SILOFAST D Capsules (Silodosin + Dutasteride)

**Composition**

SILOFAST D 4 Capsules
Each combipack contains:
10 hard gelatin capsules of Silodosin and
10 soft gelatin capsules of Dutasteride
(A) Silodosin hard gelatin capsules
Each hard gelatin capsule contains:
Silodosin .............................. 4 mg
Approved colours used in empty capsule
(B) Dutasteride soft gelatin capsules
Each soft gelatin capsule contains:
Dutasteride IP ....................... 0.5 mg
Approved colours used in empty capsule

SILOFAST D 8 Capsules
Each combipack contains:
10 hard gelatin capsules of Silodosin and
10 soft gelatin capsules of Dutasteride
(A) Silodosin hard gelatin capsules
Each hard gelatin capsule contains:
Silodosin .............................. 8 mg
Approved colours used in empty capsule
(B) Dutasteride soft gelatin capsules
Each soft gelatin capsule contains:
Dutasteride IP ....................... 0.5 mg
Approved colours used in empty capsule

**Dosage Form**

Capsules

**Description**

The symptoms associated with benign prostatic hyperplasia (BPH) are related to bladder outlet obstruction, which is comprised of two underlying components: static and dynamic. The static component is related to an increase in the prostate size, caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. The dynamic component is a function of an increase in smooth muscle tone in the prostate and bladder neck, leading to constriction of the
bladder outlet.

SILOFAST D 4/D 8 capsules are available as a combipack containing silodosin and dutasteride capsules. Silodosin is a selective antagonist of post-synaptic alpha\textsubscript{1}-adrenoreceptors, which are located in the human prostate, bladder base, bladder neck, prostatic capsule, and prostatic urethra. Blockade of these alpha\textsubscript{1}-adrenoreceptors can cause smooth muscle in these tissues to relax, resulting in an improvement in urine flow and a reduction in BPH symptoms.

Dutasteride is a synthetic 4-azasteroid compound that is a selective inhibitor of both the type I and type II isoforms of steroid 5 alpha-reductase, an intracellular enzyme that converts testosterone to 5 alpha-dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland.

### Pharmacology

#### Pharmacodynamics

**Silodosin**

**Mechanism of Action**

Silodosin is a selective antagonist of post-synaptic alpha\textsubscript{1}-adrenoreceptors, which are located in the human prostate, bladder base, bladder neck, prostatic capsule and prostatic urethra. Blockade of these alpha\textsubscript{1}-adrenoreceptors can cause smooth muscle in these tissues to relax, resulting in an improvement in urine flow and a reduction in BPH symptoms.

An *in vitro* study examining the binding affinity of silodosin to the three subtypes of the alpha\textsubscript{1}-adrenoreceptors (alpha\textsubscript{1A}, alpha\textsubscript{1B}, and alpha\textsubscript{1D}) was conducted. The results of the study demonstrated that silodosin binds with high affinity to the alpha\textsubscript{1A} subtype.

**Orthostatic Effects**

A test for postural hypotension was conducted 2 to 6 hours after the first dose in two 12-week, double-blind, placebo-controlled clinical studies. After the patient had been at rest in a supine position for 5 minutes, the patient was asked to stand. Blood pressure and heart rate were assessed at 1 minute and 3 minutes after standing. A positive result was defined as a >30 mm Hg decrease in systolic blood pressure, or a >20 mm Hg decrease in diastolic blood pressure, or a >20 bpm increase in heart rate.

<table>
<thead>
<tr>
<th>Time of Measurement</th>
<th>Test Result</th>
<th>Silodosin N=466 n (%)</th>
<th>Placebo N=457 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 minute after standing</td>
<td>Negative</td>
<td>459 (98.7)</td>
<td>454 (99.6)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>6 (1.3)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>3 minutes after standing</td>
<td>Negative</td>
<td>456 (98.1)</td>
<td>454 (99.6)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>9 (1.9)</td>
<td>2 (0.4)</td>
</tr>
</tbody>
</table>

**Cardiac Electrophysiology**

The effect of silodosin on QT interval was evaluated in a double-blind, randomized, active-(moxifloxacin) and placebo-controlled, parallel-group study in 189 healthy male subjects aged 18 to 45 years. Subjects received silodosin 8 mg, silodosin 24 mg, or placebo once daily for 5 days, or a single dose of moxifloxacin 400 mg on day 5 only. The 24 mg dose of silodosin was selected to achieve blood levels of silodosin that may be seen in a ‘worst-case’ scenario exposure (i.e. in
the setting of concomitant renal disease or use of strong cytochrome (CY) P3A4 inhibitors)

QT interval was measured during a 24-hour period following dosing on day 5 (at silodosin steady state).
Silodosin was not associated with an increase in individual corrected (QTcI) QT interval at any time during steady state measurement, while moxifloxacin, the active control, was associated with a maximum 9.59 msec increase in QTcI. There has been no signal of torsade de pointes in the post-marketing experience with silodosin outside the United States.

Dutasteride

Mechanism of Action

Dutasteride inhibits the conversion of testosterone to DHT. DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. Testosterone is converted to DHT by the enzyme, 5 alpha-reductase, which exists as two isoforms, type 1 and type 2. The type 2 isoenzyme is primarily active in the reproductive tissues, while the type 1 isoenzyme is also responsible for testosterone conversion in the skin and liver.

Dutasteride is a competitive and specific inhibitor of both type 1 and type 2 5 alpha-reductase isoenzymes, with which it forms a stable enzyme complex. Dissociation from this complex has been evaluated under in vitro and in vivo conditions and is extremely slow. Dutasteride does not bind to the human androgen receptor.

Effect on 5 Alpha DHT and Testosterone

The maximum effect of daily doses of dutasteride on the reduction of DHT is dose-dependent and is observed within 1 to 2 weeks. After 1 and 2 weeks of daily dosing with dutasteride 0.5 mg, median serum DHT concentrations were reduced by 85% and 90%, respectively. In patients with BPH treated with dutasteride 0.5 mg/day for 4 years, the median decrease in serum DHT was 94% at 1 year, 93% at 2 years, and 95% at both 3 and 4 years. The median increase in serum testosterone was 19% at both 1 and 2 years, 26% at 3 years, and 22% at 4 years, but the mean and median levels remained within the physiologic range.

In patients with BPH treated with 5 mg/day of dutasteride or placebo for up to 12 weeks prior to transurethral resection of the prostate, mean DHT concentrations in prostatic tissue were significantly lower in the dutasteride group compared with placebo (784 and 5,793 pg/g, respectively, P<0.001). Mean prostatic tissue concentrations of testosterone were significantly higher in the dutasteride group compared with placebo (2,073 and 93 pg/g, respectively, P<0.001). Adult males with genetically inherited type 2 5 alpha-reductase deficiency also have decreased DHT levels. These 5 alpha-reductase-deficient males have a small prostate gland throughout life and do not develop BPH. Except for the associated urogenital defects present at birth, no other clinical abnormalities related to 5 alpha-reductase deficiency have been observed in these individuals.

Effects on Other Hormones

In healthy volunteers, 52 weeks of treatment with dutasteride 0.5 mg/day (n=26) resulted in no clinically significant change compared with placebo (n=23) in sex hormone-binding globulin, oestradiol, luteinizing hormone, follicle-stimulating hormone, thyroxine (free T4), and dehydroepiandrosterone. Statistically significant, baseline-adjusted mean increases compared with placebo were observed for total testosterone at 8 weeks (97.1 ng/dL, P<0.003) and thyroid-stimulating hormone at 52 weeks (0.4 mcIU/mL, P<0.05). The median percentage changes from baseline within the dutasteride group were 17.9% for testosterone at 8 weeks and 12.4% for thyroid-stimulating hormone at 52 weeks. After stopping dutasteride for 24 weeks, the mean levels of testosterone and thyroid-stimulating hormone had returned to baseline in the group of subjects with available data at the visit. In subjects with BPH treated with dutasteride in a large randomized, double-blind, placebo-controlled trial, there was a median percent increase in luteinizing hormone of 12% at 6 months and 19% at both 12 and 24 months.

Other Effects

Plasma lipid panel and bone mineral density were evaluated following 52 weeks of dutasteride 0.5 mg once daily in healthy volunteers. There was no change in bone mineral density as measured by dual energy x-ray absorptiometry
compared with either placebo or baseline. In addition, the plasma lipid profile (i.e. total cholesterol, low-density lipoproteins, high-density lipoproteins, and triglycerides) was unaffected by dutasteride. No clinically significant changes in adrenal hormone responses to adrenocorticotropic hormone (ACTH) stimulation were observed in a subset population (n=13) of the 1-year healthy volunteer trial.

Pharmacokinetics

Silodosin

Absorption

The pharmacokinetic characteristics of silodosin 8 mg once daily were determined in a multi-dose, open-label, 7-day pharmacokinetic study completed in 19 healthy, target-aged (≥45 years of age) male subjects. Table 2 presents the steady-state pharmacokinetics of this study.

<table>
<thead>
<tr>
<th>C_{max} (ng/mL)</th>
<th>t_{max} (hours)</th>
<th>t_{1/2} (hours)</th>
<th>AUC_{ss} (ng•hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>61.6 ± 27.54</td>
<td>2.6 ± 0.90</td>
<td>13.3 ± 8.07</td>
<td>373.4 ± 164.94</td>
</tr>
</tbody>
</table>

C_{max} = maximum concentration, t_{max} = time to reach C_{max}, t_{1/2} = elimination half-life, AUC_{ss} = steady-state area under the concentration-time curve

Food Effect: The maximum effect of food (i.e. co-administration with a high-fat, high-calorie meal) on the pharmacokinetics of silodosin was not evaluated. The effect of a moderate-fat, moderate-calorie meal was variable and decreased silodosin C_{max} by approximately 18 to 43% and exposure AUC by 4 to 49% across three different studies.

Distribution

Silodosin has an apparent volume of distribution of 49.5 L and is approximately 97% protein-bound.

Metabolism

Silodosin undergoes extensive metabolism through glucuronidation, alcohol and aldehyde dehydrogenase, and CYP450 3A4 pathways. The main metabolite of silodosin is a glucuronide conjugate (KMD-3213G) that is formed via the direct conjugation of silodosin by UDP-glucuronosyltransferase 2B7 (UGT2B7). Co-administration with inhibitors of UGT2B7 (e.g. probenecid, valproic acid, fluconazole) may potentially increase exposure to silodosin. KMD-3213G, which has been shown in vitro to be active, has an extended half-life (approximately 24 hours) and reaches plasma exposure (AUC) approximately four times greater than that of silodosin. The second major metabolite (KMD-3293) is formed via alcohol and aldehyde dehydrogenases and reaches plasma exposures similar to that of silodosin. KMD-3293 is not expected to contribute significantly to the overall pharmacologic activity of silodosin.

Excretion

Following oral administration of ^14^C-labelled silodosin, the recovery of radioactivity after 10 days was approximately 33.5% in the urine and 54.9% in the faeces. After intravenous administration, the plasma clearance of silodosin was approximately 10 L/hour.

Pharmacokinetics in Special Populations

Race: No clinical studies specifically investigating the effects of race have been performed.

Geriatric: In a study comparing 12 geriatric males (mean age, 69 years) and 9 young males (mean age, 24 years), the exposure (AUC) and elimination half-life of silodosin were approximately 15% and 20%, respectively, greater in geriatric than young subjects. No difference in the C_{max} of silodosin was observed

Paediatric: Silodosin has not been evaluated in patients less than 18 years of age.

Renal Impairment: In a study with 6 subjects with moderate renal impairment, the total silodosin (bound and unbound)
AUC, C\text{max}, and elimination half-life were 3.2-, 3.1-, and 2-fold higher, respectively, compared with 7 subjects with normal renal function. The unbound silodosin AUC and C\text{max} were 2.0- and 1.5-fold higher, respectively, in subjects with moderate renal impairment compared with the normal controls.

In controlled and uncontrolled clinical studies, the incidence of orthostatic hypotension and dizziness was greater in subjects with moderate renal impairment treated with 8 mg silodosin daily than in subjects with normal or mildly impaired renal function.

**Hepatic Impairment:** In a study comparing 9 male patients with moderate hepatic impairment (Child-Pugh scores 7 to 9), with 9 healthy male subjects, the single-dose pharmacokinetic disposition of silodosin was not significantly altered in the patients with moderate hepatic impairment. No dosing adjustment is required in patients with mild or moderate hepatic impairment. The pharmacokinetics of silodosin in patients with severe hepatic impairment has not been studied.

**Dutasteride**

**Absorption**

Following administration of a single 0.5 mg dose of dutasteride, time to peak serum concentrations (T\text{max}) occurs within 2 to 3 hours. Absolute bioavailability in 5 healthy subjects is approximately 60% (range: 40% to 94%). When the drug is administered with food, the maximum serum concentrations were reduced by 10 to 15%. This reduction is of no clinical significance.

**Distribution**

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 albumin (99.0%) and alpha\textsubscript{1}-acid glycoprotein (96.6%). In a trial of healthy subjects (n=26) receiving dutasteride 0.5 mg/day for 12 months, semen dutasteride concentrations averaged 3.4 ng/mL (range: 0.4 to 14 ng/mL) at 12 months and, similar to serum, achieved steady-state concentrations at 6 months. On average, at 12 months, 11.5% of serum dutasteride concentrations partitioned into semen.

**Metabolism**

Dutasteride is extensively metabolized in humans. In vitro studies showed that dutasteride is metabolized by the CYP3A4 and CYP3A5 isoenzymes. Both of these isoenzymes produced the 4′-hydroxydutasteride, 6-hydroxydutasteride, and the 6,4′-dihydroxydutasteride metabolites. In addition, the 15-hydroxydutasteride metabolite was formed by CYP3A4.

Dutasteride is not metabolized in vitro by the human CYP450 isoenzymes, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. In human serum following dosing to the steady state, unchanged dutasteride, three major metabolites (4′-hydroxydutasteride, 1,2-dihydroustasteride, and 6-hydroxydutasteride), and two minor metabolites (6,4′-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The absolute stereochemistry of the hydroxyl additions in the 6 and 15 positions is not known. In vitro, the 4′-hydroxydutasteride and 1,2-dihydroustasteride metabolites are much less potent than dutasteride against both isoforms of human 5 alpha-reductase. The activity of 6 beta-hydroxydutasteride is comparable to that of dutasteride.

**Excretion**

Dutasteride and its metabolites were excreted mainly in the faeces. As a percent of dose, there was approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related metabolites (~2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine (<1%). Therefore, on average, the dose unaccounted for approximated 55% (range: 5% to 97%).

The terminal elimination half-life of dutasteride is approximately 5 weeks at the steady state. The average steady-state serum dutasteride concentration was 40 ng/mL following 0.5 mg/day for 1 year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

**Pharmacokinetics in Special Populations**

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**Pharmacokinetics in Special Populations**

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Paediatric: Dutasteride pharmacokinetics has not been investigated in subjects younger than 18 years of age.

Geriatric: No dose adjustment is necessary in the elderly. The pharmacokinetics and pharmacodynamics of dutasteride were evaluated in 36 healthy male subjects aged between 24 and 87 years following administration of a single 5 mg dose of dutasteride. In this single-dose trial, dutasteride half-life increased with age (approximately 170 hours in men aged 20 to 49 years, approximately 260 hours in men aged 50 to 69 years, and approximately 300 hours in men older than 70 years). Of 2,167 men treated with dutasteride in the three pivotal trials, 60% were aged 65 years and over, and 15% were aged 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

Gender: Dutasteride is contraindicated in pregnancy and women of childbearing potential and is not indicated for use in other women. The pharmacokinetics of dutasteride in women has not been studied.

Race: The effect of race on dutasteride pharmacokinetics has not been studied.

Renal Impairment: 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.

Hepatic Impairment: 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.

### Indications

SILOFAST D capsules are indicated for the treatment of the signs and symptoms of BPH in men with an enlarged prostate.

The silodosin capsule is not intended for use as an anti-hypertensive drug.

Dutasteride is not approved for the prevention of prostate cancer.

### Dosage And Administration

One hard gelatin capsule of silodosin (8 mg) and one soft gelatin capsule of dutasteride (0.5 mg) should be taken together after meals. The capsules should be swallowed whole.

#### Special Populations

**Silodosin**

**Renal Impairment**

Silodosin is contraindicated in patients with severe renal impairment (CCr <30 mL/min). In patients with moderate renal impairment (CCr: 30 to 50 mL/min), the dose should be reduced to 4 mg once daily taken with a meal. No dosage adjustment is needed in patients with mild renal impairment (CCr 50 to 80 mL/min)

**Hepatic Impairment**

Silodosin has not been studied in patients with severe hepatic impairment (Child-Pugh score ≥10) and is therefore contraindicated in these patients. No dosage adjustment is needed in patients with mild or moderate hepatic impairment

**Dutasteride**

**Renal Impairment**

No dose adjustment is necessary for dutasteride in patients with renal impairment

**Hepatic Impairment**

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.
Contraindications

Silodosin is contraindicated for use in the following:
- Severe renal impairment (CCr <30 mL/min)
- Severe hepatic impairment (Child-Pugh score ≥10)
- Concomitant administration with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, ritonavir)
- Patients with a history of hypersensitivity to silodosin or any of the ingredients of the capsule

Dutasteride is contraindicated for use in the following:
- Pregnancy: In animal reproduction and developmental toxicity studies, dutasteride inhibited development of the external genitalia of the male foetus. Therefore, dutasteride may cause foetal harm when administered to a pregnant woman. If dutasteride is used during pregnancy or if the patient becomes pregnant while taking dutasteride, the patient should be apprised of the potential hazard to the foetus.
- Women of childbearing potential.
- Paediatric patients.
- Patients with previously demonstrated clinically significant hypersensitivity (e.g. serious skin reactions, angio-oedema) to dutasteride or other 5 alpha-reductase inhibitors.

Warnings And Precautions

General

Silodosin
Orthostatic Effects
Postural hypotension, with or without symptoms (e.g. dizziness) may develop when beginning silodosin treatment. As with other alpha-blockers, there is potential for syncope. Patients should be cautioned about driving, operating machinery or performing hazardous tasks when initiating therapy.

Carcinoma of the Prostate
Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently co-exist. Therefore, patients thought to have BPH should be examined prior to starting therapy with silodosin to rule out the presence of carcinoma of the prostate.

Intraoperative Floppy Iris Syndrome
Intraoperative floppy iris syndrome has been observed during cataract surgery in some patients on alpha₁-blockers or previously treated with alpha₁-blockers. This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents; progressive intraoperative miosis despite pre-operative dilation with standard mydriatic drugs; and potential prolapse of the iris toward the phacoemulsification incisions. Patients planning cataract surgery should be advised to inform their ophthalmologist that they are taking silodosin.

Laboratory Test Interactions
No laboratory test interactions were observed during clinical evaluations. Treatment with silodosin for up to 52 weeks had no significant effect on the prostate-specific antigen (PSA).

Dutasteride
Increased Risk of High-grade Prostate Cancer
In men aged 50 to 75 years with a prior negative biopsy for prostate cancer and a baseline PSA between 2.5 ng/mL and
10.0 ng/mL, who were taking dutasteride for prevention of prostate cancer in the 4-year trial, there was an increased incidence of Gleason score 8–10 prostate cancer compared with men taking placebo (dutasteride 1.0% versus placebo 0.5%). In a 7-year, placebo-controlled clinical trial with another 5 alpha-reductase inhibitor (finasteride 5 mg), similar results for Gleason score 8–10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%). The 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 trial-related factors impacted the results of these trials has not been established.

**Evaluation for Other Urological Diseases**

Prior to initiating treatment with dutasteride, consideration should be given to other urological conditions that may cause similar symptoms. In addition, BPH and prostate cancer may coexist.

**Effects on PSA and the Use of PSA in Prostate Cancer Detection**

In clinical studies, dutasteride reduced serum PSA concentration by approximately 50% within 3 to 6 months of treatment. This decrease was predictable over the entire range of PSA values in patients with symptomatic BPH, although it may vary in individuals. Dutasteride may also cause decreases in serum PSA in the presence of prostate cancer. To interpret serial PSAs in men taking dutasteride, a new PSA baseline should be established at least 3 months after starting treatment and PSA monitored periodically thereafter. Any confirmed increase from the lowest PSA value while on dutasteride may signal the presence of prostate cancer and should be evaluated, even if PSA levels are still within the normal range for men not taking a 5 alpha-reductase inhibitor. Noncompliance with dutasteride may also affect the PSA test results.

To interpret an isolated PSA value in a man treated with dutasteride for 3 months or more, the PSA value should be doubled for comparison with normal values in untreated men.

The free-to-total PSA ratio (percent-free 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 receiving dutasteride, no adjustment to its value appears necessary.

Co-administration of dutasteride and tamsulosin resulted in similar changes to serum PSA as dutasteride monotherapy.

**Exposure of Women — Risk to the Male Foetus**

Dutasteride capsules should not be handled by a woman who is pregnant or who could become pregnant. Dutasteride is absorbed through the skin and could result in unintended foetal exposure. If a woman who is pregnant or who could become pregnant comes in contact with leaking dutasteride capsules, the contact area should be washed immediately with soap and water.

**Blood Donation**

Men being treated with dutasteride 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.

**Effect on Semen Characteristics**

The effects of dutasteride 0.5 mg/day on semen characteristics were evaluated in normal volunteers aged 18 to 52 years (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.

Drug Interactions

Silodosin

**Moderate and Strong CYP3A4 Inhibitors**

Two clinical drug interaction studies were conducted in which a single oral dose of silodosin was co-administered with the strong CYP3A4 inhibitor, ketoconazole, at doses of 400 mg and 200 mg, respectively, once daily for 4 days. Co-administration of 8 mg silodosin with 400 mg ketoconazole led to a 3.8-fold increase in the silodosin $C_{\text{max}}$ and a 3.2-fold increase in the AUC. Co-administration of 4 mg silodosin with 200 mg ketoconazole led to similar increases: 3.7- and 2.9-fold in the silodosin $C_{\text{max}}$ and AUC, respectively. Use of strong CYP3A4 inhibitors such as itraconazole or ritonavir may cause plasma concentrations of silodosin to increase. Concomitant administration of strong CYP3A4 inhibitors and silodosin is contraindicated.

The effect of moderate CYP3A4 inhibitors on the pharmacokinetics of silodosin has not been evaluated. Concomitant administration with moderate CYP3A4 inhibitors (e.g. diltiazem, erythromycin, verapamil) may increase the concentration of silodosin. Exercise caution and monitor patients for adverse events when co-administering silodosin with moderate CYP3A4 inhibitors particularly those that also inhibit P-glycoprotein (e.g. verapamil, erythromycin).

**Strong P-glycoprotein (P-gp) Inhibitors**

*In vitro* studies indicated that silodosin is a P-gp substrate. A drug interaction study with a strong P-gp inhibitor has not been conducted. However, in drug interaction studies with ketoconazole, a CYP3A4 inhibitor that also inhibits P-gp, significant increase in exposure to silodosin was observed. Inhibition of P-gp may lead to increased silodosin concentration. Silodosin is not recommended in patients taking strong P-gp inhibitors such as cyclosporine.

**Alpha-Blockers**

The pharmacodynamic interactions between silodosin and other alpha-blockers have not been determined. However, interactions may be expected and silodosin should not be used in combination with other alpha-blockers.

**Digoxin**

The effect of silodosin on the pharmacokinetics of digoxin was evaluated in a multiple dose, single-sequence, crossover study of 16 healthy males, aged 18 to 45 years. A loading dose of digoxin was administered as 0.5 mg twice daily for one day. Following the loading doses, digoxin (0.25 mg once daily) was administered alone for 7 days and then concomitantly with silodosin 4 mg twice a day for the next 7 days. No significant differences in digoxin AUC and $C_{\text{max}}$ were observed when digoxin was administered alone or concomitantly with silodosin. No dose adjustment is required.

**PDE5 Inhibitors**

Alpha-adrenergic blockers and phosphodiesterase-5 (PDE5) inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension. Co-administration of silodosin with a single dose of 100 mg sildenafil or 20 mg tadalafil was evaluated in a placebo-controlled clinical study that included 24 healthy male subjects, 45 to 78 years of age. Orthostatic vital signs were monitored in the 12-hour period following concomitant dosing. During this period, the total number of positive orthostatic test results was greater in the group receiving silodosin plus a PDE5 inhibitor compared with silodosin alone. No events of symptomatic orthostasis or dizziness were reported in subjects receiving silodosin with a PDE5 inhibitor.

**Other Concomitant Drug Therapy**

**Antihypertensives:** The pharmacodynamic interactions between silodosin and antihypertensives have not been rigorously investigated in a clinical study. However, approximately one-third of the patients in clinical studies used concomitant antihypertensive medications with silodosin. The incidence of dizziness and orthostatic hypotension in these patients was higher than in the general silodosin population (4.6% versus 3.8% and 3.4% versus 3.2%, respectively). Caution should be exercised during concomitant use with antihypertensives and patients should be monitored for possible
adverse events.

**Metabolic Interactions: In vitro** studies indicated that silodosin administration is not likely to inhibit the activity of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 or induce the activity of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, and P-gp.

**Food Interactions**
The effect of a moderate fat, moderate calorie meal on silodosin pharmacokinetics was variable and decreased silodosin maximum plasma concentration ($C_{\text{max}}$) by approximately 18 to 43% and exposure (AUC) by 4 to 49% across three different studies. Safety and efficacy clinical trials for silodosin were always conducted in the presence of food intake. Patients should be instructed to take silodosin with a meal to reduce risk of adverse events.

**Dutasteride**

**CYP450 Inhibitors**
Dutasteride is extensively metabolized in humans by the CYP3A4 and CYP3A5 isoenzymes. No clinical drug interaction trials have been performed to evaluate the impact of CYP3A enzyme inhibitors on dutasteride pharmacokinetics. However, based on *in vitro* data, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4/5 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, troleandomycin, and ciprofloxacin. Because of the potential for drug–drug interactions, use caution when prescribing dutasteride to patients taking potent, chronic CYP3A4 enzyme inhibitors.

Dutasteride does not inhibit the *in vitro* metabolism of model substrates for the major human CYP450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1,000 ng/mL, 25 times greater than steady-state serum concentrations in humans.

**Alpha-Adrenergic Antagonists**
The administration of dutasteride in combination with tamsulosin or terazosin has no effect on the steady-state pharmacokinetics of either alpha-adrenergic antagonist. The effect of administration of tamsulosin or terazosin on dutasteride pharmacokinetic parameters was not evaluated; the percent change in DHT concentrations was similar for dutasteride alone compared with the combination treatment.

**Calcium Channel Antagonists**
In a population pharmacokinetics analysis, a decrease in clearance of dutasteride was noted when co-administered with the CYP3A4 inhibitors verapamil (37%, n=6) and diltiazem (44%, n=5). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist that is not a CYP3A4 inhibitor, was co-administered with dutasteride (+7%, n=4).

The decrease in clearance and subsequent increase in exposure to dutasteride in the presence of verapamil and diltiazem is not considered to be clinically significant. No dose adjustment is recommended.

**Cholestyramine**
Administration of a single 5 mg dose of dutasteride followed 1 hour later by 12 g cholestyramine did not affect the relative bioavailability of dutasteride in 12 normal volunteers.

**Digoxin**
In a trial of 20 healthy volunteers, dutasteride did not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks.

**Warfarin**
In a trial of 23 healthy volunteers, 3 weeks of treatment with dutasteride 0.5 mg/day did not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or alter the effect of warfarin on prothrombin time when administered with warfarin.

**Other Concomitant Therapy**
Although specific interaction trials were not performed with other compounds, approximately 90% of the subjects in the
three randomized, double-blind, placebo-controlled safety and efficacy trials receiving dutasteride were taking other medications concomitantly. No clinically significant adverse interactions could be attributed to the combination of dutasteride and concurrent therapy when dutasteride was co-administered with anti-hyperlipidaemics, 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.

### Information for Patients

**Silodosin**

Patients should be instructed to take silodosin once daily with a meal. Patients should be instructed about the possible occurrence of symptoms related to postural hypotension (such as dizziness), and should be cautioned about driving, operating machinery, or performing hazardous tasks until they know how silodosin will affect them. This is especially important for those with low blood pressure or who are taking antihypertensive medications.

The most common side effect seen with silodosin is an orgasm with reduced or no semen. This side effect does not pose a safety concern and is reversible with discontinuation of the product.

The patient should be instructed to tell his ophthalmologist about the use of silodosin before cataract surgery or other procedures involving the eyes, even if the patient is no longer taking silodosin.

**Dutasteride**

Physicians should inform patients that dutasteride reduces serum PSA levels by approximately 50% within 3 to 6 months of therapy, although it may vary for each individual. For patients undergoing PSA screening, increases in PSA levels while on treatment with dutasteride may signal the presence of prostate cancer and should be evaluated.

Physicians should inform patients that there was an increase in high-grade prostate cancer in men treated with 5 alpha-reductase inhibitors (which are indicated for BPH treatment), including dutasteride, compared with those treated with placebo in studies looking at the use of these drugs to reduce the risk of prostate cancer.

Physicians should inform patients that dutasteride capsules should not be handled by a woman who is pregnant or who could become pregnant because of the potential for absorption of dutasteride and the subsequent potential risk to a developing male foetus. Dutasteride is absorbed through the skin and could result in unintended foetal exposure. If a pregnant woman or woman of childbearing potential comes in contact with leaking dutasteride capsules, the contact area should be washed immediately with soap and water.

Physicians should inform men treated with dutasteride that they should not donate blood until at least 6 months following their last dose, so as to prevent pregnant women from receiving dutasteride through blood transfusion. Serum levels of dutasteride are detectable for 4 to 6 months after treatment ends.

### Renal Impairment

**Silodosin**

The effect of renal impairment on silodosin pharmacokinetics was evaluated in a single dose study of six male patients with moderate renal impairment and seven male subjects with normal renal function. Plasma concentrations of silodosin were approximately three times higher in subjects with moderate renal impairment compared with subjects with normal renal function.

Silodosin should be reduced to 4 mg per day in patients with moderate renal impairment. Exercise caution and monitor patients for adverse events.

Silodosin has not been studied in patients with severe renal impairment. Silodosin is contraindicated in patients with severe renal impairment.

**Dutasteride**
No dose adjustment is necessary for dutasteride in patients with renal impairment

### Hepatic Impairment

**Silodosin**

In a study comparing nine male patients with moderate hepatic impairment (Child-Pugh scores 7 to 9), to nine healthy male subjects, the single dose pharmacokinetics of silodosin were not significantly altered in patients with hepatic impairment. No dosing adjustment is required in patients with mild or moderate hepatic impairment. Silodosin has not been studied in patients with severe hepatic impairment. Silodosin is contraindicated in patients with severe 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. However, in a clinical trial where 60 subjects received 5 mg (10 times the therapeutic dose) daily for 24 weeks, no additional adverse events were observed compared with those observed at the therapeutic dose of 0.5 mg.

### Pregnancy

**Silodosin**

Pregnancy Category B

Silodosin is not indicated for use in women.

**Dutasteride**

Pregnancy Category X

Dutasteride is contraindicated for use in women of childbearing potential and during pregnancy. Dutasteride is a 5 alpha-reductase inhibitor that prevents conversion of testosterone to DHT, a hormone necessary for the normal development of male genitalia. In animal reproduction and developmental toxicity studies, dutasteride inhibited normal development of external genitalia in male foetuses. Therefore, dutasteride may cause foetal harm when administered to a pregnant woman. If dutasteride is used during pregnancy or if the patient becomes pregnant while taking dutasteride, the patient should be apprised of the potential hazard to the foetus.

Abnormalities in the genitalia of male foetuses are an expected physiological consequence of inhibition of the conversion of testosterone to DHT by 5 alpha-reductase inhibitors. These results are similar to observations in male infants with genetic 5 alpha-reductase deficiency. Dutasteride is absorbed through the skin. To avoid potential foetal exposure, women who are pregnant or may become pregnant should not handle dutasteride capsules. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water. Dutasteride is secreted into male semen. The highest measured semen concentration of dutasteride in treated men was 14 ng/mL. Assuming exposure of a 50 kg woman to 5 mL of semen and 100% absorption, the woman's dutasteride concentration would be about 0.175 ng/mL. This concentration is more than 100 times less than concentrations producing abnormalities of male genitalia in animal studies. Dutasteride is highly protein-bound in human semen (>96%), which may reduce the amount of dutasteride available for vaginal absorption.

### Lactation

**Silodosin**

Silodosin capsules are not indicated for use in women.

**Dutasteride**

Dutasteride capsules are contraindicated for use in women of childbearing potential, including nursing women. It is not known whether dutasteride is excreted in human milk.
Paediatric Use

Silodosin
Silodosin is not indicated for use in paediatric patients. Safety and effectiveness in paediatric patients have not been established.

Dutasteride
Dutasteride capsules are contraindicated for use in the paediatric population. Safety and effectiveness in the paediatric population have not been established.

Geriatric Use

Silodosin
In double-blind, placebo-controlled, 12-week clinical studies of silodosin, 259 (55.6%) patients were below 65 years of age, 207 (44.4%) patients were 65 years of age and over, while 60 (12.9%) patients were 75 years of age and over. Orthostatic hypotension was reported in 2.3% of silodosin patients less than 65 years of age (1.2% for placebo), 2.9% of silodosin patients 65 years of age and over (1.9% for placebo), and 5.0% of patients 75 years of age and over (0% for placebo). There were otherwise no significant differences in safety or effectiveness between older and younger patients.

Dutasteride
Of 2,167 male subjects treated with dutasteride in three clinical trials, 60% were aged 65 years and older and 15% were aged 75 years and older. No overall differences in safety or efficacy were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Undesirable Effects

Silodosin

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug can not be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In U.S. clinical trials, 897 patients with BPH were exposed to 8 mg silodosin daily. This includes 486 patients exposed for 6 months and 168 patients exposed for 1 year. The population was 44 to 87 years of age, and predominantly Caucasian. Of these patients, 42.8% were 65 years of age or older and 10.7% were 75 years of age or older.

In double-blind, placebo-controlled, 12-week clinical trials, 466 patients were administered silodosin and 457 patients were administered placebo. At least one treatment-emergent adverse reaction was reported by 55.2% of silodosin-treated patients (36.8% for placebo-treated). The majority (72.1%) of adverse reactions for the silodosin-treated patients (59.8% for placebo-treated) were qualified by the investigator as mild. A total of 6.4% of silodosin-treated patients (2.2% for placebo-treated) discontinued therapy due to an adverse reaction (treatment-emergent), the most common reaction being retrograde ejaculation (2.8%) for silodosin-treated patients. Retrograde ejaculation is reversible upon discontinuation of treatment.

Adverse Reactions Observed in At Least 2% of Patients

The incidence of treatment-emergent adverse reactions listed in the following table were derived from two 12-week, multicentre, double-blind, placebo-controlled clinical studies of silodosin 8 mg daily in BPH patients. Adverse reactions that occurred in at least 2% of patients treated with silodosin and more frequently than with placebo are shown in Table 3.
Table 3: Adverse Reactions Occurring in ≥2% of Patients in 12-week, Placebo-Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Silodosin N=466 n (%)</th>
<th>Placebo N=457 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Retrograde ejaculation</td>
<td>131 (28.1)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (3.2)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12 (2.6)</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>12 (2.6)</td>
<td>7 (1.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (2.4)</td>
<td>4 (0.9)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11 (2.4)</td>
<td>10 (2.2)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>10 (2.1)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

In the above clinical trials, the following adverse events were also reported by between 1% and 2% of patients receiving silodosin and occurred more frequently than with placebo: insomnia, PSA increased, sinusitis, abdominal pain, asthenia and rhinorrhea. One case of syncope in a patient taking prazosin concomitantly and one case of priapism were reported in the silodosin treatment group.

In a 9-month open-label safety study of silodosin, one case of intraoperative floppy iris syndrome was reported.

Postmarketing Experience
The following adverse reactions have been identified during post-approval use of silodosin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

- **Skin and Subcutaneous Tissue Disorders**: Toxic skin eruption, purpura, skin rash, pruritus and urticaria.
- **Hepatobiliary Disorders**: Jaundice, impaired hepatic function associated with increased transaminase values.
- **Immune System Disorders**: Allergic-type reactions, not limited to skin reactions, including swollen tongue and pharyngeal oedema, resulting in serious outcomes.

Dutasteride

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical
trials of a drug cannot be directly compared with rates in the clinical trial of another drug and may not reflect the rates observed in practice.

The most common adverse reactions reported in subjects receiving dutasteride were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), and ejaculation disorders.

Study withdrawal due to adverse reactions occurred in 4% of subjects receiving dutasteride, and 3% of subjects receiving placebo in placebo-controlled trials with dutasteride. The most common adverse reaction leading to study withdrawal was impotence (1%).

**Monotherapy**

Over 4,300 male subjects with BPH were randomly assigned to receive placebo or 0.5 mg daily doses of dutasteride in three identical 2-year, placebo-controlled, double-blind, Phase 3 treatment trials, each followed by a 2-year, open-label extension. During the double-blind treatment period, 2,167 male subjects were exposed to dutasteride, including 1,772 exposed for 1 year and 1,510 exposed for 2 years. When including the open-label extensions, 1,009 male subjects were exposed to dutasteride for 3 years and 812 were exposed for 4 years. The population was aged 47 to 94 years (mean age: 66 years) and greater than 90% were Caucasian. Table 4 summarizes clinical adverse reactions reported in at least 1% of subjects receiving dutasteride and at a higher incidence than subjects receiving placebo.

### Table 4: Adverse Reactions Reported in ≥1% of Subjects Over a 24-Month Period and More Frequently in the Group Receiving Dutasteride than the Placebo Group (Randomized, Double-Blind, Placebo-Controlled Studies Pooled) by Time of Onset

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Adverse Reaction Time of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Months 0 to 6 (n=2,167)</td>
</tr>
<tr>
<td></td>
<td>Months 7 to 12 (n=1,901)</td>
</tr>
<tr>
<td></td>
<td>Months 13 to 18 (n=1,725)</td>
</tr>
<tr>
<td></td>
<td>Months 19 to 24 (n=1,605)</td>
</tr>
<tr>
<td>Dutasteride (n)</td>
<td>Placebo (n)</td>
</tr>
<tr>
<td>Impotence</td>
<td>4.7%</td>
</tr>
<tr>
<td></td>
<td>1.4%</td>
</tr>
<tr>
<td></td>
<td>1.0%</td>
</tr>
<tr>
<td></td>
<td>0.8%</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>1.7%</td>
</tr>
<tr>
<td></td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>0.9%</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.7%</td>
</tr>
<tr>
<td></td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>0.9%</td>
</tr>
<tr>
<td>Decreased libido</td>
<td>3.0%</td>
</tr>
<tr>
<td></td>
<td>0.7%</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>1.4%</td>
</tr>
<tr>
<td></td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>0.1%</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.4%</td>
</tr>
<tr>
<td></td>
<td>0.6%</td>
</tr>
<tr>
<td></td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>0.1%</td>
</tr>
<tr>
<td>Ejaculation disorders</td>
<td>1.4%</td>
</tr>
<tr>
<td></td>
<td>0.5%</td>
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<tr>
<td></td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>0.1%</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
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<tr>
<td></td>
<td>0.1%</td>
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<tr>
<td></td>
<td>0.0%</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>0.1%</td>
</tr>
<tr>
<td></td>
<td>0.0%</td>
</tr>
<tr>
<td>Breast disorders</td>
<td>0.5%</td>
</tr>
<tr>
<td></td>
<td>0.8%</td>
</tr>
<tr>
<td></td>
<td>1.1%</td>
</tr>
<tr>
<td></td>
<td>0.6%</td>
</tr>
<tr>
<td>Dutasteride</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>0.1%</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>0.3%</td>
</tr>
<tr>
<td></td>
<td>0.1%</td>
</tr>
</tbody>
</table>

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

Includes breast tenderness and breast enlargement.

**Long-Term Treatment (Up to 4 Years)**

*High-grade prostate cancer:* A randomized, double-blind, placebo-controlled trial enrolled 8,231 men aged 50 to 75 years with a serum PSA of 2.5 ng/mL to 10 ng/mL and a negative prostate biopsy within the previous 6 months to evaluate the role of dutasteride in prevention of prostate cancer. Subjects were randomized to receive placebo (N=4,126) or 0.5 mg daily doses of dutasteride (N=4,105) for up to 4 years. The mean age was 63 years and 91% were Caucasian. Subjects underwent protocol-mandated scheduled prostate biopsies at 2 and 4 years of treatment or had ‘for-cause biopsies’ at non-scheduled times if clinically indicated. There was a higher incidence of Gleason score 8–10 prostate cancer in men receiving dutasteride (1.0%) compared with men on placebo (0.5%). In a 7-year placebo-controlled clinical trial with another 5 alpha-reductase inhibitor (finasteride 5 mg), similar results for Gleason score 8–10 prostate cancer were observed (finasteride 1.8% versus placebo 1.1%).

No clinical benefit has been demonstrated in patients with prostate cancer treated with dutasteride.

**Reproductive and Breast Disorders**

In the three pivotal placebo-controlled BPH trials with dutasteride, each of 4 years in duration, there was no evidence of increased sexual adverse reactions (impotence, decreased libido, and ejaculation disorder) or breast disorders with increased duration of treatment. Among these three trials, there was one case of breast cancer in the dutasteride group and one case in the placebo group. No cases of breast cancer were reported in any treatment group in the 4-year CombAT trial or the 4-year REDUCE trial. The relationship between the long-term use of dutasteride and male breast neoplasia is currently unknown.

**Combination with Alpha-Blocker Therapy**

Over 4,800 male subjects with BPH were randomly assigned to receive 0.5-mg dutasteride, 0.4-mg tamsulosin, or combination therapy (0.5-mg dutasteride plus 0.4-mg tamsulosin) administered once daily in a 4-year double-blind trial. Overall, 1,623 subjects received monotherapy with dutasteride; 1,611 subjects received monotherapy with tamsulosin; and 1,610 subjects received combination therapy. The population was aged 49 to 88 years (mean age: 66 years) and 88% were Caucasian.

The most common adverse reactions reported in ≥ 1% subjects receiving combination therapy (dutasteride plus tamsulosin) were impotence, decreased libido, breast disorders (including breast enlargement and tenderness), ejaculation disorders, and dizziness. Ejaculation disorders occurred significantly more in subjects receiving combination therapy (11%) compared with those receiving dutasteride (2%) or tamsulosin (4%) as monotherapy. Trial withdrawal due to adverse reactions occurred in 6% of subjects receiving combination therapy (dutasteride plus tamsulosin) and 4% of subjects receiving dutasteride or tamsulosin as monotherapy. The most common adverse reaction in all treatment arms leading to trial withdrawal was erectile dysfunction (1% to 1.5%).

**Cardiac Failure:** In a trial with combination therapy with dutasteride and alpha-blocker, after 4 years of treatment, the incidence of the composite term cardiac failure in the combination therapy group (12/1,610; 0.7%) was higher than in either monotherapy group: dutasteride, 2/1,623 (0.1%) and tamsulosin, 9/1,611 (0.6%). Composite cardiac failure was also examined in a separate 4-year placebo-controlled trial evaluating dutasteride in men at risk for development of prostate cancer. The incidence of cardiac failure in subjects taking dutasteride was 0.6% (26/4,105) compared with 0.4% (15/4,126) in subjects on placebo. A majority of subjects with cardiac failure in both trials had comorbidities associated with an increased risk of cardiac failure. Therefore, the clinical significance of the numerical imbalances in cardiac failure is unknown. No causal relationship between dutasteride alone or in combination with tamsulosin and cardiac failure has been established. No imbalance was observed in the incidence of overall cardiovascular adverse events in either trial.

**Postmarketing Experience**

The following adverse reactions have been identified during post-approval use of dutasteride. Because these reactions
are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions have been chosen for inclusion due to a combination of their seriousness, frequency of reporting or potential causal connection to dutasteride.

**Immune System Disorders:** Hypersensitivity reactions, including rash, pruritus, urticaria, localized oedema, serious skin reactions, and angio-oedema.

**Neoplasms:** Male breast cancer.

**Psychiatric Disorders:** Depressed mood.

**Reproductive System and Breast Disorders:** Testicular pain and testicular swelling.

### Overdosage

#### Silodosin

Silodosin was evaluated at doses of up to 48 mg/day in healthy male subjects. The dose-limiting adverse event was postural hypotension. Should overdose of silodosin lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by maintaining the patient in the supine position. If this measure is inadequate, administration of intravenous fluid should be considered. If necessary, vasopressors could be used, and renal function should be monitored and supported as needed. Dialysis is unlikely to be of significant benefit since silodosin is highly (97%) protein-bound.

#### Dutasteride

In volunteer studies, single doses of dutasteride up to 40 mg (80 times the therapeutic dose) for 7 days have been administered without significant safety concerns. In a clinical study, daily doses of 5 mg (10 times the therapeutic dose) were administered to 60 subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg. There is no specific antidote for dutasteride. Therefore, in cases of suspected overdosage symptomatic and supportive treatment should be given as appropriate, taking the long half-life of dutasteride into consideration.

### Storage And Handling Instructions

Store below 30°C. Protect from light and moisture

### Packaging Information

SILOFAST D 4: Combipack blister containing 10 capsules of Silodosin and 10 capsules of Dutasteride
SILOFAST D 8: Combipack blister containing 10 capsules of Silodosin and 10 capsules of Dutasteride

*Last Updated: October 2013*

*Last Reviewed: September 2016*

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**SILOFAST D Capsules**

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