SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

SWIFSUL 0,5 mg / 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 0,367 mg tamsulosin).

Excipient(s) with known effect:

- Lecithin: each capsule contains traces of lecithin (may contain soya oil).
- Propylene glycol monocaprylate : each capsule contains 299,46 mg propylene glycol monocaprylate (equivalent to 112,80 mg propylene glycol) and traces of propylene glycol in the black ink.
- Sodium laurylsulfate: each capsule contains 0,01 mg sodium.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules.

Oblong hard gelatine capsule Nº 0EL, of 24.2 mm x 7.7 mm approx, body of brown colour and cap of beige colour with black code C001 on the cap.

Each hard capsule contains:

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SWIFSUL is indicated for the 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 SWIFSUL is one capsule taken orally approximately 30 minutes after the same meal each day (see section 5.2).

Special populations

Renal impairment

The effect of renal impairment on SWIFSUL pharmacokinetics has not been studied. However, no adjustment in dosage is anticipated for patients with renal impairment (see section 4.4 and section 5.2).

Hepatic impairment

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

Method of administration

For oral use.

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

- Hypersensitivity to the dutasteride, tamsulosin, other 5-alpha reductase inhibitors, soya, peanut or to any of the excipients of SWIFSUL listed in section 6.1.
- Women, children and adolescents.
- Patients with a history of orthostatic hypotension.
- Patients with 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 capsules (see section 4.6). If contact is made with leaking capsules, the contact area should be washed immediately with soap and water.

Prostate cancer and high-grade tumour

The clinical study investigated the effect of dutasteride 0,5 mg daily on patients with a high risk for prostate cancer (including men 50 to 75 years of age with PSA levels of 2,5 to 10

ng/mL and a negative prostate biopsy 6 months before study enrolment) compared to placebo. Results of this study revealed a higher incidence of Gleason 8 – 10 prostate cancers in dutasteride treated men (0,9 %) compared to placebo (0,6 %). The relationship between dutasteride and Gleason 8 – 10 prostate cancers is not clear. Thus, men taking SWIFSUL should be regularly evaluated for prostate cancer.

Prostate specific antigen (PSA)

Serum prostate-specific antigen (PSA) concentration is an important component in the detection of prostate cancer.

SWIFSUL causes a decrease in mean serum PSA levels by approximately 50 %, after 6 months of treatment.

Patients receiving SWIFSUL should have a new PSA baseline established after 6 months of treatment with SWIFSUL. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on SWIFSUL may signal the presence of prostate cancer or noncompliance to therapy with SWIFSUL and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5-alpha reductase inhibitor. In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.

Treatment with SWIFSUL 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 SWIFSUL. If medical practitioners elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing SWIFSUL therapy, no adjustment to its value appears necessary.

Digital rectal examination, as well as other evaluations for prostate cancer or other conditions which can cause the same symptoms as BPH, must be performed on patients prior to initiating therapy with SWIFSUL and periodically thereafter.

Cardiovascular adverse events

In 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 alpha1-adrenoceptor antagonist, primarily tamsulosin, than it was among subjects not taking the combination.

Breast neoplasia

There have been 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-alpha reductase inhibitors. Medical practitioners should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge.

Renal impairment

The treatment of patients with severe renal impairment (creatinine clearance of less than 10 mL/min) should be approached with caution as these patients have not been studied.

Hypotension

Orthostatic: A reduction in blood pressure can occur during treatment with tamsulosin, as a result of which, syncope can occur. Patients beginning treatment with SWIFSUL should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have resolved.

In order to minimise the potential for developing postural hypotension the patient should be haemodynamically stable on an alpha1-adrenoceptor antagonist prior to initiating use of PDE5 inhibitors.

Symptomatic: Caution is advised when alpha adrenergic blocking medicines including tamsulosin are co-administered with PDE5 inhibitors (e.g. sildenafil, tadalafil, vardenafil). $Alpha_1$-adrenoceptor antagonists and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two medicine classes can potentially cause symptomatic hypotension (see section 4.5).

Intraoperative Floppy Iris Syndrome

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. IFIS may increase the risk of eye complications during and after the operation. The initiation of therapy with SWIFSUL in patients for whom cataract surgery is scheduled is therefore not recommended

During pre-operative assessment, cataract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with SWIFSUL in order to ensure that appropriate measures will be in place to manage the IFIS during surgery.

Discontinuing tamsulosin 1 – 2 weeks prior to cataract surgery is anecdotally considered helpful, but the benefit and duration of stopping therapy prior to cataract surgery has not yet been established.

Leaking Capsule

Dutasteride is absorbed through the skin, therefore, women, children and adolescents 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).

Tamsulosin hydrochloride is therefore not recommended in patients taking a strong CYP3A4 inhibitor and should be used with caution in patients taking a moderate CYP3A4 inhibitor, 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

SWIFSUL has not been studied in patients with liver disease. Caution should be used in the administration of SWIFSUL to patients with mild to moderate hepatic impairment (see section 4.2, section 4.3 and section 5.2).

Excipients

SWIFSUL contains:

- Traces of soya lecithin. If you are allergic to peanut or soya, do not use SWIFSUL (see section 4.5).
- 299,46 mg propylene glycol monocaprylate (equivalent to 112.80 mg propylene glycol) in each capsule and traces of propylene glycol in the black ink.

- Less than 1 mmol sodium (23 mg) per capsule, that is to say essentially “sodium-free”.

4.5 Interactions with other medicines and other forms of interaction

No interaction studies have been performed for SWIFSUL. The following statements reflect the information available on the individual components.

Dutasteride

For information on the decrease of serum PSA levels during treatment with dutasteride and guidance concerning prostate cancer detection, please see section 4.4.

Effects of other medicines on the pharmacokinetics of dutasteride

Dutasteride is mainly eliminated via metabolism. *In vitro* studies indicate that this metabolism is catalysed by CYP3A4 and CYP3A5. No formal interaction studies have been performed with potent CYP3A4 inhibitors. However, in a population pharmacokinetic study, dutasteride serum concentrations were on average 1,6 to 1,8 times greater, respectively, in a small number of patients treated concurrently with verapamil or diltiazem (moderate inhibitors of CYP3A4 and inhibitors of P-glycoprotein) than in other patients.

Long-term combination of dutasteride with medicines that are potent inhibitors of the enzyme CYP3A4 (e.g., ritonavir, indinavir, nefazodone, itraconazole, ketoconazole administered orally) may increase serum concentrations of dutasteride. Further inhibition of 5-alpha reductase at increased dutasteride exposure, is not likely. However, a reduction of the dutasteride dosing frequency can be considered if side effects are noted. It should be noted that in the case of enzyme inhibition, the long half-life may be further prolonged and it can take more than 6 months of concurrent therapy before a new steady state is reached.

Administration of 12 g cholestyramine one hour after a 5 mg single dose of dutasteride did not affect the pharmacokinetics of dutasteride.

Effects of dutasteride on the pharmacokinetics of other medicines

In a small study in healthy men, dutasteride (0,5 mg daily) had no effect on the pharmacokinetics of tamsulosin or terazosin. There was also no indication of a pharmacodynamic interaction in this study.

Dutasteride has no effect on the pharmacokinetics of warfarin or digoxin. This indicates that dutasteride does not inhibit/induce CYP2C9 or the transporter P-glycoprotein. *In vitro*

interaction studies indicate that dutasteride does not inhibit the enzymes CYP1A2, CYP2D6, CYP2C9, CYP2C19 or CYP3A4.

Tamsulosin

Concomitant administration of tamsulosin hydrochloride with medicines which can reduce blood pressure, including anaesthetic medicines, PDE5 inhibitors and other alpha$_1$-adrenoceptor antagonists could lead to enhanced hypotensive effects. Dutasteride-tamsulosin should not be used in combination with other alpha$_1$-adrenoceptor antagonists.

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 strong 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 dutasteride-tamsulosin is used in combination with cimetidine.

A definitive medicine interaction study between tamsulosin hydrochloride and warfarin has not been conducted. Results from limited *in vitro* and *in vivo* studies are inconclusive. Diclofenac and warfarin, however, may increase the elimination rate of tamsulosin. Caution should be exercised with concomitant administration of warfarin and tamsulosin hydrochloride.

No interactions have been seen when tamsulosin hydrochloride was given concomitantly with either atenolol, enalapril, nifedipine or theophylline. Concomitant furosemide brings about a fall in plasma levels of tamsulosin, but as levels remain within the normal range posology need not be adjusted.

In vitro neither diazepam nor propranolol, trichlormethiazide, chlormadinon, amitryptyline, diclofenac, glibenclamide and simvastatin changes the free fraction of tamsulosin in human

plasma. Neither does tamsulosin change the free fractions of diazepam, propranolol, trichlormethiazide, and chlormadinone.

4.6 Fertility, pregnancy and lactation

SWIFSUL is contraindicated for use by women (see section 4.3). There have been no studies to investigate the effect of SWIFSUL on pregnancy, lactation and fertility. The following statements reflect the information available from studies with the individual components.

Pregnancy

Dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male foetus, inhibit the development of the external genitalia of the foetus (see section 4.4). Small amounts of dutasteride have been recovered from the semen in subjects receiving dutasteride. It is not known whether a male foetus will be adversely affected if his mother is exposed to the semen of a patient being treated with dutasteride (the risk of which is greatest during the first 16 weeks of pregnancy).

When the patient's partner is or may potentially be pregnant it is recommended that the patient avoids exposure of his partner to semen by use of a condom.

Breastfeeding

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

Fertility

Dutasteride has been reported to affect semen characteristics (reduction in sperm count, semen volume, and sperm motility) in healthy men. The possibility of reduced male fertility cannot be excluded.

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

4.7 Effects on ability to drive and use machines

No studies on the effects of SWIFSUL on the ability to drive and use machines have been performed. However, patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking SWIFSUL.

It is not always possible to predict to what extent SWIFSUL may interfere with the daily activities of a patient.

Patients should ensure that they do not engage in the above activities until they are aware of the measure to which SWIFSUL affects them.

4.8 Undesirable effects

Tabulated summary of adverse reactions

System organ class	**Adverse reactions**	**Dutasteride + tamsulosin[a]**	**Dutasteride**	**Tamsulosin[c]**
Nervous system disorders	Syncope	-	-	Less frequent
	Dizziness	Frequent	-	Frequent
	Headache	-	-	Less frequent
Cardiac disorders	Cardiac failure (Composite term[1])	Less frequent	Less frequent[d]	-
	Palpitations	-	-	Less frequent
Vascular disorders	Orthostatic hypotension	-	-	Less frequent
Respiratory, thoracic and mediastinal disorders	Rhinitis	-	-	Less frequent
Gastro-intestinal disorders	Constipation	-	-	Less frequent
	Diarrhoea	-	-	Less frequent
	Nausea	-	-	Less frequent
	Vomiting	-	-	Less frequent
Skin and sub-cutaneous disorders	Angioedema	-	-	Less frequent
	Stevens-Johnson syndrome	-	-	Less frequent
	Urticaria	-	-	Less frequent
	Rash	-	-	Less frequent
	Pruritus	-	-	Less frequent

Reproduc-tive system and breast disorders	Priapism	-	-	Less frequent
	Impotence[3]	Frequent	Frequent[b]	-
	Altered (decreased) libido[3]	Frequent	Frequent[b]	-
	Ejaculation disorders[3^]	Frequent	Frequent[b]	Frequent
	Breast disorders[2]	Frequent	Frequent[b]	-
General disorders and admini-stration site disorders	Asthenia	-	-	Less frequent

[a]. Dutasteride + tamsulosin: from CombAT study - the frequencies of these adverse events decrease over time of treatment, from year 1 to year 4.

[b.] Dutasteride: from BPH monotherapy clinical studies.

[c.] Tamsulosin: from EU Core Safety Profile for tamsulosin.

[d.] REDUCE study.

[1]. Cardiac failure composite term comprised of cardiac failure congestive, cardiac failure, left ventricular failure, cardiac failure acute, cardiogenic shock, left ventricular failure acute, right ventricular failure, right ventricular failure acute, ventricular failure, cardiopulmonary failure, congestive cardiomyopathy.

[2]. Includes breast tenderness and breast enlargement.

[3]. 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 not known.

[^]. Includes semen volume decreased.

Description of selected adverse reactions

Other data

The REDUCE study revealed a higher incidence of Gleason 8-10 prostate cancers in dutasteride treated men compared to placebo (see sections 4.4 and 5.1). Whether the effect of dutasteride to reduce prostate volume, or study related factors, impacted the results of this study has not been established. The following has been reported in clinical trials and post-marketing use: male breast cancer (see section 4.4).

Post marketing data

Adverse events from world-wide post-marketing experience are identified from spontaneous post-marketing reports; therefore, the true incidence is not known.

Tamsulosin (monotherapy)

During post-marketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with alpha$_1$-adrenoceptor antagonists, including tamsulosin (see section 4.4).

In addition, atrial fibrillation, arrhythmia, tachycardia, dyspnoea, epistaxis, vision blurred, visual impairment, erythema multiforme, dermatitis exfoliative, ejaculation disorder, retrograde ejaculation, ejaculation failure and dry mouth have been reported in association with tamsulosin use. The frequency of events and the role of tamsulosin in their causation cannot be reliably determined.

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 Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/.

4.9 Overdose

No data are available with regard to overdosage of SWIFSUL. The following statements reflect the information available on the individual components.

Dutasteride

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

Tamsulosin

Acute overdose with 5 mg tamsulosin hydrochloride has been reported. Acute hypotension (systolic blood pressure 70 mm Hg), vomiting and diarrhoea were observed which were treated with fluid replacement and the patient could be discharged the same day. 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 sulphate, can be administered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 21.12 Hormone inhibitors
Pharmacotherapeutic group: Alpha-adrenoreceptor antagonist
ATC code: G04CA52

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 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. It relieves obstruction by relaxing smooth muscle in the prostate and urethra, thereby improving voiding symptoms.

5.2 Pharmacokinetic properties

Bioequivalence was demonstrated between dutasteride-tamsulosin and concomitant dosing with separate dutasteride and tamsulosin capsules.

Absorption

Dutasteride

Following oral administration of a single 0,5 mg dutasteride dose, the time to peak serum concentrations of dutasteride is 1 to 3 hours. The absolute bioavailability is approximately 60 %. The bioavailability of dutasteride is not affected by food.

Tamsulosin

Tamsulosin is absorbed from the intestine and is almost completely bioavailable. Both the rate and extent of absorption of tamsulosin are reduced when taken within 30 minutes of a meal. Uniformity of absorption can be promoted by the patient always taking tamsulosin after the same meal. Tamsulosin shows dose proportional plasma exposure.

After a single dose of tamsulosin in the fed state, plasma concentrations of tamsulosin peak at around 6 hours and, in the steady state, which is reached by day 5 of multiple dosing, the mean steady state C_{max} in patients is about two thirds higher than that reached after a single dose. Although this was observed in elderly patients, the same finding would also be expected in younger patients.

Distribution

Dutasteride

Dutasteride has a large volume of distribution (300 to 500 L) and is highly bound to plasma proteins (> 99,5 %). Following daily dosing, dutasteride serum concentrations achieve 65 % of steady state concentration after 1 month and approximately 90 % after 3 months.

Steady state serum concentrations (C_{ss}) of approximately 40 ng/mL are achieved after 6 months of dosing 0,5 mg once a day. 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.

In man tamsulosin is about 99 % bound to plasma proteins. The volume of distribution is small (about 0,2 L/kg).

Biotransformation

Dutasteride

Dutasteride is extensively metabolised *in vivo*. *In vitro*, dutasteride is metabolised by the cytochrome P450 3A4 and 3A5 to three monohydroxylated metabolites and one dihydroxylated metabolite. It is not metabolised by CYP1A2, CYP2C19 or CYP2D6.

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 (see section 4.4 and 4.5). The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulphate prior to renal excretion.

Elimination

Dutasteride

The elimination of dutasteride is dose dependent and the process appears to be described by two elimination pathways in parallel, one that is saturable at clinically relevant concentrations and one that is non saturable.

Dutasteride is extensively metabolised. Following oral dosing of dutasteride 0,5 mg/day to steady state, 1,0 % to 15,4 % (mean of 5,4 %) of the administered dose is excreted as unchanged dutasteride in the faeces. The remainder is excreted in the faeces as 4 major metabolites comprising 39 %, 21 %, 7 %, and 7 % each of drug-related material and 6 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 rapidly by both the concentration dependent and concentration independent elimination pathways. Single doses of 5 mg or less showed evidence of rapid clearance and a short half-life of 3 to 9 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 3 to 5 weeks.

At therapeutic concentrations, following repeat dosing of 0,5 mg/day, the slower, linear elimination pathway is dominating, and the total clearance is linear and concentration-independent, and the half-life is approximately 3 to 5 weeks.

Tamsulosin

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

Due to the absorption rate-controlled pharmacokinetics with tamsulosin modified release capsules, the apparent elimination half-life of tamsulosin in the fed state is approximately 10 hours and in the steady state in patients approximately 13 hours.

Special populations

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 between age groups. Results indicated that no dutasteride dose-adjustment based on age is necessary.

Tamsulosin

The pharmacokinetic disposition of tamsulosin hydrochloride overall exposure (AUC) and half-life indicate that 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, so no clinically significant increase of the dutasteride plasma concentrations is anticipated for patients with renal impairment (see section 4.2).

Tamsulosin

The pharmacokinetics of tamsulosin hydrochloride have been compared in 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 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 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 on the pharmacokinetics of dutasteride in hepatic impairment has not been studied (see section 4.3). Because dutasteride is eliminated mainly through metabolism the plasma levels of dutasteride are expected to be elevated in these patients and the half-life of dutasteride be prolonged (see section 4.2 and section 4.4).

Tamsulosin

The pharmacokinetics of tamsulosin hydrochloride have been compared in ~~8~~ subjects with moderate hepatic dysfunction (Child-Pugh's classification: Grades A and B) and ~~8~~ 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

Hard capsule shell

Black iron oxide (E172)

Gelatin

Red iron oxide (E172)

Titanium dioxide (E171)

Yellow iron oxide (E172)

Contents in Dutasteride Soft Capsule

Butylhydroxytoluene (E321)

Propylene Glycol Monocaprylate, Type II

Soft Capsule Shell

Gelatin

Glycerol

Lecithin (may contain soya oil)

Titanium dioxide (E171)

Triglycerides (medium chain)

Tamsulosin Pellets

Calcium stearate

Dibutyl sebacate

Methacrylic acid - ethyl acrylate copolymer 1:1 dispersion 30 % (also contains sodium laurylsulfate and polysorbate 80)

Microcrystalline cellulose

Polysorbate 80

Silica, colloidal hydrous

Black Ink

Black Iron Oxide (E172)

Potassium Hydroxide

Propylene Glycol

Shellac (E904)

Strong ammonia solution

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 30 °C. Keep the bottle tightly closed. In addition, it should be used within 90 days of opening. Do not use after the expiry date stated on the label.

6.5 Nature and contents of container

White, high density polyethylene (HDPE) bottle with silica gel desiccant contained in the cap.
7 hard capsules in 35 ml bottle.
30 hard capsules in 100 ml bottle.
90 hard capsules in 250 ml bottle.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
Address
1 New Road,
Erand Gardens,
Midrand, 1685
P.O. Box
Private Bag X69
Bryanston, 2021
Telephone number
0860 ADCOCK (232652)
E-mail
info@adcock.com
Medical information e-mail
helpdesk.medinfo@adcock.com

8. REGISTRATION NUMBER(S)

55/21.12/0032

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 August 2023

10. DATE OF REVISION OF THE TEXT

08 August 2023