hypotension. Caution should be exercised with concomitant administration of warfarin and **Urotal** (see section 4.5).

Priapism:

Urotal has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Because this condition can lead to permanent impotence if not properly treated, patients must be advised about the seriousness of the condition (see section 4.8).

Screening for Prostate Cancer:

Prostate cancer and BPH frequently co-exist; therefore, patients should be screened for the presence of prostate cancer prior to treatment with **Urotal** and at regular intervals afterwards.

Sulfa Allergy:

In patients with sulfa allergy, allergic reaction to **Urotal** has been reported.

If a patient reports a serious or life-threatening sulfa allergy, caution is warranted when taking **Urotal**.

4.5 Interaction with other medicines and other forms of interaction

Cytochrome P_{450} inhibition:

The free fraction of tamsulosin in human plasma is not changed by diazepam, propranolol, trichlormethiazide, chlormadinon, amitryptyline, diclofenac, glibenclamide, simvastatin or warfarin. Neither does tamsulosin change the free fraction of diazepam, propranolol, trichlormethazide or chlormadinone.

No interaction at the level of hepatic metabolism have been observed during in vitro studies with liver microsomal fractions (representative of the cytochrome P_{450} linked medicine metabolism enzyme system), involving amitriptyline, glibenclamide and finasteride.

Strong and Moderate Inhibitors of CYP3A4 or CYP2D6:

Urotal is extensively metabolized, mainly by CYP3A4 and CYP2D6 (see section 5.2).

Concomitant treatment with ketoconazole (a strong inhibitor of CYP3A4) resulted in an increase in the C_{max} and AUC of tamsulosin. The effects of concomitant administration of a moderate CYP3A4 inhibitor (e.g. erythromycin) on the pharmacokinetics of **Urotal** have not been evaluated.

Concomitant treatment with paroxetine (a strong inhibitor of CYP2D6) resulted in an increase in the C_{max} and AUC of tamsulosin that had increased by a factor of 1,3 and 1,6, respectively, but these increases are not considered clinically significant.

A similar increase in exposure is expected in CYP2D6 poor metabolizers (PM) as compared to extensive metabolizers (EM). Since CYP2D6 PMs cannot be readily identified and the potential for significant increase in tamsulosin exposure exists when **Urotal** is co-administered

with strong CYP3A4 inhibitors in CYP2D6 PMs, **Urotal** should not be used in combination with strong inhibitors of CYP3A4 (e.g., ketoconazole) (sections 4.3 and 4.4).

The effects of concomitant administration of a moderate CYP2D6 inhibitor (e.g., terbinafine) on the pharmacokinetics of **Urotal** have not been evaluated.

The effects of co-administration of both a CYP3A4 and a CYP2D6 inhibitor **Urotal** have not been evaluated. However, there is a potential for significant increase in tamsulosin exposure when **Urotal** is co-administered with a combination of both CYP3A4 and CYP2D6 inhibitors. (see section 4.4*).*

Cimetidine:

Treatment with cimetidine resulted in a significant decrease in the clearance of tamsulosin hydrochloride, which resulted in a moderate increase in tamsulosin hydrochloride AUC (see section 44).

Other α-Adrenergic Blockers:

The pharmacokinetic and pharmacodynamic interactions between **Urotal** and other α-adrenergic blockers have not been determined; however, interactions between **Urotal** and other α-adrenergic blockers may be expected *(see sections 4.4. and 5.2).*

Warfarin

A definitive medicine interaction study between tamsulosin hydrochloride and warfarin was not conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Caution should be exercised with concomitant administration of warfarin and tamsulosin (*see section 4.4.).* Warfarin may increase the elimination rate of tamsulosin.

Diclofenac:

Diclofenac may increase the elimination rate of tamsulosin. Co-administration with other α_1-adrenocetor antagonist may lead to hypotensive effects.

Nifedipine, atenolol and enalapril:

Dosage adjustments are not necessary when **Urotal** are administered concomitantly with nifedipine, atenolol, or enalapril.

Digoxin and theophylline:

Dosage adjustments are not necessary when a **Urotal** is administered concomitantly with digoxin or theophylline.

Furosemide:

Urotal had no effect on the pharmacodynamics (excretion of electrolytes) of furosemide. While furosemide produced a reduction in tamsulosin hydrochloride C_{max} and AUC, these changes are expected to be clinically insignificant and do not require adjustment of the **Urotal** dosage.

4.6 Fertility, pregnancy and lactation

Urotal is not indicated for use in women.

Fertility:

Ejaculation disorders have been observed in short- and long-term clinical studies with tamsulosin. Events of ejaculation disorder, retrograde ejaculation and ejaculation failure have been reported.

4.7 Effects on ability to drive and use machines

No studies on the effects of **Urotal** on the ability to drive and use of machines have been performed. However, dizziness has been reported and patients who experience these symptoms should be cautious while driving or operating machinery.

4.8 Undesirable effects

Summary of safety profile

Adverse reactions were usually mild and transient. The frequently observed adverse reactions are dizziness, drowsiness and lethargy.

Listed summary of adverse reactions

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as: Frequent, less frequent, frequency unknown.

Gastrointestinal disorders:

Less frequent: Nausea, diarrhoea, vomiting and constipation

Frequency unknown: Dry mouth

Endocrine disorders:

Less frequent: Diaphoresis

Cardiac disorders:

Less frequent: Palpitations and tachycardia

Vascular disorders:

Less frequent: Orthostatic hypotension

Nervous system disorders:

Frequent: Dizziness, drowsiness, and lethargic

Less frequent: Headache, depression, nervousness, sleep disturbances, vertigo, hallucinations, paraesthesia, and syncope

Eye disorders:

Less frequent: Intra-operative Floppy Iris Syndrome (IFIS) in cataract surgery, and reddened sclera

Frequency unknown: Blurred vision and visual impairment

Ear and labyrinth disorders:

Less frequent: Tinnitus

Respiratory, thoracic and mediastinal disorders:

Less frequent: Nasal congestion, rhinitis, chest pain, dyspnoea, and epistaxis

Reproductive system disorders:

Frequent: Ejaculation disorders including retrograde ejaculation and ejaculation failure

Less frequent: Impotence and priapism

Renal and urinary disorders:

Less frequent: Urinary frequency and incontinence

Skin and subcutaneous tissue disorders:

Less frequent: Alopecia, arthralgia, skin rash, pruritus, urticaria, lichen planus, angioedema, and Stevens-Johnson syndrome

Frequency unknown: erythema multiforme and dermatitis exfoliative

General disorder and administration site conditions:

Less frequent: Asthenia

Hepatobiliary disorders:

Less frequent: Pancreatitis

Investigations:

Less frequent: Abnormal liver enzyme values.

Post-marketing experience:

In addition to the adverse events listed above, atrial fibrillation, dysrhythmia, tachycardia and dyspnoea have been reported in association with use of tamsulosin as in Urotal**.**

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 Alternatively all adverse events can be reported to Alkem Laboratories vial the e-mail: pharmacist.rsa@alkem.com.

4.9 Overdose

Symptoms:

Overdosage with tamsulosin hydrochloride can potentially result in severe hypotensive effects (see section 4.8). Severe hypotensive effects have been observed at different levels of overdosing.

Treatment:

In case of acute hypotension occurring after overdosage cardiovascular support should be given. Blood pressure can be restored, and heart rate brought back to normal by lying the patient down. If this does not help then volume expanders, and when necessary, vasopressors could be employed. Renal function should be monitored, and general supportive measures applied. Dialysis is unlikely to be of help as tamsulosin is very highly bound to plasma proteins. Measures, such as emesis, can be taken to impede absorption. When large quantities are involved, activated charcoal and an osmotic laxative, such as sodium sulfate, can be administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 34 Other

Pharmacotherapeutic group: Genito-urinary system, urologicals, ATC code: G04CA02

Tamsulosin is an α_1-adrenoceptor blocker. It selectively and competitively antagonises the activation of the postsynaptic α_1-adrenoceptors to the subtype α_{1A} and α_{1D} thereby causing smooth muscle relaxation of the prostate and bladder neck.

Smooth muscle tone is mediated by the sympathetic nervous stimulation of alpha adrenoceptors, which are abundant in the prostate, prostatic capsule, prostatic urethra, and

bladder neck. Blockade of these adrenoceptors can cause smooth muscles in the bladder neck and prostate to relax, resulting in an improvement in urine flow rate and a reduction in symptoms of BPH. Tamsulosin, an α_1 adrenoceptor blocker, exhibits selectivity for alpha receptors in the human prostate.

The need for surgery or catheterisation is significantly delayed. α_1-blockers can reduce blood pressure by lowering peripheral resistance. Tamsulosin is not intended for use as an antihypertensive medicine.

5.2 Pharmacokinetic properties

Absorption:

Tamsulosin is absorbed from the gastro-intestinal tract and is almost completely bioavailable. Absorption of tamsulosin is reduced by a recent meal. Uniformity of the absorption can be improved by the patient always taking tamsulosin 0,4 mg capsule after the same meal. After a single dose of tamsulosin 0,4 mg capsule taken after a meal, plasma levels of tamsulosin peak at around 6 hours. In the steady state, which is reached by day 5 of multiple dosing, C_{max} in patients is about two thirds higher than that reached after a single dose. Although this was seen in elderly patients, the same finding would also be expected in younger patients.

There are considerable inter-patient differences in plasma levels, both after single and multiple dosing.

Distribution:

Tamsulosin is about 99 % bound to plasma proteins and volume of distribution is small (about 0, 21 L.kg).

Biotransformation:

Tamsulosin has a low first pass effect, being metabolised slowly. Most tamsulosin is present in plasma in the form of unchanged medicine. It is metabolised in the liver. In rats, hardly any induction of microsomal liver enzymes was seen to be caused by tamsulosin.

In vitro results suggest that CYP3A4 and also CYP2D6 are involved in metabolism, with possible minor contributions to tamsulosin hydrochloride metabolism by other CYP isozymes. Inhibition of CYP3A4 and CYP2D6 medicine metabolising enzymes may lead to increased exposure to tamsulosin hydrochloride (see sections 4.4 and 4.5).

None of the metabolites are more active than the parent compound.

Elimination:

Tamsulosin and its metabolites are mainly excreted in the urine with about 9 % of a dose being present in the form of unchanged medicine.

The elimination half-life after a single dose is about 10 hours.

The elimination half-life in the steady state is about 13 hours. The lowering of the dose in renal impairment is not warranted.

Special Populations*:*

Renal impairment:

The pharmacokinetics of tamsulosin, as in **Urotal** is not significantly influenced by renal function. This suggests that no dose adjustment of tamsulosin is necessary in patients with renal impairment.

Proprietary name:	UROTAL
Dosage form:	Capsules
Active Ingredient:	Tamsulosin hydrochloride
Strength per dosage unit:	0,4 mg per capsule

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium stearate, hypromellose, microcrystalline cellulose, methacrylic acid polymer dispersion (Eudragit L30D-55), talc and triacetin.

Capsules content: gelatine, FD & C Blue No.2, iron oxide red, iron oxide yellow and titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister in the outer carton until required for use.

Store all medicine out of reach of children.

6.5 Nature and contents of container

Aluminium and aluminium blister pack of 10 tablets packed into an outer carton.

6.6 Special precautions for disposal

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

Proprietary name:	UROTAL
Dosage form:	Capsules
Active Ingredient:	Tamsulosin hydrochloride
Strength per dosage unit:	0,4 mg per capsule

7 MARKETING AUTHORISATION HOLDER

Alkem Laboratories (Pty) Ltd.

R21 Corporate Park

121 Sovereign Drive

Block A, Office 202

Irene Ext.30, Centurion, 0157

8 MARKETING AUTHORISATION NUMBER(S)

To be allocated by authority.

9 DATE OF REVISION OF THE TEXT

To be allocated by authority.