

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

DUODART, Dutasteride-tamsulosin hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule for oral use contains 0.5 mg dutasteride and 0.4 mg tamsulosin hydrochloride (*see List of Excipients*).

3. PHARMACEUTICAL FORM

Capsules: oblong hard-shell capsules with a brown body and an orange cap with either 'GS 7CZ' or 'GS TEV' printed on in black ink.

4. CLINICAL PARTICULARS

4.1 Indications

DUODART treats and prevents progression of benign prostatic hyperplasia (BPH) through alleviating symptoms, reducing prostate size (volume), improving urinary flow rate and reducing the risk of acute urinary retention (AUR) and the need for BPH-related surgery.

4.2 Dosage and Administration

Adult males (including elderly)

The recommended dose of *DUODART* is one capsule (0.5 mg/ 0.4 mg) taken orally approximately 30 minutes after the same meal each day. Capsules should be swallowed whole and not chewed or opened. Contact with the contents of the dutasteride capsule contained within the hard-shell capsule may result in irritation of the oropharyngeal mucosa.

Renal impairment

The effect of renal impairment on dutasteride-tamsulosin pharmacokinetics has not been studied. However, no adjustment in dosage is anticipated for patients with renal impairment (*see Pharmacokinetics*).

Hepatic impairment

The effect of hepatic impairment on dutasteride-tamsulosin pharmacokinetics has not been studied (*see Warnings and Precautions and Pharmacokinetics*).

4.3 Contraindications

DUODART is contraindicated in patients with known hypersensitivity to dutasteride, other 5 α -reductase inhibitors, tamsulosin hydrochloride or any component of the preparation (*see List of Excipients*).

DUODART is contraindicated for use in women and children (*see Pregnancy and Lactation*).

4.4 Warnings and Precautions

Prostate cancer

In a 4-year study of over 8,000 men aged 50 to 75, with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL (the REDUCE study), 1,517 men were diagnosed with prostate cancer. There was a higher incidence of Gleason 8 to 10 prostate cancers in the *AVODART* group (n=29, 0.9%) compared to the placebo group (n=19, 0.6%). There was no increased incidence in Gleason 5-6 or 7-10 prostate cancers. No causal relationship between *AVODART* and high grade prostate cancer has been established. The clinical significance of the numerical imbalance is unknown. Men taking *DUODART* should be regularly evaluated for prostate cancer risk including PSA testing.

In an additional 2-year follow-up study with the original patients from the *AVODART* chemoprevention study (REDUCE), a low rate of new prostate cancers were diagnosed (dutasteride [n=14, 1.2%] and placebo [n=7, 0.7%]), with no new identified cases of Gleason 8–10 prostate cancers.

Long-term follow up (up to 18 years) of another 5-ARI (finasteride) in a chemoprevention study showed no statistically significant difference between finasteride and placebo in the rates of overall survival (HR 1.02, 95% CI 0.97-1.08) or survival after prostate cancer diagnoses (HR 1.01, 95% CI 0.85-1.20).

Prostate specific antigen (PSA)

PSA concentration is an important component of the screening process to detect prostate cancer. *DUODART* causes a decrease in mean serum PSA levels by approximately 50% after 6 months of treatment.

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

Treatment with *DUODART* does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established.

Total serum PSA levels return to baseline within 6 months of discontinuing treatment.

The ratio of free to total PSA remains constant even under the influence of *DUODART*. If clinicians elect to use percent-free PSA as an aid in the detection of prostate cancer in men undergoing *DUODART* therapy, no adjustment to its value is necessary.

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

Cardiovascular adverse events

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 *AVODART* 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 ($\leq 1\%$) and variable between the studies. No imbalance was observed in the incidence of cardiovascular adverse events overall in either trial. No causal relationship between *AVODART* (alone or in combination with an alpha blocker) and cardiac failure has been established (*see Clinical Studies*).

In a meta-analysis of 12-randomised, placebo- or comparator-controlled clinical studies (n=18,802) that evaluated the risks of developing cardiovascular adverse events from the use of *AVODART* (by comparison with controls), no consistent statistically significant increase in the risk of heart failure (RR 1.05; 95% CI 0.71, 1.57), acute myocardial infarction (RR 1.00; 95% CI 0.77, 1.30) or stroke (RR 1.20; 95% CI 0.88, 1.64) were found.

Breast cancer

There have been rare reports of male breast cancer reported in men taking *AVODART* in clinical trials and during the post-marketing period. However, epidemiological studies showed no increase in the risk of developing male breast cancer with the use of 5-ARIs. Prescribers should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge.

Hypotension

As with other alpha-1 adrenergic blockers, orthostatic hypotension can occur in patients treated with tamsulosin, which in rare cases can result in syncope.

Patients beginning treatment with *DUODART* should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness and vertigo) until the symptoms have resolved.

Caution is advised when alpha adrenergic blocking agents including tamsulosin are coadministered with PDE5 inhibitors. Alpha adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension (*see Interactions*).

Intraoperative Floppy Iris Syndrome

Intraoperative 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. IFIS may increase the risk of eye complications during and after the operation.

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

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

Leaking capsules

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

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 Interactions*). 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 (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 three to five weeks, caution should be used in the administration of *DUODART* to patients with liver disease (*see Dosage and Administration and Pharmacokinetics*).

Excipients

This medicinal product contains the colouring agent FD&C Yellow 6, which may cause allergic reactions.

4.5 Interactions

There have been no drug interaction studies for *DUODART*. The following statements reflect the information available on the individual components.

Dutasteride

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

Phase II data showed a decrease in clearance of dutasteride when co-administered with the CYP3A4 inhibitors verapamil (37%) and diltiazem (44%). In contrast no decrease in clearance was seen when amlodipine, another calcium channel antagonist, was co-administered with dutasteride. A decrease in clearance and subsequent increase in exposure to dutasteride, in the presence of CYP3A4 inhibitors, is unlikely to be clinically significant due to the wide margin of safety (up to 10-times the recommended dose has been given to patients for up to six months), therefore no dose adjustment is necessary.

In vitro, dutasteride is not metabolised by human cytochrome P450 isoenzymes CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 and CYP2D6.

Dutasteride neither inhibits human cytochrome P450 drug-metabolising enzymes *in vitro* nor induces cytochrome P₄₅₀ isoenzymes CYP1A, CYP2B, and CYP3A in rats and dogs *in vivo*.

In vitro studies demonstrate that dutasteride does not displace warfarin, acenocoumrol, phenprocoumon diazepam, or phenytoin from plasma protein, nor do these model compounds displace dutasteride. Compounds that have been tested for drug interactions in man include tamsulosin, terazosin, warfarin, digoxin, and cholestyramine, and no clinically significant pharmacokinetic or pharmacodynamic interactions have been observed.

Although specific interaction studies were not performed with other compounds, approximately 90% of the subjects in large Phase III studies receiving dutasteride were taking other medications concomitantly. No clinically significant adverse interactions were observed in clinical trials when dutasteride was co-administered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.

Tamsulosin

There is a theoretical risk of enhanced hypotensive effects when tamsulosin hydrochloride is co-administered with drugs which can reduce blood pressure, including anaesthetic agents, PDE5 inhibitors and other alpha-1 adrenergic blockers. *DUODART* should not be used in combination with other alpha-1 adrenergic blockers.

Concomitant administration of tamsulosin hydrochloride and ketoconazole (a strong CYP3A4 inhibitor) resulted in an increase of the C_{max} and AUC of tamsulosin hydrochloride by a factor of 2.2 and 2.8 respectively. Concomitant administration of tamsulosin hydrochloride and paroxetine (a strong CYP2D6 inhibitor) resulted in an increase of the C_{max} and AUC of tamsulosin hydrochloride by a factor of 1.3 and 1.6 respectively. A similar increase in exposure is expected in CYP2D6 poor metabolisers as

compared to extensive metabolisers when co-administered with a 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 Warnings and Precautions*).

Concomitant administration of tamsulosin hydrochloride (0.4 mg) and cimetidine (400 mg every six hours for six days) resulted in a decrease in the clearance (26%) and an increase in the AUC (44%) of tamsulosin hydrochloride. Caution should be used when *DUODART* is used in combination with cimetidine.

A definitive drug-drug 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.

In three studies, no interactions were seen when tamsulosin (0.4 mg for seven days followed by 0.8 mg for seven days) was given concomitantly with atenolol, enalapril or nifedipine for three months; therefore no dose adjustments are necessary when these drugs are co-administered with *DUODART*.

Concomitant administration of tamsulosin hydrochloride (0.4 mg/day for two days, followed by 0.8 mg/day for five to eight days) and a single intravenous dose of theophylline (5 mg/kg) resulted in no change in the pharmacokinetics of theophylline; therefore no dose adjustment is necessary.

Concomitant administration of tamsulosin hydrochloride (0.8 mg/day) and a single intravenous dose of furosemide (20 mg) produced an 11% to 12% reduction in the C_{max} and AUC of tamsulosin hydrochloride, however these changes are expected to be clinically insignificant and no dose adjustment is necessary.

4.6 Pregnancy and Lactation

There have been no studies to investigate the effect of *DUODART* on pregnancy, lactation and fertility. The following statements reflect the information available on the individual components.

Fertility

Dutasteride

The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal volunteers aged 18 to 52 (n=27 dutasteride, n=23 placebo) throughout 52 weeks of treatment and 24 weeks of post treatment follow-up. At 52 weeks, the mean percent reduction from baseline in total sperm count, semen volume, and sperm motility were 23%, 26%, and 18%, respectively, in the dutasteride group when adjusted for changes from baseline in the placebo group. Sperm concentration and sperm morphology were unaffected. After 24 weeks of follow-up, the mean percent change in total sperm count in the dutasteride group remained 23% lower than baseline. While mean values for all semen parameters at all time points remained within the normal ranges and did not meet

predefined criteria for a clinically significant change (30%), two subjects in the dutasteride group had decreases in sperm count of greater than 90% from baseline at 52 weeks, with partial recovery at the 24-week follow-up. The clinical significance of dutasteride's effect on semen characteristics for an individual patient's fertility is not known.

Tamsulosin

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

4.7 Pregnancy

DUODART is contraindicated for use by women.

Dutasteride

Dutasteride 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 genital organs in a male foetus carried by a woman exposed to dutasteride.

Tamsulosin

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

Lactation

DUODART is contraindicated for use in women.

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

4.8 Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *DUODART* on the ability to perform tasks that require judgement, motor or cognitive skills. However, patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking *DUODART*.

Adverse Reactions

There have been no clinical trials conducted with *DUODART*; however, coadministration information is available from the CombAT (Combination of Avodart and Tamsulosin) study, a comparison of dutasteride 0.5mg and tamsulosin 0.4mg once daily for four years as co-administration or as monotherapy.

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

Dutasteride and Tamsulosin Co-administration

Clinical Trial Data

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

Adverse Reaction	Incidence during treatment period			
	Year 1	Year 2	Year 3	Year 4
Combination ^a (n)	(n=1610)	(n=1428)	(n=1283)	(n=1200)
Dutasteride	(n=1623)	(n=1464)	(n=1325)	(n=1200)
Tamsulosin	(n=1611)	(n=1468)	(n=1281)	(n=1112)
Impotence ^b				
Combination	6%	2%	<1%	<1%
Dutasteride	5%	2%	<1%	<1%
Tamsulosin	3%	1%	<1%	1%
Altered (decreased) libido ^b				
Combination	5%	<1%	<1%	0%
Dutasteride	4%	1%	<1%	0%
Tamsulosin	2%	<1%	<1%	<1%
Ejaculation disorders ^b				
Combination	9%	1%	<1%	<1%
Dutasteride	1%	<1%	<1%	<1%
Tamsulosin	3%	<1%	<1%	<1%
Breast disorders ^c				
Combination	2%	<1%	<1%	<1%
Dutasteride	2%	1%	<1%	<1%
Tamsulosin	<1%	<1%	<1%	0%
Dizziness				
Combination	1%	<1%	<1%	<1%
Dutasteride	<1%	<1%	<1%	<1%
Tamsulosin	1%	<1%	<1%	0%

^a Combination = dutasteride 0.5 mg once daily plus tamsulosin 0.4 mg once daily.

^b These sexual adverse events are associated with dutasteride treatment (including monotherapy and combination with tamsulosin). These adverse events may persist after treatment discontinuation. The role of dutasteride in this persistence is unknown. ^c

Includes breast tenderness and breast enlargement.

Dutasteride Monotherapy

Clinical Trial Data

In three phase III placebo controlled studies of dutasteride (n=2167) treatment compared to placebo (n=2158), investigator-judged drug-related adverse events after one and two years of therapy were similar in type and frequency to those observed in the dutasteride monotherapy arm of the CombAT study (see table above).

No change in the adverse event profile was apparent over a further 2 years in an open-label extension phase of these studies.

Postmarketing Data

In addition to the adverse events reported from clinical trial data, postmarketing adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$) and very rare ($< 1/10,000$) including isolated reports. Frequency categories determined from post-marketing data refer to reporting rate rather than true frequency.

Immune system disorders

Very rare: Allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema.

Psychiatric disorders

Very rare: Depressed mood

Skin and subcutaneous tissue disorders

Rare: Alopecia (primarily body hair loss), Hypertrichosis

Reproductive system and breast disorders

Very rare: Testicular pain and testicular swelling

Tamsulosin Monotherapy

Clinical Trial Data and Post marketing Data

GSK does not hold the safety database for any single ingredient tamsulosin product; therefore the adverse reactions and frequency categories below are based on information available in the public domain. In the table below, common and uncommon reactions are consistent with those identified in a clinical trial setting and the frequency categories generally reflect incidence over placebo. Rare and very rare reactions are consistent with those identified from post marketing reports and the frequency categories reflect reporting rates.

System Organ Class	Frequency Category			
	Common ($\geq 1/100$)	Uncommon ($\geq 1/1000$)	Rare ($\geq 1/10,000$)	Very rare ($< 1/10,000$) including isolated cases
	<1/10)	<1/100)	<1/1000)	
Cardiac disorders		Palpitations		
Gastrointestinal disorders		Constipation Diarrhoea Vomiting		
General disorders and administration site disorders		Asthenia		
Nervous system disorders	Dizziness		Syncope	
Reproductive system and breast disorders	Abnormal ejaculation			Priapism
Respiratory, thoracic and mediastinal disorders		Rhinitis		
Immune system disorders		Rash Pruritis Urticaria	Angioedema	StevensJohnson syndrome
Vascular disorders		Postural hypotension		

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 adrenergic blocker therapy; including tamsulosin (*see Warnings and Precautions*).

Post-marketing experience: In addition atrial fibrillation, arrhythmia, tachycardia, dyspnoea, epistaxis, vision blurred, visual impairment, erythema multiforme, dermatitis exfoliative and dry mouth have been reported in association with tamsulosin use.

4.9 Overdose

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

Dutasteride

In volunteer studies single doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) for 7 days have been administered without significant safety concerns. In clinical studies doses of 5 mg daily have been administered to patients 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 normalization 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 Pharmacodynamics

Pharmacotherapeutic group: Alpha-adrenoreceptor antagonists ATC code: G04C A52

DUODART is a combination of two drugs with complementary mechanisms of action to improve symptoms in patients with BPH: dutasteride, a dual 5 α -reductase inhibitor (5 ARI) and tamsulosin hydrochloride, an antagonist of α 1a-adrenoreceptors.

The pharmacodynamics of *DUODART* as a fixed dose combination would not be expected to be different from those of dutasteride and tamsulosin co-administered as separate components.

Dutasteride

Dutasteride is a dual inhibitor of 5 alpha-reductase. It inhibits both type 1 and type 2, 5 alpha-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.

Dutasteride lowers DHT levels, reduces prostate volume, improves lower urinary tract symptoms and urine flow and reduces the risk of AUR and BPH-related surgery.

The maximum effect of daily doses of dutasteride on the reduction on DHT is dose-dependent and is observed within 1-2 weeks. After 1 week and 2 weeks of daily dosing of dutasteride 0.5 mg, median serum DHT concentrations were reduced by 85% and 90%, respectively.

In BPH patients treated with 0.5 mg of dutasteride daily, the median decrease in DHT was 94% at 1 year and 93% at 2 years and the median increase in serum testosterone was 19% at both 1 and 2 years. This is an expected consequence of 5 alpha-reductase inhibition and did not result in any known adverse events.

Tamsulosin

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.

Tamsulosin increases maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra, thereby relieving obstruction. It also improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role. Alpha-1 adrenergic blockers can reduce blood pressure by lowering peripheral resistance.

5.2 Pharmacokinetics

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

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 dutasteridetamsulosin in the fed state compared to the fasted state. Food had no effect on AUC of tamsulosin.

Absorption

Dutasteride

Dutasteride is administered orally in solution as a soft gelatin capsule. Following administration of a single 0.5 mg dose, peak serum concentrations of dutasteride occur within 1 to 3 hours.

Absolute bioavailability in man is approximately 60% relative to a 2 hour intravenous infusion. The bioavailability of dutasteride is not affected by food.

Tamsulosin

Tamsulosin hydrochloride is absorbed from the intestine and is almost completely bioavailable. Tamsulosin hydrochloride exhibits linear kinetics, following single and multiple dosing, with achievement of steady state concentrations by the fifth day of once-a-day dosing. The rate of absorption of tamsulosin hydrochloride is reduced by a recent meal. Uniformity of absorption can be promoted by the patient always taking tamsulosin hydrochloride approximately 30 minutes after the same meal each day.

Distribution

Dutasteride

Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to plasma proteins (>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 nanograms/mL are achieved after 6 months of dosing 0.5 mg once a day. Similarly to serum, dutasteride concentrations in semen achieved steady state at 6 months. After 52 weeks of therapy, semen dutasteride concentrations averaged 3.4 nanograms/mL (range 0.4 to 14 nanograms/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 16L, which is suggestive of distribution into extracellular fluids in the body.

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

Biotransformation

Dutasteride

In vitro, dutasteride is metabolised by the human cytochrome P₄₅₀ isoenzyme CYP3A4 to two minor monohydroxylated metabolites, but it is not metabolised by CYP1A2, CYP2A6, CYP2E1, CYP2C8, CYP2C9, CYP2C19, CYP2B6 or CYP2D6.

In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride and 6-hydroxydutasteride) and 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The five human serum

metabolites of dutasteride have been detected in rat serum, however the stereochemistry of the hydroxyl additions at the 6 and 15 positions in the human and rat metabolites is not known.

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 metabolizing enzymes may lead to increased exposure to tamsulosin. (*see Warnings and Precautions and Interactions*) The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

Elimination

Dutasteride

Dutasteride is extensively metabolised. Following oral dosing of dutasteride 0.5 mg/day to steady state in humans, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as dutasteride in the faeces. The remainder is excreted in the faeces as 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 therapeutic concentrations, the terminal half-life of dutasteride is 3 to 5 weeks.

Serum concentrations remain detectable (greater than 0.1 nanograms/mL) for up to 4 to 6 months after discontinuation of treatment.

At low serum concentrations (less than 3 nanograms/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 nanograms/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 clearance dominates and the total clearance is linear and concentration-independent.

Tamsulosin

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

Elderly

Dutasteride

Dutasteride pharmacokinetics and pharmacodynamics were evaluated in 36 healthy male subjects between the ages of 24 and 87 years following administration of a single 5 mg dose of dutasteride. Exposure of dutasteride, represented by AUC and C_{max} values, was not statistically different when comparing age groups. Half-life was not statistically different when comparing the 50-69 year old group to the greater than 70 years old group, which encompasses the age of most men with BPH. No differences in drug effect as measured by DHT reduction were observed between age groups. Results indicated that no dutasteride dose-adjustment based on age is necessary.

Tamsulosin

Cross-study comparison 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 adjustment in dosage is anticipated for patients with renal impairment.

Tamsulosin

The pharmacokinetics of tamsulosin hydrochloride have been compared in 6 subjects with mild-moderate ($30 \leq CL_{cr} < 70 \text{ mL/min/1.73m}^2$) or moderate-severe ($10 \leq CL_{cr} < 30 \text{ mL/min/1.73m}^2$) renal impairment and 6 normal subjects ($CL_{cr} > 90 \text{ mL/min/1.73m}^2$). 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 endstage renal disease ($CL_{cr} < 10 \text{ mL/min/1.73m}^2$) have not been studied.

Hepatic impairment

Dutasteride

The effect on the pharmacokinetics of dutasteride in hepatic impairment has not been studied (*see Warnings and Precautions*). Because dutasteride is extensively metabolised, exposure could be higher in hepatically impaired patients.

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.

Clinical Studies

The following statements reflect the information available on dutasteride and tamsulosin administered separately or as co-administration therapy.

AVODART 0.5mg/day, tamsulosin 0.4mg/day or the co-administration of *AVODART* 0.5mg plus tamsulosin 0.4mg was evaluated in 4844 male subjects with enlarged prostates (greater than or equal to 30cc) in a multi-centre, double blind, parallel group study over 4 years.

The primary efficacy endpoint at 2 years of treatment was the level of improvement from baseline in the international prostate symptom score (IPSS). The combination of dutasteride and tamsulosin provides superior improvement in symptoms than either component alone. After 2 years of treatment, co-administration therapy showed a statistically significant adjusted mean improvement in symptom scores from baseline of 6.2 units. The adjusted mean improvements in symptom scores observed with the individual therapies were -4.9 units for *AVODART* and -4.3 units for tamsulosin.

The adjusted mean improvement in flow rate from baseline was 2.4 ml/sec for the combination, 1.9 ml/sec for *AVODART* and 0.9 ml/sec for tamsulosin. The adjusted mean improvement in BPH Impact Index (BII) from baseline was -2.1 units for the combination, -1.7 for *AVODART* and -1.5 for tamsulosin. These improvements in flow rate and BII were statistically significant for co-administration therapy compared to both monotherapies.

The reduction in total prostate volume and transition zone volume after 2 years of treatment was statistically significant for co-administration therapy compared to tamsulosin monotherapy alone.

The primary efficacy endpoint at 4 years of treatment was time to first event of AUR or BPH-related surgery. After 4 years of treatment, combination therapy significantly reduced the risk of AUR or BPH-related surgery (65.8% reduction in risk $p < 0.001$ [95% CI 54.7% to 74.1%]) compared to tamsulosin monotherapy. The incidence of AUR or BPH-related surgery by Year 4 was 4.2% for combination therapy and 11.9% for tamsulosin ($p < 0.001$). Compared to *AVODART* monotherapy, combination therapy reduced the risk of AUR or BPH-related surgery by 19.6%; the difference between treatment groups was not significant ($p = 0.18$ [95% CI -10.9% to 41.7%]). The incidence

of AUR or BPH-related surgery by Year 4 was 4.2% for combination therapy and 5.2% for *AVODART*.

Clinical progression was defined as a composite of worsening symptoms, (IPSS), and BPH-related events of AUR, incontinence, UTI, and renal insufficiency. Combination therapy was associated with a statistically significantly lower rate of clinical progression compared with tamsulosin ($p < 0.001$, 44.1% risk reduction [95 % CI: 33.6% to 53.0%]) after 4 years. The rates of clinical progression for combination therapy, tamsulosin, and *AVODART* were: 12.6%, 21.5%, and 17.8%, respectively.

The statistically significant adjusted mean improvement in symptom scores (IPSS) from baseline was maintained from year 2 to year 4. The adjusted mean improvements in symptom scores observed were -6.3 units for combination therapy, -5.3 units for *AVODART* monotherapy and -3.8 units for tamsulosin monotherapy.

After 4 years of treatment, the adjusted mean improvement in flow rate (Q_{max}) from baseline was 2.4 ml/sec for combination therapy, 2.0 ml/sec for *AVODART* monotherapy and 0.7 ml/sec for tamsulosin monotherapy. Compared with tamsulosin, the adjusted mean improvement from baseline in Q_{max} was statistically significantly greater with combination therapy at each 6-month assessment from Month 6 to Month 48 ($p < 0.001$).

Compared with *AVODART*, the adjusted mean improvement from baseline in Q_{max} was not statistically significantly different than with combination therapy ($p = 0.050$ at Month 48).

Combination therapy was significantly superior ($p < 0.001$) to tamsulosin monotherapy and to *AVODART* monotherapy for the improvement in health outcome parameters BII and BPH-related Health Status (BHS) at 4 years. The adjusted mean improvement in BII from baseline was -2.2 units for the combination, -1.8 for *AVODART* and -1.2 for tamsulosin. The adjusted mean improvement in BHS from baseline was -1.5 units for the combination, -1.3 for *AVODART* and -1.1 for tamsulosin.

The reduction in total prostate volume and transition zone volume after 4 years of treatment was statistically significant for combination therapy compared to tamsulosin monotherapy alone.

Dutasteride

Dutasteride 0.5 mg/day or placebo was evaluated in 4325 male subjects with enlarged prostates (greater than 30 cc) in three primary efficacy 2-year multi-centre, placebo controlled, double-blind studies.

In men with BPH, dutasteride treats and prevents disease progression by reducing the risk of both (acute urinary retention) AUR and the need for surgical intervention (SI) and by providing statistically significant improvement of lower urinary tract symptoms (LUTS), maximum urinary flow rate (Q_{max}) and prostate volume relative to placebo. These improvements in LUTS, Q_{max} and prostate volume were seen through to 24 months, and LUTS and Q_{max} continued to improve for a further 2 years in open label extension studies. In addition, reductions in prostate volume were sustained for a further 2 years in open label extension studies.

Cardiac failure

In a 4-year comparison of *AVODART* coadministered with tamsulosin and *AVODART* or tamsulosin monotherapy in men with BPH (the CombAT study), the incidence of the composite term cardiac failure in the combination group (14/1610, 0.9%) was higher than in either monotherapy group: *AVODART*, 4/1623 (0.2%) and tamsulosin, 10/1611, (0.6%). The relative risk estimate for time to first cardiac failure event was 3.57 [95% CI 1.17, 10.8] for combination treatment compared to *AVODART* monotherapy and 1.36 [95% CI 0.61, 3.07] compared to tamsulosin monotherapy.

In a 4-year chemoprevention, comparison study of placebo and dutasteride in 8231 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), there was a higher incidence of the composite term cardiac failure in subjects taking *AVODART* (30/4105, 0.7%) versus placebo (16/4126, 0.4%) for a relative risk estimate for time to first cardiac failure event of 1.91 [95% CI 1.04, 3.50]. In a post-hoc analysis of concomitant alpha blocker use, there was a higher incidence of the composite term cardiac failure in subjects taking *AVODART* and an alpha blocker concomitantly (12/1152, 1.0%), compared to subjects not taking dutasteride and an alpha blocker concomitantly: *AVODART* and no alpha blocker (18/2953, 0.6%), placebo and an alpha blocker (1/1399, <0.1%), placebo and no alpha blocker (15/2727, 0.6%). No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (*see Warnings and Precautions*).

Prostate cancer and high grade tumours

In a 4-year comparison of placebo and *AVODART* in 8231 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), 6,706 subjects had prostate needle biopsy data available for analysis to determine Gleason Scores. There were 1517 subjects diagnosed with prostate cancer in the study. The majority of biopsy-detectable prostate cancers in both treatment groups were diagnosed as low grade (Gleason 5-6). There was no difference in the incidence of Gleason 7-10 cancers (p=0.81).

There was a higher incidence of Gleason 8-10 prostate cancers in the *AVODART* group (n=29, 0.9%) compared to the placebo group (n=19, 0.6%) (p=0.15). In Years 1-2, the number of subjects with Gleason 8-10 cancers was similar in the *AVODART* group (n=17, 0.5%) and the placebo group (n=18, 0.5%). In Years 3-4, more Gleason 8-10 cancers were diagnosed in the *AVODART* group (n=12, 0.5%) compared with the placebo group (n=1, <0.1%) (p=0.0035). There are no data available on the effect of dutasteride beyond 4 years in men at risk of developing prostate cancer. The percentage of subjects diagnosed with Gleason 8-10 cancers was consistent across study time periods (Years 1-2 and Years 3-4) in the *AVODART* group (0.5% in each time period), while in the placebo group, the percentage of subjects diagnosed with Gleason 8-10 cancers was lower during Years 3-4 than in Years 1-2 (<0.1% versus 0.5%, respectively). In a 4 year BPH study (CombAT) where there were no protocol-mandated biopsies and all diagnoses of prostate cancer were based on for-cause biopsies, the rates of Gleason 8-10 cancer were (n=8,

0.5%) for *AVODART*, (n=11, 0.7%) for tamsulosin and (n=5, 0.3%) for combination therapy (*see Warnings and Precautions*).

The results of an epidemiological, population-based study (n=174,895) in community practice settings show that the use of 5-ARIs to treat BPH/LUTS is not associated with an increased risk of prostate cancer mortality (hazard ratio adjusted for competing risks: 0.85, 95% CI 0.72, 1.01) when compared with the use of alpha-blockers. Similar results were reported in an epidemiological study (n=13,892) of men with prostate cancer in the UK (adjusted hazard ratio for prostate cancer mortality for 5-ARI users versus non-users: 0.86; 95% CI 0.69, 1.06). A prospective cohort study, the Health Professional's Followup Study (n=38,058), also found that 5-ARI use was not associated with fatal prostate cancer (adjusted HR: 0.99; 95% CI 0.58, 1.69).

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

In the REDUCE study, patients with a prior negative biopsy for prostate cancer and baseline PSA between 2.5 ng/mL and 10.0 ng/mL, *AVODART* treatment caused a decrease in mean serum PSA by approximately 50% after six months of treatment with a large variability (standard deviation of 30%) among patients. The PSA suppression observed at six months was similar in men who did or who did not develop biopsydetectable prostate cancer during the study (*see Warnings and Precautions*).

Incidence of breast cancer

In BPH monotherapy clinical trials, providing 3374 patient years of exposure to *AVODART*, there were 2 cases of male breast cancer reported in *AVODART* -treated patients, one after 10 weeks and one after 11 months of treatment and 1 case in a patient who received placebo. In subsequent clinical trials in BPH and 8231 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 providing 17489 patient years exposure to *AVODART* and 5027 patient years exposure to *AVODART* and tamsulosin combination, there were no reported breast cancer cases in any of the treatment groups.

Two case control, epidemiological studies, one conducted in a US (n=339 breast cancer cases and n=6,780 controls) and the other in a UK (n=398 breast cancer cases and n=3,930 controls) healthcare database, showed no increase in the risk of developing male breast cancer with the use of 5 ARIs (*see Warnings and Precautions*). Results from the first study did not identify a positive association for male breast cancer (relative risk for ≥ 1 year of use before breast cancer diagnosis compared with < 1 year of use: 0.70: 95% CI 0.34, 1.45). In the second study, the estimated odds ratio for breast cancer associated with the use of 5-ARIs compared with non-use was 1.08: 95% CI 0.62, 1.87).

The relationship between long-term use of *AVODART* and male breast cancer has not been established.

Tamsulosin

Tamsulosin rapidly (from one week) increases maximum urinary flow rate by reducing smooth muscle tension in the prostate and urethra, thereby relieving obstruction. It also

improves the complex of irritative and obstructive symptoms in which bladder instability and tension of the smooth muscles of the lower urinary tract play an important role.

5.3 Pre-clinical Safety Data

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

□ Carcinogenesis, mutagenesis

Dutasteride and tamsulosin hydrochloride showed no evidence of genotoxicity in a wide range of in vitro and in vivo tests.

Dutasteride

In a carcinogenicity study in rats, dutasteride produced an increase in benign interstitial cell tumours in the testis at the high dose (158-fold clinical exposure). However, the endocrine mechanisms believed to be involved in the production of interstitial cell hyperplasia and adenomas in the rat are not relevant to humans. There were no clinically relevant effects on tumour profile in a carcinogenicity study in mice.

Tamsulosin

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

□ Reproductive toxicology

Dutasteride

Dutasteride produced a reversible decrease in fertility in male rats consistent with the pharmacological activity of 5 alpha-reductase inhibition on accessory reproductive organs. This is considered to have no clinical relevance as there was no effect on sperm development, concentration or motility.

Feminisation of the external genitalia was noted in male fetuses of female rats and rabbits orally dosed with dutasteride. However, intravenous administration of dutasteride to pregnant Rhesus monkeys during embryofetal development at doses of up to 2010 nanograms/animal/day did not produce adverse maternal or fetal toxicity. This dose represents a multiple of at least 186-fold (nanograms/kg basis) the potential maximum daily dose in a 50 kg woman, resulting from exposure to 5 mL semen (assuming 100% absorption) from a dutasteride-treated man.

Tamsulosin

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Mono-di-glycerides of caprylic/capric acid, Butylhydroxytoluene, Gelatin, Glycerol, Titanium Dioxide, Purified Water, Cellulose, Microcrystalline, Methacrylic acid - ethyl acrylate copolymer, Talc, Triethyl citrate, Carrageenan, Potassium Chloride, Hypromellose, Triglycerides, medium chain, Lecithin, Carnauba wax, Maize Starch, Yellow Iron Oxide, Red Iron Oxide, FD&C Yellow 6

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 months

6.4 Special Precautions for Storage

Store up to 30 °C.

6.5 Nature and Contents of Container

DUODART capsules are packed into the following container closure systems:

Opaque, white high density polyethylene (HDPE) bottles with polypropylene childresistant closures with induction-seal liners.

6.6. Instructions for Use/Handling

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

Not all presentations are available in every country.

7. **Manufacturer** (name, address, company)

Catalent Germany Schorndorf GmbH Steinbeisstrasse 2, 73614 Schorndorf, Germany

8. **Marketing Authorisation Holder**

GlaxoSmithKline GmbH & Co. KG, Prinzregentenplatz 9, 81675 Munich, Germany

9. **Version number: GDS15/IPI12**

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