SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE:

DUODART Capsules

0,5 mg dutasteride/0,4 mg tamsulosin hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each capsule contains 0,5 mg dutasteride (0,01 % *m/m* butylhydroxytoluene, as the antioxidant) and 0,4 mg tamsulosin hydrochloride.

The capsule shell contains < 0,1 mg FD&C Yellow 6 per capsule.

Sugar-free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

An oblong, hard-shell capsule with a brown body and an orange cap, printed with 'GS 7CZ' on one side in black ink. Each capsule contains an oblong, dull yellow soft gelatin capsule and white to off-white pellets.

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:

Adult males (including elderly):

The recommended dose of DUODART is one capsule taken orally approximately 30 minutes after the same meal each day (see section 5.2 Absorption).

Renal impairment:

The effect of renal impairment on DUODART pharmacokinetics has not been studied. However, no adjustment in dosage is anticipated for patients with renal impairment (see section 5.2 Renal impairment).

Hepatic impairment:

The effect of hepatic impairment on DUODART pharmacokinetics has not been studied (see section 4.4 and section 5.2 Hepatic impairment).

Paediatric population:

DUODART is contraindicated in the paediatric population (under 18 years of age) (see section 4.3 and section 4.6).

Method of administration:

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

4.3 Contraindications:

DUODART is contraindicated in patients with known hypersensitivity to dutasteride, other 5α-reductase inhibitors, tamsulosin hydrochloride or any component of the medicine.

DUODART is contraindicated for use in women and children (see section 4.6).

DUODART is contraindicated in patients with a history of orthostatic hypotension.

DUODART is contraindicated in severe hepatic impairment.

4.4 Special warnings and precautions for use:

Prostate cancer:

In a 4-year study of over 8 000 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2,5 ng/mL and 10,0 ng/mL (the REDUCE study), 1 517 men were diagnosed with prostate cancer. There was a higher incidence of Gleason 8-10 prostate cancers in the dutasteride group (n = 29, 0,9 %) compared to the placebo group (n = 19, 0,6 %). There was no increased incidence in Gleason 5-6 or 7-10 prostate cancers.

In an additional 2-year follow-up study with the original patients from the dutasteride chemoprevention study (REDUCE), there was a higher incidence of new prostate cancers in the dutasteride group (n=14,1.2% compared to the placebo group (n=7,0.7%). However, no new cases of Gleason 8–10 prostate cancers were identified in the 2-year follow-up study. Men taking DUODART should be regulatory evaluated for prostate cancer risk, including PSA testing.

Long-term follow up (up to 18 years) of another 5-ARI (finasteride) in a chemoprevention study showed no statistically significant difference between finasteride and placebo in the rates of overall survival (HR 1,02, 95 % CI 0,97-1,08) or survival after prostate cancer diagnoses (HR 1,01, 95 % CI 0,85-1,20).

Prostate specific antigen (PSA):

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

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

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

Treatment with DUODART 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 DUODART. If clinicians 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.

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

Cardiovascular adverse events:

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

In two 4-year clinical studies, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low (≤ 1 %) and variable between the studies.

In a meta-analysis of 12-randomised, placebo- or comparator-controlled clinical studies (n=18 802) that evaluated the risks of developing cardiovascular adverse events from the use of dutasteride (by comparison with controls), no consistent statistically significant increase in the risk of heart failure (RR 1,05; 95 % CI 0,71, 1,57), acute myocardial infarction (RR 1,00; 95 % CI 0,77, 1,30) or stroke (RR 1,20; 95 % CI 0,88, 1,64) were found.

Breast cancer:

There have been rare reports of male breast cancer reported in men taking dutasteride in clinical trials and during the post-marketing period. However, epidemiological studies showed no increase in the risk of developing male breast cancer with the use of 5-ARIs. 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 DUODART 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 DUODART. 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 DUODART in order to ensure that appropriate measures will be in 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.

Leaking capsules:

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

Inhibitors of CYP3A4 and CYP2D6:

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). DUODART is therefore not recommended in patients taking a strong CYP3A4 inhibitor (e.g. erythromycin), a strong or moderate CYP2D6 inhibitor, a combination of both CYP3A4 and CYP2D6 inhibitors, or in patients known to be poor metabolisers of CYP2D6.

Hepatic impairment:

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolised and has a half-life of 3 to 5 weeks, caution should be used in the administration of DUODART to patients with liver disease.

Excipient warnings: The capsule shell contains the colouring agent FD&C yellow 6, which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction:

There have been no interaction studies for DUODART. The following statements reflect 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 the presence of inhibitors of CYP3A4.

Phase II data showed a decrease in clearance of dutasteride when co-administered 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 *in vitro* nor induces cytochrome P450 isoenzymes CYP1A, CYP2B, and CYP3A in rats and dogs *in vivo*.

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.

Although specific interaction studies were not performed with other medicines, approximately 90 % of the subjects in large Phase III studies receiving dutasteride were taking other medications concomitantly. No clinically significant adverse interactions were observed in clinical trials when dutasteride was co-administered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, 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 agents, PDE5 inhibitors and other alpha-1 adrenergic blockers. DUODART should not be used in combination with other alpha-1 adrenergic blockers.

Concomitant administration of tamsulosin hydrochloride and ketoconazole (a strong CYP3A4 inhibitor) resulted 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) resulted 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) resulted in a decrease in the clearance (26 %) and an increase in the AUC (44 %) of tamsulosin hydrochloride. Caution should be used when DUODART is used in combination with cimetidine.

A definitive interaction study between tamsulosin hydrochloride and warfarin has not been conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

DUODART is contra-indicated for use in women.

Dutasteride: DUODART has not been studied in women, because pre-clinical data suggests that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external organs in a male foetus carried by a woman exposed to dutasteride.

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

Lactation:

DUODART is contra-indicated for use in women.

It is not known whether dutasteride or tamsulosin are excreted in breast milk.

Fertility:

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

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

4.7 Effects on the ability to drive and use machines:

DUODART 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 DUODART.

4.8 Undesirable effects:

There have been no clinical trials conducted with DUODART; however, co-administration information is available from the CombAT (Combination of dutasteride and tamsulosin) study, a comparison of dutasteride 0,5 mg and tamsulosin 0,4 mg once daily for four years as co-administration or as monotherapy.

Information on the adverse event profiles of the individual components (dutasteride and tamsulosin) is also provided.

Dutasteride and Tamsulosin Co-administration:

Clinical Trial Data:

The following investigator-judged medicine-related adverse events (with a cumulative incidence of greater than or equal to 1 %) have been reported during the CombAT study (Table reflects selective safety information).

Adverse Reaction	Incidence during treatment period			
	Year 1	Year 2	Year 3	Year 4
Combination[a] (n)	(n = 1 610)	(n = 1 428)	(n = 1 283)	(n = 1 200)
Dutasteride	(n = 1 623)	(n = 1 464)	(n = 1 325)	(n = 1 200)
Tamsulosin	(n = 1 611)	(n = 1 468)	(n = 1 281)	(n = 1 112)
Impotence[b]				
Combination	6 %	2 %	< 1 %	< 1 %
Dutasteride	5 %	2 %	< 1 %	< 1 %
Tamsulosin	3 %	1 %	< 1 %	1 %
Altered (decreased) libido[b]				
Combination	5 %	< 1 %	< 1 %	0 %
Dutasteride	4 %	1 %	< 1 %	0 %
Tamsulosin	2 %	< 1 %	< 1 %	< 1 %
Ejaculation disorders[b]				
Combination	9 %	1 %	< 1 %	< 1 %
Dutasteride	1 %	< 1 %	< 1 %	< 1 %
Tamsulosin	3 %	< 1 %	< 1 %	< 1 %
Breast disorders[c]				
Combination	2%	< 1 %	< 1 %	< 1 %
Dutasteride	2%	1 %	< 1 %	< 1 %
Tamsulosin	< 1 %	< 1 %	< 1 %	0 %
Dizziness				
Combination	1 %	< 1 %	< 1 %	< 1 %
Dutasteride	< 1 %	< 1 %	< 1 %	< 1 %
Tamsulosin	1 %	< 1 %	< 1 %	0 %

[a] Combination = dutasteride 0,5 mg once daily plus 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.

Dutasteride Monotherapy:

Post-marketing Data:

The following side effects have been reported:

Immune system disorders: allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema

Psychiatric disorders: depressed mood

Skin and subcutaneous tissue disorders: alopecia (primarily body hair loss), hypertrichosis

Reproductive system and breast disorders: testicular pain and testicular swelling.

Tamsulosin Monotherapy:

Clinical Trial Data:

Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 and < 1/10), uncommon (≥ 1/1 000 and < 1/100), rare (≥ 1/10 000 and < 1/1 000) and very rare (< 1/10 000) including isolated reports.

Immune system disorders:

Uncommon: rash, pruritus, urticaria

Rare: angioedema

Very rare: Stevens-Johnson syndrome

Nervous system disorders:

Common: dizziness

Rare: Syncope

Cardiac disorders:

Uncommon: palpitations

Vascular disorders:

Uncommon: postural hypotension

Respiratory, thoracic and mediastinal disorders:

Uncommon: rhinitis

Gastrointestinal disorders:

Uncommon: constipation, diarrhoea, vomiting

Reproductive system and breast disorders:

Common: abnormal ejaculation

Very rare: priapism

General disorders and administration site disorders:

Uncommon: asthenia

Post-marketing Data:

The following side effects have been reported:

Eye disorders: 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, visual impairment

Cardiac disorders: In addition, atrial fibrillation, dysrhythmia, tachycardia and dyspnoea have been reported in association with tamsulosin use

Respiratory, thoracic and mediastinal disorders: epistaxis

Gastrointestinal disorders: dry mouth

Skin and subcutaneous tissue disorders: erythema multiforme and dermatitis exfoliative.

Reporting of side effects:

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers 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

4.9 Overdose:

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

Tamsulosin: In case of acute hypotension occurring after overdosage with tamsulosin hydrochloride cardiovascular support should be given. Restoration of blood pressure and normalisation of heart rate may be accomplished by lying the patient down. If this is inadequate, administration of volume expanders and if necessary, vasopressors should then be used, and renal function should be monitored and supported as 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:

A 21.12 Hormone Inhibitors

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 5 alpha-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 α_1-receptors in the prostate are of the α_{1a} subtype.

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

Dutasteride: Dutasteride lowers DHT levels, reduces prostate volume, improves lower urinary tract symptoms.

The maximum effect of daily doses 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:

The single dose bioequivalence study was performed in both the fasted and fed states. A 30 % reduction in C_{max} was observed for the tamsulosin component of dutasteride-tamsulosin in the fed state compared to the fasted state. Food had no effect on AUC of tamsulosin.

Absorption:

Dutasteride: Following administration of a single 0,5 mg dose, peak serum concentrations of dutasteride occur within 1 to 3 hours.

Absolute bioavailability in man is approximately 60 %. The bioavailability of dutasteride is not affected by food.

Tamsulosin: Tamsulosin hydrochloride is absorbed from the intestine and is almost completely bioavailable. Tamsulosin hydrochloride exhibits linear kinetics, following single and multiple dosing, with achievement of steady state concentrations by the fifth day of once-a-day dosing. The rate of absorption of tamsulosin hydrochloride is reduced by a recent meal. Uniformity 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 is highly bound to plasma proteins (greater 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 averaged 11,5 %.

Tamsulosin: The mean steady-state apparent volume of distribution of tamsulosin hydrochloride after intravenous administration to ten healthy male adults was 16 L, which is suggestive of 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).

Metabolism:

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

In human serum, following dosing to steady state, unchanged dutasteride, three major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), have been detected.

Tamsulosin: There is no enantiomeric bioconversion from tamsulosin hydrochloride (R(-) isomer) to the S(+) isomer in humans. Tamsulosin hydrochloride is extensively metabolised by cytochrome P450 enzymes in the liver and less than 10 % of the dose is excreted in urine unchanged. However, the pharmacokinetic profile of the metabolites in humans has not been established. *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 drug 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 of drug-related material and six minor metabolites (less than 5 % each).

Only trace amounts of unchanged dutasteride (less than 0,1 % of the dose) are 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 greater than 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 Patient Populations:

No pharmacokinetic studies have been conducted on special patient populations for dutasteride-tamsulosin. The following statements reflect the information available on the individual components.

- **Elderly:**

  Dutasteride: Exposure of dutasteride, represented by AUC and C_{max} values, 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 diminishes 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: The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate ($30 \leq CL_{cr} < 70$ mL/min/1,73 m^2) or moderate-severe ($10 \leq CL_{cr} < 30$ mL/min/1,73 m^2) renal impairment and 6 normal subjects ($CL_{cr} > 90$ mL/min/1,73 m^2). While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to alpha-1 acid glycoprotein (AAG), the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in tamsulosin hydrochloride capsules dosing. However, patients with end-stage renal disease ($CL_{cr} < 10$ mL/min/1,73 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.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Mono-di-glycerides of caprylic/capric acid, butylhydroxytoluene, gelatin, glycerol, titanium dioxide, purified water, microcrystalline cellulose, methacrylic acid - ethyl acrylate copolymer, ferric oxide, talc, triethyl citrate, carrageenan, potassium chloride, hypromellose, triglycerides, medium chain, lecithin, carnauba wax, maize starch, yellow iron oxide, red iron oxide, FD&C Yellow 6.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

24 months.

6.4 Special precautions for storage:

Store at or below 25 ºC.

Keep the container well closed.

6.5 Nature and contents of container:

7, 30 or 90 capsules will be packed into opaque, white high-density polyethylene (HDPE) bottles with polypropylene child-resistant closures with induction-seal liners.

6.6 Special precautions for disposal:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBER:

44/21.12/0850

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

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