SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DUOZAQ 0,5 mg/0,4 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The hard capsules contain: one dutasteride 0,5 mg soft gelatin capsule and tamsulosin hydrochloride (HCl) pellets in the equivalent weight of 0,4 mg of tamsulosin HCl.

DUOZAQ 0,5 mg/0,4 mg is sugar free.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Hard capsule.

DUOZAQ 0,5 mg/0,4 mg is a hard capsule with brown body and orange cap. The hard capsules contain: one dutasteride 0,5 mg soft gelatin capsule (yellow) and tamsulosin HCl pellets (white to off-white) in the equivalent weight of 0,4 mg of tamsulosin HCl.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DUOZAQ 0,5 mg/0,4 mg is indicated for treatment of moderate to severe symptoms of benign prostatic hyperplasia (BHP).

4.2 Posology and method of administration

Posology

Adult males (including elderly)

The recommended dose of DUOZAQ 0,5 mg/0,4 mg is one capsule taken orally approximately 30 minutes after the same meal each day (See section 5.2 – Absorption).

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.

Special populations

Renal impairment

The effects of renal impairment on DUOZAQ 0,5 mg/0,4 mg pharmacokinetics have not been studied. However, no adjustment in dose is anticipated for patients with renal impairment (see section 5.2 – Renal impairment).

Hepatic impairment

The effects of hepatic impairment on DUOZAQ 0,5 mg/0,4 mg pharmacokinetics have not been studied (see sections 4.4 and 5.2 – Hepatic impairment).

Method of administration

DUOZAQ 0,5 mg/0,4 mg is to be taken orally approximately 30 minutes after the same meal each day (see section 5.2).

4.3 Contraindications

- hypersensitivity to dutasteride, other 5α-reductase inhibitors, tamsulosin hydrochloride or to any of the excipients of DUOZAQ 0,5 mg/0,4 mg listed in section 6.1
- use in women and children (see section 4.6)
- patients with history or orthostatic hypotension
- severe hepatic impairment.

4.4 Special warnings and precautions for use

Leaking Capsule

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). DUOZAQ 0,5 mg/0,4 mg 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 DUOZAQ 0,5 mg/0,4 mg to patients with liver disease (see sections 4.2, 4.3 and 5.2).

Combination therapy with tamsulosin and cardiac failure

In patients with other risk factors for cardiac failure, DUOZAQ 0,5 mg/0,4 mg may increase the risk to develop cardiac failure.

In two 4-year clinical studies, the incidence of cardiac failure (a composite term of reported events, primary 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.

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

Prior to initiating therapy with DUOZAQ 0,5 mg/0,4 mg, as well as periodically thereafter, a digital rectal examination, as well as other evaluations for prostate cancer, should be performed on patients with BHP.

DUOZAQ 0,5 mg/0,4 mg causes a decrease in mean PSA levels by approximately 50 % after six months of treatment.

Patients receiving DUOZAQ 0,5 mg/0,4 mg should have a new PSA baseline established before starting treatment with DUOZAQ 0,5 mg/0,4 mg and after 6 months of treatment. It is recommended to monitor PSA values regularly thereafter.

Any confirmed increase from PSA level during DUOZAQ 0,5 mg/0,4 mg therapy may signal the presence of prostate cancer (particularly high- grade cancer) or non-compliance to therapy with DUOZAQ 0,5 mg/0,4 mg and should be carefully evaluated, even if those

values are still within the normal range for men not taking a 5α-reductase inhibitor. In the interpretation of a PSA value for a patient on DUOZAQ 0,5 mg/0,4 mg therapy, previous PSA values should be sought for comparison.

DUOZAQ 0,5 mg/0,4 mg therapy 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 DUOZAQ 0,5 mg/0,4 mg. If healthcare professionals elect to use percent free PSA as an acid in the detection of prostate cancer in men undergoing dutasteride therapy, no adjustment to its value is necessary.

Prostate cancer and high grade tumours

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 compared to the placebo group . There was no increased incidence in Gleason 5-6 or 7-10 prostate cancer. Men taking DUOZAQ 0,5 mg/0,4 mg should be regularly evaluated for prostate cancer risk including PSA testing.

Breast cancer in men

In clinical trials and during the post-marketing period, breast cancer has been reported in men taking dutasteride, as in DUOZAQ 0,5 mg/0,4 mg. 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, as in DUOZAQ 0,5 mg/0,4 mg, which can result in syncope.

Patients beginning treatment with DUOZAQ 0,5 mg/0,4 mg 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 DUOZAQ 0,5 mg/0,4 mg. IFIS may increase the risk of eye complications during and after the operation.

During pre-operative assessment, contract surgeons and ophthalmic teams should consider whether patients scheduled for cataract surgery are being or have been treated with DUOZAQ 0,5 mg/0,4 mg in order to ensure that appropriate measures will be in place to manage IFIS should it occur 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.

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.

Non-alcoholic fatty liver disease and other liver diseases

It has been observed that patients may experience metabolic changes (e.g. glucose intolerance) and non-alcoholic fatty liver disease (NAFLD), during the use of dutasteride as contained in DUOZAQ. This includes the possibility of other liver diseases e.g. cirrhosis and liver necrosis. Patients at high risk for metabolic diseases should be carefully assessed before commencing treatment and during therapy.

4.5 Interaction with other medicines and other forms of interaction

Although no interaction studies have been conducted for DUOZAQ 0,5 mg/0,4 mg, the following statements reflect the information available on the individual active ingredients:

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 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.

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 form plasma protein, nor do these medicines displace dutasteride.
Medicines that have been tested for interaction 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 medicines (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 medicine, PDE5 inhibitors and other alpha-1 adrenergic blockers. DUOZAQ 0,5 mg/0,4 mg 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 CYP2D 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 increase in the AUC of tamsulosin hydrochloride. Caution should be used when DUOZAQ 0,5 mg/0,4 mg 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

Pregnancy

DUOZAQ 0,5 mg/0,4 mg is contraindicated for use in women.

Dutasteride: DUOZAQ 0,5 mg/0,4 mg 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.

Breastfeeding

DUOZAQ 0,5 mg/0,4 mg is contraindicated for use in women.

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

Fertility

Male patients on treatment with DUOZAQ 0,5 mg/0,4 mg are advised to use condoms.

Dutasteride: Dutasteride reduces sperm count and sperm motility which may be irreversible after discontinuation on sperm counts or sperm function have not been evaluated.

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

DUOZAQ 0,5 mg/0,4 mg may cause orthostatic hypotension which may interfere with driving and operating machinery. Patients should be informed about the occurrence of symptoms related to orthostatic hypotension, such as dizziness when taking DUOZAQ 0,5 mg/0,4 mg.

4.8 Undesirable effects

a). Summary of the safety profile

There have been no clinical trials conducted with DUOZAQ 0,5 mg/0,4 mg, 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 monotherapy.

b). Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Nervous system disorders	Frequent	Dizziness
Cardiac disorders	Less frequent	Cardiac failure, 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
Reproductive system and breast disorders	Frequent	Impotence, altered (decreased) libido, ejaculation disorders, breast disorders (breast tenderness and breast enlargement)

c) Dutasteride Monotherapy:

System Organ Class	Frequency	Side effects
Immune system disorders	Frequency unknown	Allergic reactions including rash, pruritus, urticarial, localised oedema, and angioedema
Psychiatric disorders	Frequency unknown	Depressed mood

Cardiac disorders	Less frequent	Cardiac failure, 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
Skin and subcutaneous tissue disorders	Frequency unknown	Alopecia (primarily body hair loss), hypertrichosis
Reproductive system and breast disorders	Frequent	Testicular pain and testicular swelling, impotence, altered (decreased libido), ejaculation disorders, breast disorders (breast tenderness and breast enlargement)

d) Tamsulosin Monotherapy

System Organ Class	**Frequency**	**Side effects**
Immune system disorders	Less frequent	Rash, pruritus, urticaria, angioedema, Steven-Johnson syndrome
Nervous system disorders	Frequent Less frequent	Dizziness Headache, syncope
Eye disorders	Frequency unknown	Intra-operative Floppy Iris Syndrome (IFIS), blurred vision, visual impairment

Cardiac disorders	Less frequent Frequency unknown	Palpitations Atrial fibrillation*, dysrhythmia, tachycardia, dyspnoea
Skin and subcutaneous tissue disorders	Frequency unknown	Erythema multiforme, dermatitis exfoliative
Vascular disorders	Less frequent	Postural hypotension
Respiratory, thoracic, and mediastinal disorders	Less frequent Frequency unknown	Rhinitis Epistaxis
Hepato-biliary disorders	Frequency unknown	Non-alcoholic fatty liver disease (NAFLD), cirrhosis, liver necrosis and other liver diseases.
Gastrointestinal disorders	Less frequent	Constipation, diarrhoea, vomiting, nausea
Reproductive system and breast disorders	Frequent Less frequent	Abnormal ejaculation Priapism
General disorders and administrative site conditions	Less frequent	Asthenia

* Post-marketing adverse effects

<u>Reporting of suspected adverse reactions</u>

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.

An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 OVERDOSE

Management of 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 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

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists

ATC code: G04CA52

Pharmacological classification: A21.12 Hormone inhibitors

Mechanism of action

Dutasteride-tamsulosin is a combination of two medicines, dutasteride, a dual 5 α-reductase inhibitor (5 ARI) and tamsulosin hydrochloride an antagonist of α_{1a} -adrenoreceptors.
Dutasteride inhibits both type 1 and type 2, 5α-reductase isoenzymes, which are responsible for the conversion of testosterone to 5 alpha-dihydrotestosterone (DHT), DHT is the androgen primarily responsible for hyperplasia of glandular prostatic tissue.
Tamsulosin inhibits $\alpha_{1\alpha}$ - 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 pharmacodynamics effects of dutasteride-tamsulosin have not been studied.

Dutasteride: Dutasteride lowers DHT levels, reduces prostate volume, improves lower urinary tract symptoms.
The maximum effects 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 prostrate 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 concentration 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 concentration 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 prompted 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 concentrate achieve 65 % of steady state concentration after one month and approximately 90 % after three months. Steady state

serum concentration (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 achieve steady state at six months. After 52 weeks of therapy, semen dutasteride concentration 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 %), primary alpha-1 acid glycoprotein (AAG), with linear binding over a wide concentration range (20 to 600 ng/mL).

Biotransformation

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

In human serum, the 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 medicine metabolising enzymes may lead to increased exposure to tamsulosin.
The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulphate prior to renal excretion.

Elimination

Dutasteride: Dutasteride is extensively metabolised. Following oral dosing of dutasteride 0,5 mg/day to steady state in humans, 1,0 % to 15,4 % (mean of 5,4 %) of the administrated dose is excreted as dutasteride in the faeces as four major metabolites comprising 39 %, 21 %, 7 %, and 7 % each of medicine-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 concentration (less than 3 ng/mL), dutasteride is cleared by both the concentration-dependant and concentrate-independent elimination pathways. Single doses of 5 mg or less showed evidence of clearance and half-life of three to nine days.
At serum concentrations greater than 3 mg/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 concentration remain detectable (greater then 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 active ingredients.

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 40 % overall higher exposure (AUC) in subjects of age 55 to 75 years compare 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≤ CL_{cr} < 70 mL/min/1,73 m²) or moderate-severe (10≤ CL_{cr} < 30 mL/min/1,173 m²) renal impairment and 6 normal subjects (CL_{cr} > 90 mL/min/1,73 m²). While a change in overall plasma concentration of Tamsulosin hydrochloride was observed as a 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 m²) 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: Grade 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 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

Dutasteride soft capsules

Butylhydroxytoluene (BHT)

Gelatin

Glycerol

Glycerol monocaprylocaprate

Lecithin (soya)

Titanium dioxide

Triglycerides, medium chain

Yellow iron oxide

Tamsulosin pellets

Magnesium stearate

Methacrylic acid –Ethyl acrylate copolymer (1:1)

Methacrylic acid –Ethyl acrylate copolymer (1:1) Dispersion (30%)

Microcrystalline cellulose

Purified talc

Sodium hydroxide

Titanium dioxide (E171)

Triacetin

Talc

Hard capsules

Carrageenan

Hypromellose

Potassium chloride

Red iron oxide (E172)

Sunset yellow (E110)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ºC.

Keep blisters in outer carton until required for use.

Keep bottle closed until required for use.

6.5 Nature and contents of container

30 capsules: Alu-Alu blisters are packed in a printed outer carton.

HDPE bottles containing 30 capsules are packed in a printed outer carton.

*Not all pack presentations may be marketed.

6.6 Special precautions for disposal

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).

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER

56/21.12/0796

9. DATE OF FIRST AUTHORISATION

25 July 2023