**NAME OF THE MEDICINE**
Dutasteride/tamsulosin hydrochloride

**Structure:**

![Chemical structure of Dutasteride and Tamsulosin hydrochloride]

**Dutasteride:**
- Chemical Name: 4-Azaandrost-1-ene-17-carboxamide, N-(2,5-Bis(trifluoromethyl)phenyl)-3-oxo-, (5alpha, 17beta)-
- Molecular Formula: C\textsubscript{27}H\textsubscript{30}F\textsubscript{6}N\textsubscript{2}O\textsubscript{2}
- CAS Number: 164656-23-9

**Tamsulosin hydrochloride:**
- Chemical Name: (-)-(R)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride
- Molecular Formula: C\textsubscript{20}H\textsubscript{28}N\textsubscript{2}O\textsubscript{5}S · HCl
- CAS Number: 106463-17-6

**DESCRIPTION**

* Dutasteride - Dutasteride is a white to pale yellow powder. It is practically insoluble in water, and soluble in organic solvents, dimethyl sulfoxide, acetone, methanol, ethanol and isopropanol.

* Tamsulosin Hydrochloride - White or almost white crystalline powder. It is sparingly soluble in water, and slightly soluble in the following solvents; Acetone, Ethanol, Ethyl acetate and Methanol.
The pKa values for tamsulosin are as follows: pKa1 = 8.4 (secondary amine) and pKa2 = 10.7 (sulphonamide). The partition coefficient is clogP = 2.2 (calculated using Property Calculator 4.7).

PHARMACOLOGY

Pharmacodynamics:

Mechanism of Action

Dutasteride-tamsulosin 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 α1a-adrenoreceptors.

Dutasteride inhibits both type 1 and type 2, 5 α-reductase isoenzymes, which are responsible for the conversion of testosterone to 5 α-dihydrotestosterone (DHT). DHT is the androgen primarily responsible for hyperplasia of glandular prostatic tissue.

Tamsulosin inhibits α1a adrenergic receptors in the stromal prostatic smooth muscle and bladder neck. Approximately 75% of the α1-receptors in the prostate are of the α1a subtype.

Pharmacodynamic Effects

The pharmacodynamic effects of dutasteride-tamsulosin have not been studied; however, the effects of the combination would not be expected to be different from those of dutasteride and tamsulosin administered separately.

Dutasteride

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 one to two weeks. After one week and two weeks of daily dosing of dutasteride 500µg, median serum DHT concentrations were reduced by 85% and 90%, respectively.

In BPH patients treated with 500µg of dutasteride daily, the median decrease in DHT was 94% at one year and 93% at two years, and the median increase in serum testosterone was 19% at both one and two years. This is an expected consequence of 5 alpha-reductase inhibition and did not result in any known adverse events.

Tamsulosin

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.

The tamsulosin HCl component in DUODART has not been shown to be bioequivalent to the tamsulosin HCl product currently available in Australia. The clinical efficacy of the two tamsulosin formulations has been shown to be similar. Due to differences in pharmacokinetics, small differences in some adverse event rates have been reported.
When the Australian formulation of tamsulosin (tamsulosin OCAS 0.4 mg) was compared to a tamsulosin formulation equivalent to DUODART (tamsulosin MR 0.4 mg), the incidences of all treatment emergent adverse events attributable to \(\alpha\) adrenergic blockade were 6.9% (non-cardiovascular 4.4% and cardiovascular 2.5%) for the OCAS formulation and 7.8% (non-cardiovascular 5.1% and cardiovascular 3.2%) for the MR formulation. Non-cardiovascular events included all abnormal ejaculation-related events, headache, asthenia, fatigue, somnolence, rhinitis, nasal dryness, nasal congestion and nasal obstruction. Cardiovascular events included all dizziness-related events, palpitations, tachycardia, hypotension, orthostatic hypotension, dizziness postural, syncope, orthostatic/circulatory collapse and depressed level of loss of consciousness. The most common treatment emergent adverse events were dizziness (1.4% vs 1.3%) and retrograde ejaculation (1.7% vs 1.4%). If switching between tamsulosin formulations, patients should be advised of these differences and monitored accordingly. Patients should also be reminded to adhere to the dosage and administration requirements for each product.

**Pharmacokinetics:**

Bioequivalence was demonstrated between DUODART and concomitant dosing with separate dutasteride and tamsulosin capsules. (The formulation of tamsulosin used in these studies is not bioequivalent to the tamsulosin HCl product currently available in Australia. However, the clinical efficacy of the two different tamsulosin formulations has been shown to be similar.)

The tamsulosin HCl component of DUODART consists of a multi-unit pelletised preparation which has modified release properties. The individual pellets consist of a drug core and an outer coating layer which reduces the rate of dissolution of the drug.

The single dose bioequivalence study was performed in both the fasted and fed states. A 30% reduction in Cmax 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*

Dutasteride is administered orally in solution as a soft gelatin capsule. Following administration of a single 500µg 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.

As noted above, there are differences in the pharmacokinetics of DUODART and the current Australian tamsulosin formulation. The following table has been taken from published literature:
### Distribution

**Dutasteride**

Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to plasma proteins (greater than 99.5%).

Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after one month and approximately 90% after three months. Steady state serum concentrations (C_{ss}) of approximately 40 ng/mL are achieved after six months of dosing 500µg once a day. Similarly to serum, dutasteride concentrations in semen achieved steady state at six months. After 52 weeks of therapy, semen dutasteride concentrations averaged 3.4 ng/mL (range 0.4 to 14 ng/mL). Dutasteride partitioning from serum into semen averaged 11.5%.

**Tamsulosin**

The mean steady-state apparent volume of distribution of tamsulosin hydrochloride after intravenous administration to ten healthy male adults was 16 L, which is suggestive of distribution into extracellular fluids in the body.

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

### Metabolism

**Dutasteride**

Dutasteride is extensively metabolised in humans. While not all metabolic pathways have been identified, *in vitro* studies show that dutasteride is metabolised by the CYP3A4 isoenzyme to 2 minor mono-hydroxylated metabolites. Dutasteride is not metabolised *in vitro* by human cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and 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), have been detected. *In vitro*, 4'-hydroxydutasteride and 1,2-dihydrodutasteride metabolites are much
less potent than dutasteride against both isoforms of human 5α-reductase. The activity of 6β-hydroxydutasteride is comparable to that of dutasteride.

**Tamsulosin**
There is no enantiomeric bioconversion from tamsulosin hydrochloride [R(-) isomer] to the S(+)-isomer in humans. Tamsulosin hydrochloride is extensively metabolized 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. The metabolites of tamsulosin hydrochloride undergo extensive conjugation to glucuronide or sulfate prior to renal excretion.

**Elimination**

**Dutasteride**
Dutasteride is extensively metabolized. Following oral dosing of dutasteride 500µg/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 low serum concentrations (less than 3 ng/mL), dutasteride is cleared rapidly by both the concentration-dependent and concentration-independent elimination pathways. Single doses of 5 mg or less showed evidence of rapid clearance and a short half-life of 3 to 9 days.

At serum concentrations greater than 3 ng/mL, dutasteride is cleared slowly (0.35 to 0.58 L/h) primarily by linear, non-saturable elimination with terminal half-life of 3 to 5 weeks. At therapeutic concentrations, the terminal half-life of dutasteride is 3 to 5 weeks, and following repeat dosing of 500µg/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 following intravenous administration. Following the administration of DUODART, the tamsulosin half-life was reported to be 12 to 14 hours. Approximately 10% is excreted unchanged in urine.

**Special Populations:**

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

**Elderly**

**Dutasteride**
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 Cmax values, was not statistically different when comparing age groups. Half-life was not statistically different when comparing the 50 to 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 500µg 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 ≤ CLcr < 70 mL/min/1.73m²) or moderate-severe (10 ≤ CLcr < 30 mL/min/1.73m²) renal impairment and 6 normal subjects (CLcr > 90 mL/min/1.73m²). While a change in the overall plasma concentration of tamsulosin hydrochloride was observed as the result of altered binding to AAG, the unbound (active) concentration of tamsulosin hydrochloride, as well as the intrinsic clearance, remained relatively constant. Therefore, patients with renal impairment do not require an adjustment in tamsulosin hydrochloride capsules dosing. However, patients with end stage renal disease (CLcr <10 mL/min/1.73m²) have not been studied.

**Hepatic impairment**

**Dutasteride**

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, 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.

**Children**

Duodart is contraindicated for use in children.
**CLINICAL TRIALS**

*Dutasteride co-administered with tamsulosin*

The following statements reflect the information available on dutasteride and tamsulosin when administered together as separate medications. No clinical studies have been conducted with the fixed-dose combination capsule, DUODART (see Pharmacodynamics).

Dutasteride 500µg/day (n=1,623), tamsulosin 400µg/day (n=1,611) or the combination of dutasteride 500µg plus tamsulosin 400µg (n=1,610) administered once daily [total number of patients = 4844] were evaluated in men with moderate to severe symptoms of BPH who had prostate volumes ≥30mL and a PSA values within the range 1.5 – 10 ng/mL in a multicenter, multinational, randomized double-blind, parallel group study (CombAT). Approximately 52% of subjects had previous exposure to 5α-reductase inhibitor or alpha-blocker treatment.

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 dutasteride and -4.3 units for tamsulosin.

The adjusted mean improvement in flow rate from baseline was 2.4 ml/sec for co-administration therapy, 1.9 ml/sec for dutasteride and 0.9 ml/sec for tamsulosin. The adjusted mean improvement in BPH Impact Index (BII) from baseline was -2.1 units for co-administration therapy, -1.7 for dutasteride 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.

**Table 1  Results following 2 years of treatment**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time-point</th>
<th>Combination</th>
<th>Dutasteride</th>
<th>Tamsulosin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>-1.3</td>
<td>-1.8</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(-1.69, -0.86)</td>
<td>(-2.23, -1.40)</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qmax (mL/sec)</td>
<td>[Baseline] Months 24 (change from baseline)</td>
<td>[10.9] 2.4</td>
<td>[10.6] 1.9</td>
<td>[10.7] 0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.52</td>
<td>1.53</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.003</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.18, 0.86)</td>
<td>(1.20, 1.87)</td>
</tr>
<tr>
<td>Prostate Volume</td>
<td>[Baseline] Months 24 (% change from baseline)</td>
<td>[54.7] -26.9</td>
<td>[54.6] -28.0</td>
<td>[55.8] 0.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.1</td>
<td>-26.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.19</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-16, 2.8)</td>
<td>(-28.9, -24.9)</td>
</tr>
</tbody>
</table>
The primary efficacy endpoint at 4 years of treatment was time to first event of AUR or BPH-related surgery. The study was powered to show a statistical difference between combination therapy and tamsulosin, but not between combination therapy and dutasteride or between tamsulosin and dutasteride. 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 dutasteride 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 dutasteride.

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 dutasteride 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 dutasteride monotherapy and -3.8 units for tamsulosin monotherapy.

After 4 years of treatment, the adjusted mean improvement in flow rate (Qmax) from baseline was 2.4 ml/sec for combination therapy, 2.0 ml/sec for dutasteride monotherapy and 0.7 ml/sec for tamsulosin monotherapy. Compared with tamsulosin, the adjusted mean improvement from baseline in Qmax was statistically significantly greater with combination therapy at each 6-month assessment from Month 6 to Month 48 (\( p<0.001 \)). Compared with dutasteride, the adjusted mean improvement from baseline in Qmax 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 dutasteride 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 dutasteride and -1.2 for tamsulosin. The adjusted mean improvement in BHS from baseline was -1.5 units for the combination, -1.3 for dutasteride 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.

After 4 years of treatment, the incidence of the composite term cardiac failure in the combination group (14/1610, 0.9%) was higher than in either monotherapy group: dutasteride, 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 dutasteride monotherapy and 1.36 [95% CI 0.61, 3.07] compared to tamsulosin monotherapy. The reason for the observed imbalance is not known. There was no difference between treatment groups in incidence of overall cardiovascular events. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (see PRECAUTIONS).

### Table 2  Results following 4 years of treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time-point</th>
<th>Combination</th>
<th>Dutasteride</th>
<th>Tamsulosin</th>
<th>Risk Reduction Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint with study powered treatment comparison</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of AUR or BPH Related Surgery</td>
<td>Month 48</td>
<td>4.2%</td>
<td></td>
<td>11.9%</td>
<td>65.8% p&lt;0.001 (54.7%, 74.1%)</td>
</tr>
<tr>
<td><strong>Other endpoints and treatment comparisons</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of AUR or BPH Related Surgery</td>
<td>Month 48</td>
<td>4.2%</td>
<td>5.2%</td>
<td>19.6% p=0.18 (-10.9%, 41.7%)</td>
<td></td>
</tr>
<tr>
<td>Clinical Progression*</td>
<td>Month 48</td>
<td>12.6%</td>
<td>17.8%</td>
<td>31.2% p&lt;0.001 (17.7%, 42.5%)</td>
<td></td>
</tr>
<tr>
<td>**Risk Reduction Estimate (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPSS (units)</td>
<td>[Baseline] Month 48</td>
<td>[16.6] -6.3</td>
<td>[16.4] -5.3</td>
<td>-0.96 (p&lt;0.001 (-1.40, -0.52)</td>
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</tr>
<tr>
<td>Qmax (mL/sec)</td>
<td>[Baseline] Month 48</td>
<td>[10.9] 2.4</td>
<td>[10.6] 2.0</td>
<td>0.35 (p=0.05 (0.00, 0.70)</td>
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<tr>
<td>Prostate Volume</td>
<td>[Baseline] (mL)</td>
<td>[54.7] -27.3</td>
<td>[54.6] -28.0</td>
<td>0.7 (p=0.42 (-1.1, 2.5)</td>
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<tr>
<td>Prostate Transition Zone Volume</td>
<td>[Baseline] (mL)</td>
<td>[27.7] -17.9</td>
<td>[30.3] -26.5</td>
<td>8.6 (p=0.053 (-0.1, 17.4)</td>
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<tr>
<td><strong>Adjusted mean difference (95%CI)</strong></td>
<td></td>
<td></td>
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</table>

Table entries are given as percentage change from baseline.
**BPH Impact Index (BII) (units)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 48 (change from baseline)</th>
</tr>
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<tbody>
<tr>
<td><strong>BPH Impact</strong></td>
<td>[5.3]</td>
<td>[5.3]</td>
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<tr>
<td><strong>Index (BII)</strong></td>
<td>-2.2</td>
<td>-1.8</td>
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<tr>
<td></td>
<td>-0.32</td>
<td>p&lt;0.001 (-0.51, -0.13)</td>
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<td>[5.3]</td>
<td>[5.3]</td>
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<tr>
<td></td>
<td>-1.2</td>
<td>p&lt;0.001 (-1.13, -0.75)</td>
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</table>

**IPSS Question 8 (BPH-related Health Status)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 48 (change from baseline)</th>
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<tr>
<td><strong>IPSS Question 8</strong></td>
<td>[3.6]</td>
<td>[3.6]</td>
</tr>
<tr>
<td><strong>Health Status</strong></td>
<td>-1.5</td>
<td>-1.3</td>
</tr>
<tr>
<td></td>
<td>-0.23</td>
<td>p&lt;0.001 (-0.32, -0.13)</td>
</tr>
<tr>
<td></td>
<td>[3.6]</td>
<td>[3.6]</td>
</tr>
<tr>
<td></td>
<td>-1.1</td>
<td>p&lt;0.001 (-0.55, -0.37)</td>
</tr>
</tbody>
</table>

*Clinical progression was a composite measure defined as one of the following: symptom deterioration by International Prostate Symptom Score ≥ 4 points on two consecutive visits; BPH-related AUR; BPH-related urinary incontinence; recurrent BPH-related urinary tract infection or urosepsis; BPH-related renal insufficiency

In REDUCE (a 4-year, double-blind, randomized parallel group study comparing dutasteride 500 μg/day or placebo in men at increased risk of developing prostate cancer), there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride (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 (primarily tamsulosin, alfuzosin, doxazosin and terazosin), there was a higher incidence of the composite term cardiac failure in subjects taking dutasteride and an alpha blocker concomitantly (12/1152, 1.0%), compared to subjects not taking dutasteride and an alpha blocker concomitantly: dutasteride 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%). The reason for the observed imbalance is not known. There was no difference between treatment groups in incidence of overall cardiovascular events. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (see PRECAUTIONS).

**Dutasteride monotherapy**

The efficacy and safety of dutasteride 500 μg/day in the treatment and prevention of progression of BPH in 4325 males (aged 47 to 94 years with BPH who had enlarged prostates (greater than 30 ccs) and a Prostate Specific Antigen (PSA) value within the range 1.5-10 ng/mL) was demonstrated in three pivotal, randomised, double-blind, placebo-controlled, 2-year multicentre studies (ARIA3001, ARIA3002 and ARIB3003). Of the 4325 males enrolled in the studies, 2167 received dutasteride and 2158 received placebo.

Pooled data from the three pivotal studies show that, in men with BPH, dutasteride reduces the risk of both acute urinary retention (AUR) and the need for surgical intervention (SI). Improvements in BPH related symptoms, increased maximum urinary flow rates, and decreasing prostate volume suggest dutasteride reverses the progression of BPH in men with an enlarged prostate.

Pooled efficacy data from the three pivotal studies is summarised below:

**Acute Urinary Retention (AUR) and Surgical Intervention:**

Relative to placebo dutasteride significantly reduces both the risk and incidence of AUR by 57% (4.2% for placebo versus 1.8% for dutasteride) and the need for BPH-related surgical intervention by 48% (4.1% for placebo versus 2.2% for dutasteride) over 24 months.
Table 3: Rates of occurrence and risk reduction of urological events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 2158)</th>
<th>Avodart (n = 2167)</th>
<th>Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute urinary retention (AUR)</td>
<td>4.2% (n=90)</td>
<td>1.8% (n=39)</td>
<td>57% (p&lt; 0.001)</td>
</tr>
<tr>
<td>BPH-related surgical intervention</td>
<td>4.1% (n=89)</td>
<td>2.2% (n=47)</td>
<td>48% (p&lt;0.001)</td>
</tr>
</tbody>
</table>

Lower Urinary Tract Symptoms (LUTS) assessed by AUA-SI:
Symptoms were quantified using the AUA-SI (American Urological Association Symptom Index), a seven-item questionnaire that evaluates urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia) by rating on a 0 to 5 scale with a maximum score of 35. Entry criteria included a screening score of $\geq 12$ (moderate to severe symptoms). A reduction in score signifies an improvement in symptoms.

The AUA-SI results at each of the scheduled visits, pooled across the three pivotal studies (ARIA3001, ARIA3002, and ARIB3003), are presented in Figure 1. The baseline AUA-SI score across the three studies was approximately 17 units in both treatment groups. Statistically significant improvements in symptom score in patients treated with dutasteride compared to placebo were noted from Month 6 through to Month 24 (p<0.001). At Month 24, the mean decrease from baseline in AUA-SI symptom scores was -4.8 units for dutasteride and -2.4 units for placebo.

Figure 1: Pooled AUA-SI Mean Values (At Visit)
Maximum Urinary Flow (Qmax):

The Qmax results at each of the scheduled visits, pooled across the three pivotal studies (ARIA3001, ARIA3002, and ARIB3003), are presented in Figure 2. Baseline Qmax was approximately 10 mL/sec (normal Qmax ≥ 15 mL/sec) in both treatment groups across the three studies. Statistically significant improvement in Qmax in patients treated with dutasteride compared to placebo was noted from Month 1 through to Month 24. At Month 24, treatment urinary flow had improved by 0.8 mL/sec and 2.4 mL/sec in the placebo and dutasteride groups respectively.

Figure 2: Pooled Maximum Urinary Flow (Qmax) Mean Values (mL/sec) (At Visit)

![Figure 2: Pooled Maximum Urinary Flow (Qmax) Mean Values (mL/sec) (At Visit)](image)

Earliest on-set of statistically significant improvement

Prostate Volume:
In patients treated with dutasteride, prostate volume was shown to reduce as early as one month after initiation of treatment and reductions continued through to Month 24 (p<0.001). Dutasteride led to a mean reduction of prostate volume of 23.6% (from 54.9cc at baseline to 42.1cc) at Month 12 compared with a mean reduction of 0.5% (from 54.0cc to 53.7cc) in the placebo group. At 24 months, dutasteride decreased prostate volume by 25.7% (from 54.9cc at baseline to 41.2cc) compared with an increase of 1.7% (from 54.0cc to 54.1cc) in the placebo group.

Pooled safety data from the three pivotal studies show that the adverse reaction profile of dutasteride (500 μg/day for 24 months) was similar to that of placebo (see ADVERSE REACTIONS).

Breast neoplasia:
In dutasteride BPH monotherapy clinical trials, providing 3374 patient years of exposure to dutasteride, there were 2 cases of breast cancer reported in dutasteride-treated patients, one after 10 weeks and one after 11 months of treatment, and 1 case in a patient who
received placebo. The relationship between long-term use of dutasteride and male breast cancer is unknown.

**Tamsulosin monotherapy**

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.

**INDICATIONS**

DUODART is indicated for the management of moderate to severe symptomatic benign prostatic hyperplasia (BPH).

**CONTRAINDICATIONS**

DUODART is contraindicated in:

- patients with known hypersensitivity to dutasteride, other 5 α-reductase inhibitors, tamsulosin hydrochloride or any component of the preparation.
- women and children (see Pregnancy and Lactation).
- patients with a history of orthostatic hypotension
- patients with severe hepatic impairment (child-Pugh scores >9).
- patients with severe renal impairment (creatinine clearance less than 10 mL/min).
- combination with another α-1 adrenergic blocker.

**PRECAUTIONS**

DUODART should be prescribed after careful benefit risk assessment and after consideration of alternative treatment options including monotherapies.

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).

DUODART must be taken approximately 30 minutes after the same meal each day (see Dosage and Administration). Taking DUODART on an empty stomach may increase the potential for cardiovascular related adverse events such as orthostatic hypotension.

**Combination Therapy with Tamsulosin and 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, alfuzosin, doxazosin and terazosin) than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was ≤1%. The reason for the imbalance of cardiac failure in the two trials is not known. No imbalance was observed in the incidence of cardiovascular adverse events overall in either trial. No causal relationship between dutasteride (alone or in combination with an alpha blocker) and cardiac failure has been established (see CLINICAL TRIALS).

**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 DUODART and periodically thereafter.

PSA concentration is an important component of the screening process to detect prostate cancer. Generally, a serum PSA concentration greater than 4 ng/mL (Hybritech) requires further evaluation and consideration of prostate biopsy. Physicians should be aware that a baseline PSA less than 4 ng/mL in patients taking DUODART does not exclude a diagnosis of prostate cancer.

Dutasteride causes a decrease in serum PSA levels by approximately 50% after 6 months in patients with BPH, even in the presence of prostate cancer. Although there may be individual variation, the reduction in PSA by approximately 50% is predictable as it was observed over the entire range of baseline PSA values (1.5 to 10 ng/mL). Therefore to interpret an isolated PSA value in a man treated with DUODART for 6 months or longer, PSA values should be doubled for comparison with normal ranges in untreated men. This adjustment preserves the sensitivity and specificity of the PSA assay and maintains its ability to detect prostate cancer.

Patients receiving DUODART should have a new PSA baseline established after 6 months of treatment with dutasteride. 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 (particularly high grade 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 5α-reductase inhibitor (see CLINICAL TRIALS). In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.

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 dutasteride. 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.

**Prostate cancer and high grade tumours**

In a study in men at high risk of developing prostate cancer there was an increased incidence of Gleason score 8-10 prostate cancer observed for men taking Avodart compared with men taking placebo.

5 alpha reductase inhibitors may increase the risk of development of high-grade prostate cancer. Whether the effect of 5 alpha reductase inhibitors to reduce prostate volume, or study-related factors, impacted the results of these studies has not been established.
Orthostatic 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.

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.

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 and to report such symptoms without delay to their doctor. They should also be cautioned to avoid situations where injury could result should these symptoms occur.

Patients switching from the current Australian tamsulosin product should be advised of the differences between this product and DUODART (see Pharmacokinetics) and the potential for orthostatic hypotension (particularly if DUODART is taken on an empty stomach). Patients should be advised to take DUODART approximately 30 minutes after the same meal each day and never on an empty stomach, as well as the need to maintain vigilance for signs of dizziness and vertigo.

Blood Donation

Men being treated with any dutasteride-containing products, including DUODART, should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

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. This syndrome is characterised by the combination of a flaccid iris that billows as a result of intra-operative irrigation currents, prolapse of the iris toward the phaco-emulsification incisions, and progressive intra-operative miosis despite pre-operative dilation with standard mydriatic drugs. IFIS may lead to increased procedural complications during the operation.

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

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

Sulphur allergy

A causal relationship between tamsulosin and sulfur allergy has not been established, however there is a theoretical risk of an allergic reaction when tamsulosin is taken by patients with a history of sulfur allergy. If a patient reports a serious or life threatening sulphur allergy, caution is warranted when administering DUODART.
Renal Impairment

Severe renal impairment, with creatinine clearance of less than 10 mL/min, is a CONTRAINDICATION, as these patients have not been studied.

Hepatic Impairment

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized and has a half-life of 3 to 5 weeks, caution should be used in the administration of dutasteride-tamsulosin to patients with liver disease (see Dosage and Administration and Pharmacokinetics).

DUODART is contraindicated in patients with severe hepatic impairment.

Effects on Fertility

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.

Dutasteride

No animal fertility studies have been conducted with co-administration of dutasteride and tamsulosin.

Treatment of sexually mature male rats with dutasteride at doses up to 500 mg/kg/day (110-fold the expected clinical exposure of parent drug) for up to 31 weeks resulted in dose- and time-dependant decreases in fertility, reduced cauda epididymal (absolute) sperm counts (at 50 and 500 mg/kg/day), reduced weights of the epididymis, prostate and seminal vesicles, and microscopic changes in the male reproductive organs. The fertility effects were reversed by recovery week 6 at all doses and sperm counts were normal at the end of a 14-week recovery period. The 5α-reductase-related changes consisted of cytoplasmic vacuolation of tubular epithelium in the epididymides and decreased cytoplasmic content of epithelium, consistent with decreased secretory activity in the prostate and seminal vesicles. The microscopic changes were no longer present at recovery week 14 in the low dose group and were partly recovered in the remaining treatment groups. Low levels of dutasteride were detected in the serum of untreated female rats mated to males dosed at 10 mg/kg/day and above for 29 weeks.

The effects of dutasteride 500µg /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

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

Use in Pregnancy (Category X):

DUODART is contraindicated for use in women.

**Dutasteride**

As with other 5-alpha reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male foetus, inhibit the development of the external genitalia of the foetus. Small amounts of dutasteride have been recovered from the semen in subjects receiving dutasteride. Based on studies in animals, it is unlikely that a male foetus will be adversely affected if his mother is exposed to the semen of a patient being treated with dutasteride (the risk of which is greatest during the first 16 weeks of pregnancy). However, as with all 5-alpha reductase inhibitors, 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.

Use in Lactation:

DUODART is contraindicated for use in women.

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

Carcinogenicity:

**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**

Oral (dietary) administration of tamsulosin for up to 2 years in rats and mice was associated with an increased incidence of pituitary adenoma, mammary gland hyperplasia, mammary gland fibroadenoma and (in mice only) mammary gland adenocarcinoma. These effects occurred at plasma tamsulosin concentrations (AUC) up to 10 times lower than those expected in men undergoing treatment with tamsulosin, but they were observed only in female animals and are probably due to the hyperprolactinaemic effect of tamsulosin. It is not known if tamsulosin elevates prolactin during prolonged administration in humans. The relevance for human risk of the findings of prolactin-mediated endocrine tumours in female rodents is unknown.

Genotoxicity:

Dutasteride and tamsulosin hydrochloride showed no evidence of genotoxicity in a wide range of in vitro and in vivo tests.
Interactions with other medicines:

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

Interactions of dutasteride and tamsulosin with cytochrome P450 Inhibitors

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.

Long-term combination of dutasteride with drugs 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.

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 metabolized by human cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP2D6.

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

Tamsulosin: Strong and Moderate Inhibitor of CYP3A4 or CYP2D6: Tamsulosin is extensively metabolized, mainly by CYP3A4 or CYP 2D6.

Concomitant treatment with ketoconazole (a strong inhibitor of CYP3A) has resulted in increases in the C\text{max} and AUC of tamsulosin. The effects of concomitant administration of a moderate CYP3A4 inhibitor (e.g., erythromycin) on the pharmacokinetics of tamsulosin have not been evaluated. Concomitant treatment with paroxetine (a strong inhibitor of CYP2D6) has also resulted in increases in the C\text{max} and AUC of tamsulosin. The effects of concomitant administration of a moderate CYP2D6 inhibitor (e.g. terbinafine) on the pharmacokinetics of tamsulosin have not been evaluated. The effects of concomitant administration of both a CYP3A4 and a CYP2D6 inhibitor with tamsulosin have not been evaluated. However, there is a potential for significant increase in tamsulosin exposure when tamsulosin 0.4 mg is coadministered with a combination of both CYP3A4 and CYP2D6 inhibitors.

Interactions of dutasteride and tamsulosin with particular drugs or classes of drugs

Cimetidine:
Concomitant administration of tamsulosin hydrochloride (400 µg) and cimetidine (400 mg every 6 hours for 6 days) resulted in a decrease in the clearance (26%) and an increase in the AUC (44%) of tamsulosin hydrochloride. Caution should be used when dutasteride-tamsulosin is used in combination with cimetidine.

**Alpha-adrenergic Antagonists**
There is a risk of additive hypotensive effects when tamsulosin hydrochloride is co-administered with drugs which can reduce blood pressure, including anaesthetic agents and other α-1 adrenergic blockers. Concurrent administration of DUODART and other drugs containing α-1 adrenergic blockers is therefore contraindicated (see Contraindications).

**PDE-5 Inhibitors**
Caution is advised when alpha-adrenergic antagonists, including tamsulosin-containing products such as DUODART, are coadministered with PDE-5 inhibitors. Alpha-adrenergic antagonists and PDE-5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these 2 drug classes can potentially cause symptomatic hypotension.

**Warfarin**
*Dutasteride:* In vitro studies demonstrate that dutasteride does not displace warfarin. No clinically significant interactions have been observed following concomitant administration of dutasteride and tamsulosin.

*Tamsulosin:* 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.

**Nifedipine, Atenolol, Enalapril**
*Tamsulosin:* In three studies, no interactions were seen when tamsulosin (400 µg for seven days followed by 800 µg for 7 days) was given concomitantly with atenolol, enalapril or nifedipine for 3 months; therefore no dose adjustments are necessary when these drugs are co-administered with DUODART.

**Digoxin and Theophylline**
*Dutasteride:* Dutasteride does not alter the steady-state pharmacokinetics of digoxin.

*Tamsulosin:* Dosage adjustments are not necessary when tamsulosin is administered concomitantly with digoxin.

Concomitant administration of tamsulosin hydrochloride (400 µg/day for two days, followed by 800µg/day for five to eight days) and a single i.v. dose of theophylline (5 mg/kg) resulted in no change in the pharmacokinetics of theophylline; therefore no dose adjustment is necessary.

**Furosemide**
*Tamsulosin:* Concomitant administration of tamsulosin hydrochloride (800 µg /day) and a single i.v. dose of furosemide (20 mg) produced an 11% to 12% reduction in the Cmax and AUC of tamsulosin hydrochloride, however these changes are expected to be clinically insignificant and no dose adjustment is necessary.

**Calcium Channel Blockers**
*Dutasteride:* Coadministration of verapamil or diltiazem decreases dutasteride clearance and leads to increased exposure to dutasteride. However, the change in dutasteride
exposure is not considered clinically significant. No dosage adjustment of dutasteride is recommended.

**Cholestyramine**

* Dutasteride: Administration of a single 5-mg dose of dutasteride followed 1 hour later by a 12 g dose of cholestyramine does not affect the relative bioavailability of dutasteride.

**Other products**

* Dutasteride: *In vitro* studies demonstrate that dutasteride does not displace diazepam, or phenytoin from plasma protein, nor do these model compounds displace dutasteride.

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.

A drug interaction study with tamsulosin or terazosin administered in combination with dutasteride for two weeks showed no evidence of pharmacokinetic or pharmacodynamic interactions.

Tamsulosin binds extensively to plasma proteins and may displace other protein-bound drugs. Conclusive clinical trials data are not available.

**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 EFFECTS**

There have been no clinical trials conducted with DUODART; however, co-administration information for Years 1 and 2 is available from the CombAT (Combination of Avodart and Tamsulosin) study, a comparison of dutasteride 500 µg and tamsulosin 400 µg 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.
<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Incidence during treatment period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Year 1</td>
</tr>
<tr>
<td>Combination a (n)</td>
<td>(n=1610)</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>(n=1623)</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>(n=1611)</td>
</tr>
<tr>
<td>Total incidence of drug-related</td>
<td></td>
</tr>
<tr>
<td>adverse events</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>22%</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>15%</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>13%</td>
</tr>
<tr>
<td>Impotence*</td>
<td></td>
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<tr>
<td>Combination</td>
<td>6%</td>
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<tr>
<td>Dutasteride</td>
<td>5%</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>3%</td>
</tr>
<tr>
<td>Altered (decreased) libido*</td>
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<tr>
<td>Combination</td>
<td>5%</td>
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<tr>
<td>Dutasteride</td>
<td>4%</td>
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<td>Tamsulosin</td>
<td>2%</td>
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<tr>
<td>Ejaculation disorders*</td>
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<tr>
<td>Combination</td>
<td>9%</td>
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<tr>
<td>Dutasteride</td>
<td>1%</td>
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<tr>
<td>Tamsulosin</td>
<td>3%</td>
</tr>
<tr>
<td>Breast disorders*b</td>
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<tr>
<td>Combination</td>
<td>2%</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>2%</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>1%</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>1%</td>
</tr>
</tbody>
</table>

* Composite of similar event terms
a Combination = dutasteride 0.5 mg once daily plus tamsulosin 0.4 mg once daily.
b Includes breast tenderness and breast enlargement.
Dutasteride Monotherapy

Clinical Trial Data
In three phase III placebo controlled studies of dutasteride treatment (n=2167) 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.

Post Marketing Data
Adverse drug reactions are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥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.

Skin and subcutaneous tissue disorders:
Rare: Alopecia (primarily body hair loss), hypertrichosis.

Tamsulosin Monotherapy

Clinical Trial Data and Post marketing Data

Priapism
Rarely, tamsulosin, like other α1-antagonists, has been associated with priapism (persistent painful penile erection unrelated to sexual activity). Patients should be informed that this reaction is extremely rare, but if not brought to immediate medical attention, can lead to permanent erectile dysfunction.

Abnormal ejaculation
Patients should also be advised on the potential for abnormal ejaculation, such as retrograde ejaculation, to occur upon commencement of tamsulosin treatment.

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.
<table>
<thead>
<tr>
<th>Frequency Category</th>
<th>System Organ Class</th>
<th>Common (&lt;1/100 &lt;1/10)</th>
<th>Uncommon (≥1/100 &lt;1/100)</th>
<th>Rare (≥1/10,000 &lt;1/1000)</th>
<th>Very rare (&lt;1/10,000) including isolated cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td>Palpitations</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td>Constipation</td>
<td>Diarrhoea</td>
<td>Vomiting</td>
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<td>General disorders and administration site disorders</td>
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<td>Asthenia</td>
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<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Dizziness</td>
<td>Syncope</td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td></td>
<td>Abnormal ejaculation</td>
<td>Priapism</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>Rhinitis</td>
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<tr>
<td>Immune system disorders</td>
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<td>Rash</td>
<td>Angioedema</td>
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<tr>
<td>Vascular disorders</td>
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<td>Postural hypotension</td>
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</table>

During post marketing surveillance, reports of Intraoperative Floppy Iris Syndrome (IFIS), a variant of small pupil syndrome, during cataract surgery have been associated with α-1 adrenergic blocker therapy; including tamsulosin (see Warnings and Precautions). Infrequent reports of skin desquamation have also been received.

**DOSAGE AND ADMINISTRATION**

DUODART must be taken approximately 30 minutes after the same meal each day. Patients should be advised that DUODART should not be taken on an empty stomach as this may increase the potential for cardiovascular related adverse events such as orthostatic hypotension.

For advice on switching from tamsulosin monotherapy to DUODART combination therapy, please read the information under Pharmacodynamic effects.

**Populations**

- **Adult males (including elderly)**

The recommended dose of DUODART is one capsule (500 µg dutasteride /400 µg tamsulosin) taken orally approximately 30 minutes after the same meal each day (see Pharmacokinetics – 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.
Renal impairment

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

Hepatic impairment

The effect of hepatic impairment on DUODART pharmacokinetics has not been studied (see Warnings and Precautions and Pharmacokinetics – Hepatic impairment). DUODART is contraindicated in patients with severe hepatic impairment.

OVERDOSAGE

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 500 µg.

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

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

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.

PRESENTATION AND STORAGE CONDITIONS

Store below 25°C.

DUODART capsules (dutasteride 500µg/tamsulosin hydrochloride 400µg): oblong, hard-shell capsules with a brown body and an orange cap imprinted with GS 7CZ in black ink [each containing one oblong, opaque, dull-yellow dutasteride soft gelatin capsule (500µg dutasteride) and white to off-white tamsulosin hydrochloride pellets (400µg tamsulosin hydrochloride)].

DUODART capsules are packed into the following container closure systems:
Opaque, white high density polyethylene (HDPE) bottles with polypropylene child-resistant closures with induction-seal liners:
7 capsules in 40 mL bottle
30 capsules in 100 mL bottle
90* capsules in 200 mL bottle
* This pack size not currently marketed.

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POISON SCHEDULE OF THE MEDICINE
Schedule 4 – Prescription Only Medicine

Date of TGA Approval: 19 August 2011

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