PROFESSIONAL INFORMATION FOR DUOFLOW

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DUOFLOW 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.
Sugar free.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard
Orange cap and brown body hard capsules containing white to off-white pellets and one yellow soft gelatine capsule with an oily and yellowish liquid.

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 DUOFLOW is one capsule taken orally approximately 30 minutes after the same meal each day (see section 5.2 – Absorption).

Special populations

Renal impairment
The effect of renal impairment on DUOFLOW 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 DUOFLOW pharmacokinetics has not been studied (see sections 4.3 and 5.2 – Hepatic impairment).

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

- Hypersensitivity to dutasteride, other 5-alpha reductase inhibitors, tamsulosin hydrochloride (including tamsulosin induced angio-oedema), soya or any of the excipients (see section 6.1).
- Women and children (see section 4.6).
- Patients with a history or orthostatic hypotension.
- Patients with severe hepatic impairment.

4.4 Special warnings and precautions for use

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). DUOFLOW 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 DUOFLOW to patients with liver disease (see section 4.3 and 5.2).

Combination therapy with tamsulosin and cardiac failure
DUOFLOW 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.
Other data available for dutasteride or alpha1 -adrenoceptor antagonists do not support a conclusion on increased cardiovascular risks (see section 5.1).

Effects on prostate specific antigen (PSA) and prostate cancer detection
Digital rectal examination, as well as other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with DUOFLOW and periodically thereafter.
DUOFLOW causes a decrease in mean PSA levels by approximately 50 % after six months of treatment.
Patients receiving DUOFLOW should have a new PSA baseline established before starting treatment with DUOFLOW and after 6 months of treatment with DUOFLOW. It is recommended to monitor PSA values regularly thereafter.
Any confirmed increase from lowest PSA level while on DUOFLOW may signal the presence of prostate cancer (particularly high grade cancer) or non-compliance to therapy with DUOFLOW 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 DUOFLOW, previous PSA values should be sought for comparison.
Treatment with DUOFLOW 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 DUOFLOW. 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.

Prostate cancer and high grade tumours
It is documented that the REDUCE study, a 4-year, multicentre, randomised, double-blind, placebo controlled 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 the dutasteride group compared to the placebo group. There was no increased incidence in Gleason 5 - 6 or 7 - 10 prostate cancers. Men taking DUOFLOW should be regularly evaluated for prostate cancer risk including PSA testing.

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 (see section 5.1). 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 DUOFLOW 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 DUOFLOW 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 DUOFLOW 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.

Excipients with known effects
This medicinal product contains the colouring agent Sunset Yellow (E110), and lecithin from soya which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction
There have been no interaction studies for dutasteride/tamsulosin combination therapy. The following statements reflect the information available on the individual components.

Dutasteride

Effects of other medicines on the pharmacokinetics of dutasteride
In vitro metabolism studies show that dutasteride is metabolised by human cytochrome P450 isoenzyme CYP3A4 and CYP3A5. 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 and diltiazem.
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.

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.

Effects of dutasteride on the pharmacokinetics of other medicines
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 colestyramine and no clinically significant interactions have been observed.
No clinically significant adverse interactions were observed in clinical trials when dutasteride was co-administered with anti-hyperlipidaemic, 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 coadministered with medicines which can reduce blood pressure, including anaesthetic medicines, PDE5 inhibitors and other alpha1 adrenergic blockers. DUOFLOW should not be used in combination with other alpha1 adrenergic blockers.
Concomitant administration of tamsulosin hydrochloride and ketoconazole (a strong CYP3A4 inhibitor) resulted in an increased plasma exposure of tamsulosin hydrochloride. Concomitant administration of tamsulosin hydrochloride and paroxetine (a strong CYP2D6 inhibitor) resulted in an increased plasma exposure of tamsulosin hydrochloride. A similar increase in exposure is expected in CYP2D6 poor metabolisers as compared to extensive metabolisers when coadministered 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 and an increase in the exposure of tamsulosin hydrochloride. Caution should be used when DUOFLOW 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.
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, chlormadinone, amitriptyline, diclofenac, glibenclamide and simvastatin change 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
DUOFLOW is contraindicated for use by women. There have been no studies to investigate the effect of dutasteride/tamsulosin combination therapy on pregnancy, lactation and fertility. The following statements reflect the information available from studies with the individual components.

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

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

Fertility
Male patients on treatment with DUOFLOW are advised to use condoms.

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 ability to drive and use machines
DUOFLOW 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 DUOFLOW.

4.8 Undesirable effects

a. Summary of the safety profile
There have been no clinical trials conducted with DUOFLOW; however, coadministration 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. The higher incidence of adverse events in the co-administration therapy group reported in the first year of treatment was due to a higher incidence of reproductive disorders, specifically ejaculation disorders, observed in this group.

b. Tabulated list of adverse reactions
The data presented here relate to the co-administration of dutasteride and tamsulosin.
Information on the adverse event profiles of the individual components (dutasteride and tamsulosin) are provided thereafter.

Dutasteride and tamsulosin

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	Frequent	Dizziness
Cardiac disorders	Less frequent	Cardiac failure (Composite term[1])
Reproductive system and breast disorders	Frequent	Impotence [3], altered (decreased) libido [3], ejaculation disorders^, breast disorders[2]

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.

Dutasteride and tamsulosin

System Organ Class	Frequency	Adverse reactions
Immune system disorders	Frequency unknown	Allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema
Cardiac disorders	Less frequent	Cardiac failure (Composite term[1])
Psychiatric disorders	Frequency unknown	Depression
Skin and subcutaneous tissue disorders	Frequency unknown	Alopecia, hypertrichosis
Reproductive system and breast disorders	Frequent	Impotence [3], altered (decreased) libido [3], ejaculation disorders^, breast disorders[2]
	Frequency unknown	Testicular pain and testicular swelling.

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.

Tamsulosin

System Organ Class	Frequency	Adverse reactions
Nervous system disorders	Frequent	Dizziness
	Less frequent	Syncope, headache
Eye disorders	Frequency unknown	Intra-operative Floppy Iris Syndrome (IFIS), including blurred vision, visual impairment
Cardiac disorders	Less frequent	Palpitations
	Frequency unknown	Atrial fibrillation, dysrhythmia, tachycardia, dyspnoea
Vascular disorders	Less frequent	Postural hypotension
Respiratory, thoracic and mediastinal disorders	Less frequent	Rhinitis
	Frequency unknown	Epistaxis
Gastrointestinal disorders	Less frequent	Constipation, diarrhoea, vomiting, nausea
Skin and subcutaneous tissue disorders	Less frequent	Rash, pruritus, urticaria, angioedema, Stevens-Johnson syndrome
	Frequency unknown	Erythema multiforme, dermatitis exfoliative
Reproductive system and breast disorders	Frequent	Abnormal ejaculation
	Less frequent	Priapism
General disorders and administrative site conditions	Less frequent	Asthenia

c. Description of selected adverse reactions
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.

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/8.

4.9 Overdose
No data are available with regard to overdosage of dutasteride/tamsulosin combination therapy. The following statements reflect the information available on the individual components.

Dutasteride: It is documented that in volunteer studies, single daily doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) have been administered for 7 days without significant safety concerns. In clinical studies, doses of 5 mg daily have been administered to subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0,5 mg.
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

Pharmacological classification: A 21.12 Hormone Inhibitors.
Pharmacotherapeutic group: Alpha adrenoreceptor antagonists
ATC code: G04CA52

Dutasteride-tamsulosin is a combination of two medicines: dutasteride, a dual 5-alpha reductase inhibitor (5 ARI) and tamsulosin hyrochloride, and antagonist of α_{1a} α_{1d} adrenoreceptors.
These medicines have complementary mechanisms of action that rapidly improve symptoms, urinary flow and reduce the risk of acute urinary retention (AUR) and the need for BPH related surgery.

Dutasteride inhibits both type 1 and type 2, 5-alpha reductase isoenzymes, which are responsible for the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for prostate growth and BPH development. Tamsulosin inhibits α_{1a} and α_{1d} 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.

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.

Hair distribution
The effect of dutasteride on hair distribution was not formally studied during the phase III programme, however, 5-alpha reductase inhibitors could reduce hair loss and may induce hair growth in subjects with male pattern hair loss (male androgenetic alopecia).

Thyroid function
There is no evidence that dutasteride adversely affects thyroid function.

Breast neoplasia
A causal relationship between the occurrence of male breast cancer and long term use of dutasteride has not been established.

Effects on male fertility
The possibility of reduced male fertility cannot be excluded.

Cardiovascular adverse events
It is documented that dutasteride taken in combination with tamsulosin, the incidence of the composite term cardiac failure in the combination group was higher than in either monotherapy.

Prostate cancer and high grade tumours
It is documented that there was a higher incidence of Gleason 8-10 prostate cancers in the patients taking dutasteride for 3 to 4 years.
The relationship between dutasteride and high grade prostate cancer is not clear.

Effects on sexual function:
Dutasteride-tamsulosin combination and dutasteride monotherapy are known to cause sexual function adverse effects (see section 4.8). As observed in other clinical studies, the incidence of adverse events related to sexual function decreases over time with continued therapy.

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

Tamsulosin: Tamsulosin is absorbed from the intestine and is almost completely bioavailable.
Tamsulosin 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 approximately 30 minutes after the same meal each day (see section 4.2).

Distribution

Dutasteride: Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 litres). 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 (Css) 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 liters, which is suggestive of distribution into extracellular fluids in the body.
Tamsulosin hydrochloride is extensively bound to human plasma proteins (94 % to 99 %), primarily alpha1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL).

Biotransformation

Dutasteride: *In vitro*, dutasteride is metabolised by the human cytochrome P450 isoenzyme CYP3A4 to three monohydroxylated metabolites and one dihydroxylated metabolite. It is not metabolised by CYP1A2, CYP2C9, CYP2C19 or CYP2D6.
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 medicine-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.
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-hydroxydutasterlde), 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 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: 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.
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.

Pharmacokinetics in special patient groups

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 Cmax 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 (see section 4.2).

Tamsulosin: The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate (30 Cl_{cr}r < 70 mL/min/1,73 m^2) or moderate-severe (10 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 alpha1 acid glycoprotein (MG), 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 4.3).
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 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

Capsule content
Butylhydroxytoluene (E-321)
Glycerol monocaprylocaprate
Microcrystalline cellulose
Magnesium stearate
Methacrylic acid –Ethyl acrylate copolymer (1:1)
Talc

Enteric coating
Methacrylic acid –Ethyl acrylate copolymer (1:1)
Purified talc
Sodium hydroxide
Titanium dioxide (E-171)
Triacetin

Capsule, soft
Gelatine
Glycerol
Lecithin (soya) (E-322)
Titanium Dioxide (E-171)
Triglycerides
Yellow Iron Oxide (E-172)

Capsule shell, hard
Carrageenan (E-407),
Hypromellose
Potassium chloride
Red Iron Oxide (E-172)
Sunset Yellow (E-110)
Titanium Dioxide (E-171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 years.
5 weeks after first opening of the 30 capsules pack size.
18 weeks after first opening of the 90 capsules pack size.

6.4 Special precautions for storage
Store at or below 30 °C.
Store in original packaging.

6.5 Nature and contents of container

Bottles
HDPE bottles sealed with an aluminium foil with child resistance closures.
Pack size: 30 or 90 hard capsules

Blisters
Aluminium/Aluminium blisters.
Pack size: 30 or 90 hard capsules
Not all pack sizes may be marketed.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Activo Health (Pty) Ltd
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8. REGISTRATION NUMBER(S)

56/21.12/0034

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 February 2024

10. DATE OF REVISION OF THE TEXT