MODULE 1.3.1.1 PROFESSIONAL INFORMATION FOR UROMAX CO HARD CAPSULES

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

UROMAX CO 0,5/0,4 mg HARD CAPSULES

(Dutasteride 0,5 mg and tamsulosin 0,4 mg hard capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 0,5 mg dutasteride and 0,4 mg tamsulosin hydrochloride, (equivalent to 0,37 mg tamsulosin).

For the full list of excipients, **see section 6.1**.

3. PHARMACEUTICAL FORM

UROMAX CO hard capsules are oblong hard gelatine capsules, Nº 0EL, of approximately 24,2 mm x 7,7 mm, body of brown colour and cap of beige colour with black code C001 on the cap. Each capsule contains:

- One oblong soft gelatine capsule of Dutasteride (approximately 16,5 x 6,5 mm) of light yellow colour, filled with transparent liquid.
- Approximately 183,8 mg of modified release tamsulosin pellets with white to off-white colour.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).

4.2 Posology and method of administration

Posology

Adult males (including elderly):

The recommended dose of UROMAX CO is one capsule taken orally approximately 30 minutes after the same meal each day **(see section 5.2)**. The capsules should be swallowed whole and not chewed or opened. Contact with the contents of the dutasteride capsule contained within the hard-shell capsule may result in irritation of the oropharyngeal mucosa.

Renal impairment:

UROMAX CO pharmacokinetics have not been studied in patients with impaired renal function. However, no adjustment is anticipated in these patients **(see section 5.2)**.

Hepatic impairment:

UROMAX CO pharmacokinetics have not been studied in patients with hepatic impairment **(see section 4.4 and section 5.2)**.

Method of administration:

For oral use.

4.3 Contraindications

UROMAX CO is contraindicated in:

- Patients with known hypersensitivity to dutasteride, other 5α-reductase inhibitors, tamsulosin hydrochloride, peanut or soya oil as it contains lecithin soy or any of the other ingredients of UROMAX CO.
- Women and children **(see section 4.6)**.
- Patients with a history of orthostatic hypotension.
- Severe hepatic impairment.

4.4 Special warnings and precautions for use

Dutasteride is absorbed through the skin, therefore, women and children must avoid contact with leaking capsule **(see section 4.6)**. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water.

Concomitant administration of tamsulosin hydrochloride with strong inhibitors of CYP3A4 (e.g. ketoconazole), or to a lesser extent, with strong inhibitors of CYP2D6 (e.g. paroxetine) can increase tamsulosin exposure **(see section 4.5)**. UROMAX CO is therefore not recommended in patients taking a strong CYP3A4 inhibitor (e.g. erythromycin), a strong or moderate CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6.

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Caution should be exercised when administering UROMAX CO to patients with liver disease because dutasteride undergoes extensive hepatic metabolism and has a half-life of 3 to 5 weeks.

Combination therapy with tamsulosin and cardiac failure:

UROMAX CO may increase the risk to develop cardiac failure in patients with other risk factors for cardiac failure.

A higher incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) were reported among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. However, the incidence of cardiac failure was shown to be low and variable.

Effects on prostate specific antigen (PSA) and prostate cancer detection:

Digital rectal examination, as well as the other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with UROMAX CO and periodically thereafter.

UROMAX CO causes a decrease in mean PSA levels by approximately 50 % after six months of treatment.

Patients receiving UROMAX CO should have a new PSA baseline established before starting treatment with UROMAX CO and after 6 months of treatment with UROMAX CO. It is recommended to monitor PSA values regularly thereafter.

Any confirmed increase from lowest PSA level while on UROMAX CO may signal the presence of prostate cancer (particularly high-grade cancer) or non-compliance to therapy with UROMAX CO and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5α-reductase inhibitor. In the interpretation of a PSA value for a patient taking UROMAX CO, previous PSA values should be sought for comparison.

Treatment with UROMAX CO does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established.
Total serum PSA levels return to baseline within 6 months of discontinuing treatment.
The ratio of free to total PSA remains constant even under the influence of UROMAX CO. If medical practitioners elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing dutasteride therapy, no adjustment to its value is necessary.

Prostate cancer and high grade tumours:
Men taking UROMAX CO should be regularly evaluated for prostate cancer risk including PSA testing.

Breast cancer in men:
Medical practitioners should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge.

Hypotension:
Orthostatic hypotension can occur in patients treated with tamsulosin, which can result in syncope. Patients beginning treatment with UROMAX CO should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness and vertigo) until the symptoms have resolved.
Caution is advised when alpha adrenergic blocking medicines including tamsulosin 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 may cause symptomatic hypotension **(see section 4.5)**.

Intra-operative Floppy Iris Syndrome:

Intra-operative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients treated with alpha-1 adrenergic blockers, including tamsulosin, as in UROMAX CO. IFIS may increase the risk of eye complications during and after the operation.

During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with UROMAX CO in order to ensure that appropriate measures will be in a place to manage IFIS if it occurs during surgery. Discontinuing tamsulosin 1-2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping of therapy prior to cataract surgery has not yet been established.

4.5 Interaction with other medicines and other forms of interaction

There have been no interaction studies for UROMAX CO. The following statements reflects the information available on the individual components.

Dutasteride:

In vitro metabolism studies show that dutasteride is metabolised by human cytochrome P450 isoenzyme CYP3A4. Therefore, blood concentrations of dutasteride may increase in presence of inhibitors of CYP3A4.

Dutasteride clearance was decreased during co-administration with the CYP3A4 inhibitors verapamil (37 %) and diltiazem (44 %). In contrast, no decrease in clearance

was seen when amlodipine, another calcium channel antagonist, was co-administered with dutasteride.

A decrease in clearance and subsequent increase in exposure to dutasteride, in the presence of CYP3A4 inhibitors, is unlikely to be clinically significant due to the wide margin of safety (up to 10 times the recommended dose has been given to patients for up to six months), therefore no dose adjustment is necessary.

In vitro, dutasteride is not metabolised by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 and CYP2D6. Dutasteride neither inhibits human cytochrome P450 drug-metabolising enzymes nor induces cytochrome P450 isoenzymes CYP1A, CYP2B, and CYP3A. In *vitro* studies demonstrate that dutasteride does not displace warfarin, diazepam, or phenytoin from plasma protein, nor do these medicines displace dutasteride.

Medicines that have been tested for interactions in man include tamsulosin, terazosin, warfarin, digoxin and cholestyramine and no clinically significant interactions have been observed. No clinically significant adverse interactions were observed when dutasteride was co-administered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking medicines, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.

Tamsulosin:

There is a risk of enhanced hypotensive effects when tamsulosin hydrochloride is co-administered with medicines which can reduce blood pressure, including anaesthetic medicines, PDE5 inhibitors and other alpha-1 adrenergic blockers. UROMAX CO

should not be used concomitantly with other alpha-1 adrenergic blockers.

Co-administration of tamsulosin hydrochloride and ketoconazole (a strong CYP3A4 inhibitor) may result in an increase of the C_{max} and AUC of tamsulosin hydrochloride by a factor of 2,2 and 2,8, respectively. Concomitant administration of tamsulosin hydrochloride and paroxetine (a strong CYP2D6 inhibitor) may result in an increase of the C_{max} and AUC of tamsulosin hydrochloride by a factor of 1,3 and 1,6 respectively. A similar increase in exposure is expected in CYP2D6 poor metabolisers as compared to extensive metabolisers when co-administered with a CYP3A4 inhibitor.
The effects of co-administration of both CYP3A4 and CYP2D6 inhibitors with tamsulosin hydrochloride have not been evaluated clinically, however there is a potential for significant increase in tamsulosin exposure **(see section 4.4)**.

Concomitant administration of tamsulosin hydrochloride (0,4 mg) and cimetidine (400 mg every six hours for six days) may result in a decrease in the clearance (26 %) and an increase in the AUC (44 %) of tamsulosin hydrochloride. Caution should be used when UROMAX CO is used in combination with cimetidine.

There are no data on interactions between tamsulosin hydrochloride and warfarin. However, diclofenac and warfarin may increase the elimination rate of tamsulosin. Caution should be exercised when warfarin is co-administered with tamsulosin hydrochloride.

4.6 Fertility, pregnancy and lactation

Pregnancy

UROMAX CO is contraindicated for use in women.

Even though tamsulosin hydrochloride showed no evidence of foetal harm, suppression of circulating levels of dihydrotestoterone may inhibit the development of the external organs in a male foetus carried by a woman exposed to dutasteride.

For information on preclinical data, ***see* section 5.3**.

Lactation

UROMAX CO is contraindicated for use in women. It is not known whether dutasteride or tamsulosin are excreted in human milk.

Fertility

Men using UROMAX CO should be advised to use condoms.

Dutasteride reduces sperm count and sperm motility which may be irreversible after discontinuation of treatment.

Effects of tamsulosin hydrochloride on sperm counts or sperm function have not been evaluated.

4.7 Effects on ability to drive and use machines

UROMAX CO may cause orthostatic hypotension and therefore may interfere with driving and operating machinery and patients should be informed about the occurrence of symptoms related to orthostatic hypotension, such as dizziness when taking UROMAX CO.

217 **4.8 Undesirable effects**

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System organ class	Dutasteride + tamsulosin combination [a]	Dutasteride	Tamsulosin
Nervous system disorders	*Less frequent*: dizziness.		*Less frequent:* dizziness, headache and syncope.
Cardiac disorders	*Less frequent:* cardiac failure	*Less frequent:* cardiac failure	*Less frequent:* palpitations.
Vascular disorders			*Less frequent:* postural hypotension.
Respiratory, thoracic and mediastinal disorders			*Less frequent:* rhinitis.
Gastrointestinal disorders			*Less frequent:* constipation, diarrhea, nausea and vomiting.
Skin and subcutaneous disorders			*Less frequent:* angioedema, Stevens-Johnson

			syndrome, urticaria, rash, pruritis
Reproductive system and breast disorders	*Frequent:* ejaculation disorders[b], altered or decreased libido[b], impotence[b]. *Less frequent*: breast disorders[c].	*Frequent:* impotence[b], altered or decreased libido[b]. *Less frequent:* ejaculation disorders[b], breast disorders[c].	*Frequent:* abnormal ejaculation, impotence[b]. *Less frequent:* ejaculation disorders[b], decreased libido[b], breast disorders[c], priapism.
General disorders and administrative site conditions			*Less frequent:* asthenia.

Superscript key:

- ***a****- combination of dutasteride 0,5 mg and tamsulosin 0,4 mg once daily.*
- ***b****- these sexual adverse events are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse events may persist after treatment discontinuation. The role of dutasteride in this persistence is unknown.*
- ***c****- includes breast tenderness and breast enlargement.*

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220 ***Post marketing data***

System organ class	Dutasteride monotherapy	Tamsulosin monotherapy

Immune system disorders	*Frequency not known:* allergic reactions including rash, pruritus, urticaria, oedema and angioedema.	
Psychiatric disorders	*Frequency not known:* depression.	
Eye disorders		*Frequency not known:* Reports of Intra-operative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with alpha-1 adrenergic blocker therapy; including tamsulosin (**see section 4.4**), blurred vision and visual impairment.
Cardiac disorders		*Frequency not known:* atrial fibrillation, dysrrhythmia, tachycardia and dyspnoea.
Respiratory, thoracic and mediastinal disorders)		*Frequency not known:* epistaxis.
Skin and	*Less frequent:* alopecia	*Frequency not known:*

subcutaneous tissue disorders	(primarily body hair loss) and hypertrichosis.	erythema multiforme and dermatitis exfoliative.
Reproductive system and breast disorders	*Frequency not known:* testicular swelling pain and testicular swelling.	

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222 **Reporting of suspected adverse reactions**

223 Reporting suspected adverse reactions after authorisation of the medicine is
224 important. It allows continued monitoring of the benefit/risk balance of the medicine.
225 Healthcare professionals are asked to report any suspected adverse reactions to
226 SAHPRA via the 6.04 Adverse Drug Reaction Reporting Form, found online under
227 SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla
228 Medpro (Pty) Ltd (by e-mail: drugsafetysa@cipla.com.

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230 **4.9 Overdose**

231 **Dutasteride:** There is no specific antidote for dutasteride therefore, in cases of
232 suspects overdosage symptomatic and supportive treatment should be given as
233 appropriate.

234 **Tamsulosin:** In case of acute hypotension occurring after overdosage with tamsulosin
235 hydrochloride cardiovascular support should be given. Restoration of blood pressure
236 and normalisation of heart rate may be accomplished by lying the patient down. If this
237 is inadequate, administration of volume expanders and if necessary, vasopressors
238 should then be used, and renal function should be monitored and supported as
239 needed. Laboratory data indicate that tamsulosin hydrochloride is 94 % to 99 %

protein bound; therefore, dialysis is unlikely to be of benefit in removing tamsulosin from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A21.12 Hormone Inhibitors

Mechanism of action:

Dutasteride-tamsulosin is a combination of two medicines: dutasteride, a dual 5 α-reductase inhibitor (5 ARI) and tamsulosin hydrochloride, an antagonist of α_{1a}-adrenoreceptors.

Dutasteride inhibits both type 1 and type 2, 5α-reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for hyperplasia of glandular prostatic tissue. Tamsulosin inhibits α_{1a} adrenergic receptors in the stromal prostatic smooth muscle and bladder neck. Approximately 75 % of the α1-receptors in the prostate are of the α_{1a} subtype.

The pharmacodynamic effects of tamsulosin-dutasteride have not been studied.

Dutasteride:

Dutasteride lowers DHT levels, reduces prostate volume and improves lower urinary tract symptoms. The maximum effect of dutasteride on the reduction on DHT is dose-dependent and is observed within one to two weeks.

Tamsulosin:

Tamsulosin increases maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra, thereby relieving obstruction.

5.2 Pharmacokinetic properties:

An interaction study did not demonstrate a Pharmacokinetic or Pharmacodynamic interaction between tamsulosin and dutasteride. Therefore, the Pharmacokinetic characteristics of the individual components are valid also for the combination of both medicines.

Absorption:

Dutasteride

After oral administration of a single 0,5 mg dose of dutasteride, peak serum concentrations of dutasteride are reached within one to three hours. Absolute bioavailability is approximately 60 %. Food does not have a clinically significant effect on the bioavailability of dutasteride.

Tamsulosin

Tamsulosin hydrochloride is absorbed from the intestine and is almost completely bioavailable. Tamsulosin hydrochloride exhibits linear kinetics, following single and

multiple administration, with achievement of steady state concentrations by the fifth day of once daily dosing. The modified release formulation of tamsulosin is food dependent. The rate of absorption can be promoted by the patient always taking tamsulosin hydrochloride approximately 30 minutes after the same meal each day.

Distribution:

Dutasteride

Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride plasma protein-binding is higher than 99,5%.

Following daily dosing, dutasteride serum concentrations achieve 65 % of steady state concentration after one month and approximately 90 % after three months. Steady state serum concentrations (C_{ss}) of approximately 40 ng/mL are achieved after six months of dosing 0,5 mg once a day. Similarly, to serum, dutasteride concentrations in semen achieved steady state at six months. After 52 weeks of therapy, semen dutasteride concentrations averaged 3,4 ng/mL (range 0,4 to 14 ng/mL). Dutasteride partitioning from serum into semen average 11,5 %.

Tamsulosin

The mean steady-state apparent volume of distribution of tamsulosin hydrochloride suggested distribution into extracellular fluids in the body.

Tamsulosin hydrochloride is extensively bound to human plasma proteins (94 to 99 %), primarily alpha-1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL).

Biotransformation:

Dutasteride

In vitro, dutasteride is metabolised by human cytochrome P450 isoenzyme CYP3A4 to two minor monohydroxylated metabolites, but it is not metabolised by CYP1A2, CYP2C9, CYP2C19 or CYP2D6.

Three major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and two minor metabolites (6,4'-dihydroxydutasteride and 15-hydrodutasteride) have been detected in serum.

Tamsulosin

There is no enantiomeric bioconversion from tamsulosin hydrochloride (R-isomer) to the S-isomer in humans. Tamsulosin hydrochloride undergoes extensive hepatic metabolism by cytochrome P450 enzymes and less than 10 % of the dose is excreted in urine unchanged. *In vitro* results indicate that CYP3A4 and CYP2D6 are involved in metabolism of tamsulosin as well as some minor participation of other CYP isoenzymes. Inhibition of hepatic medicine metabolising enzymes may lead to increased exposure to tamsulosin. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulphate prior to renal excretion.

Elimination:

Dutasteride

Dutasteride is extensively metabolised. Following oral dosing of dutasteride 0,5 mg/day to steady state in humans, 1,0 to 15,4 % (mean of 5,4 %) of the administered

dose is excreted as dutasteride in the faeces. The remainder is excreted in the faeces as four major metabolites comprising 39 %, 21 %, 7 % and 7 % each medicine-related material and six minor metabolites (less than 5 % each). Less than 0,1 % of the unchanged dutasteride dose is detected in human urine.

At low serum concentrations (less than 3 ng/mL), dutasteride is cleared by both the concentration-dependent and concentration-independent elimination pathways. Single doses of 5 mg or less showed evidence of clearance and a half-life of three to nine days.

At serum concentrations above 3 ng/mL, dutasteride is cleared slowly (0,35 to 0,58 L/h) primarily by linear, non-saturable elimination with terminal half-life of three to five weeks. At therapeutic concentrations, the terminal half-life of dutasteride is three to five weeks and following repeat dosing of 0,5 mg/day, the slower clearance dominates and the total clearance is linear and concentration-independent. Serum concentrations remain detectable (greater than 0,1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

Tamsulosin

Tamsulosin half-life is 5 to 7 hours. Approximately 10 % is excreted unchanged in urine.

Special populations:

Pharmacokinetic studies have not been conducted on special patient populations for dutasteride-tamsulosin. The following statements reflect the information available on the individual components.

The elderly

Dutasteride: Exposure (AUC and C_{max} values) of dutasteride, was not statistically different when comparing age groups. No differences in medicine effect as measured by DHT reduction were observed between age groups. Results indicated that no dutasteride dose-adjustment based on age is necessary.

Tamsulosin: The pharmacokinetic disposition of tamsulosin hydrochloride may be slightly prolonged in elderly males compared to young, healthy male volunteers. Intrinsic clearance is independent of tamsulosin hydrochloride binding to AAG, but diminished with age, resulting in a 40 % overall higher exposure (AUC) in subjects of age 55 to 75 years compared to subjects of age 20 to 32 years.

Renal impairment

Dutasteride: The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0,1 % of a steady-state 0,5 mg dose of dutasteride is recovered in human urine, therefore no adjustment in dosage is anticipated for patients with renal impairment.

Tamsulosin: Changes in renal function do not have a major impact on the clearance of tamsulosin, because the medicine is mainly eliminated by hepatic metabolism. Therefore, dose adjustment is not necessary in patients with renal impairment. However, renal disease can alter the levels of plasma proteins.

The level of α1-AGP increases and the level of albumin generally decrease in patients with reduced renal function.

Importantly, as tamsulosin is predominantly cleared by the liver, the AUC increase is more closely correlated with the higher concentration of α1-AGP than with creatinine clearance (CL_{CR}), thus indicating that reduced CL_{CR}, by itself, does not substantially alter tamsulosin pharmacokinetics.

However, patients with end-stage renal disease (CL_{cr} < 10 mL/min1,73 m^2) have not been studied.

Hepatic impairment

Dutasteride: The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied (see **section 4.4**)

Tamsulosin: The pharmacokinetics of tamsulosin hydrochloride have been compared in subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and normal subjects. While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride does not change significantly with only a modest (32 %) change in intrinsic clearance of unbound tamsulosin hydrochloride. Therefore, patients with moderate hepatic dysfunction do not require an adjustment in tamsulosin hydrochloride dosage. Tamsulosin hydrochloride has not been studied in patients with severe hepatic dysfunction.

5.3 Preclinical safety data

Non-clinical studies have not been conducted with UROMAX CO. Dutasteride and tamsulosin hydrochloride individually have been extensively evaluated in animal toxicity tests and findings were consistent with the known pharmacological actions of 5-alpha-reductase inhibitors and alpha1- adrenoceptor antagonists. The following statements reflect the information available on the individual components.

Dutasteride:

General toxicity, genotoxicity and carcinogenicity studies did not show any particular risk to humans.

Reproduction toxicity studies in male rats have shown a decreased weight of the prostate and seminal vesicles, decreased secretion from accessory genital glands and a reduction in fertility indices (caused by the pharmacological effect of dutasteride). The clinical relevance of these findings is unknown.
As with other 5-alpha-reductase inhibitors, feminisation of male foetuses in rats and rabbits has been noted when dutasteride was administered during gestation. Dutasteride has been found in blood from female rats after mating with dutasteride treated males. When dutasteride was administered during gestation to primates, no feminisation of male foetuses was seen at blood exposures sufficiently in excess of those likely to occur via human semen. It is unlikely that a male foetus will be adversely affected following seminal transfer of dutasteride.

Tamsulosin:

General toxicity and genotoxicity studies did not show any particular risk to humans other than those related to the pharmacological properties of tamsulosin.

In carcinogenicity studies in rats and mice, tamsulosin hydrochloride produced an increased incidence of proliferative changes of the mammary glands in females. These findings, which are probably mediated by hyperprolactinaemia and only occurred at high dose levels, are regarded as not clinically relevant.

High doses of tamsulosin hydrochloride resulted in a reversible reduction in fertility in male rats considered possibly due to changes of semen content or impairment of ejaculation. Effects of tamsulosin on sperm counts or sperm function have not been evaluated.

Administration of tamsulosin hydrochloride to pregnant female rats and rabbits at higher than the therapeutic dose showed no evidence of foetal harm.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contents of hard-shell capsule:

- Black iron oxide (E172)
- Gelatine
- Red iron oxide (E172)
- Titanium dioxide (E171)
- Yellow iron oxide (E172)

Contents of dutasteride soft gel capsule:

- Butylhydroxytoluene (E321)
- Gelatine
- Glycerol
- Propylene glycol, monocaprylate type II
- Titanium dioxide (E171)

Contents of tamsulosin pellets:

- Calcium stearate
- Cellulose microcrystalline
- Dibutyl sebacate
- Methacrylic acid-ethyl acrylate copolymer (1:1)
- Polysorbate 80
- Silica, colloidal hydrous

Black ink composition:

- Black iron oxide (E172)
- Potassium hydroxide (E525)
- Propylene glycol (E1520)
- Shellac (E904)
- Strong ammonia solution (E527)

Contains antioxidant and preservative: butylhydroxytoluene 0,006 % *w/w*

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C. UROMAX CO hard capsules must be used within 90 days of opening.

Keep out of reach of children.

6.5 Nature and contents of container

UROMAX CO is marketed in HDPE bottles that are fitted with silica gel desiccant-containing polypropylene caps in the following packs:

- 7 hard capsules in 35 mL bottle
- 30 hard capsules in 100 mL bottle
- 90 hard capsules in 250 mL bottle

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Dutasteride is absorbed through the skin, therefore contact with leaking capsules must be avoided. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water **(see section 4.4)**.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

54/18.10/0097

9 DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

13 October 2020

10 DATE OF REVISION OF THE TEXT

Not applicable.