For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

SILOXIO D 8

1. Generic Name

Silodosin and Dutasteride Capsules 8 mg.

2. Qualitative and quantitative Composition:

SILOXIO D 8

Each Hard Gelatin Capsule Contains:

Silodosin JP…….…. 8 mg.

Colours: Titanium Dioxide I.P.

(As film coated tablet)

Dutasteride I.P…….0.5 mg

Colours: Yellow oxide of iron & Titanium Dioxide I.P.

(As film coated tablet)

Approved colours used in capsules shells.

The excipients used are Akoat-512, Sodium lauryl sulphate (S.L.S.), magnesium stearate I.P., Colloidal silicon Dioxide, Col. Iron Oxide (Ferric Oxide USPNF) Yellow, Croscarmellose sodium I.P., Lactose I.P., Microcrystalline cellulose I.P., Povidone I.P., Starch IP (Maize), Pearlitol SD 200, Pregelatinised starch I.P., sodium starch glycolate.

3. Dosage form and strength

Dosage form: Hard gelatin capsule

Strength: Silodosin and Dutasteride 8 mg.

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for the treatment of the signs and symptoms of Benign Prostatic Hyperplasia (BPH) in men with an enlarged prostate.

4.2. Posology and method of administration

Posology

The recommended dosage is 1 capsule once daily or as directed by the Physician.

Method of administration

For oral administration only.

Silodosin/Dutasteride capsules should be swallowed whole and must not be opened, crushed or chewed. The capsules may be taken with or without food.

4.3. Contraindications

Silodosin/Dutasteride is contraindicated in patients with hypersensitivity to silodosin, dutasteride, other 5-alpha reductase inhibitors, or any other component of the product.

Silodosin is contraindicated for use in the following:

- Severe renal impairment (CCr <30 mL/min)

- Concomitant administration with strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, itraconazole, ritonavir).

Dutasteride is contraindicated for use in the following:

- Women and children and adolescents.
- Patients with severe hepatic impairment.

4.4. Special warnings and precautions for use

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.

Renal Impairment

In a clinical pharmacology study, plasma concentrations (AUC and Cmax) of silodosin were approximately three times higher in subjects with moderate renal impairment compared with subjects with normal renal function, while half-lives of silodosin doubled in duration. The dose of silodosin should be reduced to 4 mg in patients with moderate renal impairment. Exercise caution and monitor such patients for adverse events. Silodosin is contraindicated in patients with severe renal impairment.

Hepatic Impairment

Silodosin has not been tested in patients with severe hepatic impairment, and therefore, should not be prescribed to such patients.

Pharmacokinetic Drug-Drug Interactions

In a drug interaction study, co-administration of a single 8 mg dose of silodosin with 400 mg ketoconazole, a strong CYP3A4 inhibitor, caused a 3.8-fold increase in maximum plasma silodosin concentrations and 3.2-fold increase in silodosin exposure (i.e., AUC). Concomitant use of ketoconazole or other strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin, ritonavir) is therefore contraindicated.

Pharmacodynamic Drug-Drug Interactions

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. A specific pharmacodynamic interaction study between silodosin and antihypertensive agents has not been performed. However, patients in the Phase 3 clinical studies taking concomitant antihypertensive medications with silodosin did not experience a significant increase in the incidence of syncope, dizziness, or orthostasis. Nevertheless, exercise caution during concomitant use with antihypertensives and monitor patients for possible adverse events.

Caution is also advised when alpha-adrenergic blocking agents including silodosin are co-administered with PDE5 inhibitors. Alpha-adrenergic blockers and PDE5 inhibitors are both vasodilators that can lower blood pressure. Concomitant use of these two drug classes can potentially cause symptomatic hypotension.

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 alpha-1 blockers or previously treated with alpha-1 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 preoperative dilation with standard mydriatic drugs; and potential prolapse of the iris toward the phacoemulsification incisions. Patients planning cataract surgery should be told 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 prostate-specific antigen (PSA).

Dutasteride

Combination therapy should be prescribed after careful benefit risk assessment due to the potential increased risk of adverse events (including cardiac failure) and after consideration of alternative treatment options including monotherapies.

Cardiac failure

In two 4-year clinical studies, the incidence of cardiac failure (a composite term of reported events, primarily cardiac failure and congestive cardiac failure) was higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. In these two trials, the incidence of cardiac failure was low (≤1%) and variable between the studies.

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

Digital rectal examination, as well as other evaluations for prostate cancer, must be performed on patients prior to initiating therapy with dutasteride and periodically thereafter. Serum prostate-specific antigen (PSA) concentration is an important component in the detection of prostate cancer. Dutasteride causes a decrease in mean serum PSA levels by approximately 50%, after 6 months of treatment. Patients receiving dutasteride should have a new PSA baseline established after 6 months of treatment. It is recommended to monitor PSA values regularly thereafter. Any confirmed increase from lowest PSA level while on dutasteride may signal the presence of prostate cancer (particulary high grade cancer) or noncompliance to therapy with dutasteride and should be carefully evaluated, even if those values are still within the normal range for men not taking a 5α-reductase inhibitor. In the interpretation of a PSA value for a patient taking dutasteride, previous PSA values should be sought for comparison.

Treatment with dutasteride does not interfere with the use of PSA as a tool to assist in the diagnosis of prostate cancer after a new baseline has been established. Total serum PSA levels return to baseline within 6 months of discontinuing treatment. The ratio of free to total PSA remains constant even under the influence of dutasteride. If clinicians elect to use percent free PSA as an aid in the detection of prostate cancer in men undergoing dutasteride therapy, no adjustment to its value appears necessary.

Prostate cancer and high grade tumours

Results of one clinical study (the REDUCE study) in men at increased risk of prostate cancer revealed a higher incidence of Gleason 8-10 prostate cancers in dutasteride treated men compared to placebo. The relationship between dutasteride and high grade prostate cancer is not clear. Men taking dutasteride should be regularly evaluated for prostate cancer risk including PSA testing.

Leakings

Dutasteride is absorbed through the skin, therefore, women, children and adolescents must avoid contact with leaking s. If contact is made with leaking s, the contact area should be washed immediately with soap and water.

Hepatic impairment

Dutasteride was not studied in patients with liver disease. Caution should be used in the administration of dutasteride to patients with mild to moderate hepatic impairment.

Breast neoplasia

Breast cancer has been reported in men taking dutasteride in clinical trials and during the post-marketing period. Physicians should instruct their patients to promptly report any changes in their breast tissue such as lumps or nipple discharge. Currently it is not clear if there is a causal relationship between the occurrence of male breast cancer and long term use of dutasteride.

4.5. Drugs interactions

There have been no drug interaction studies for Silodosin/Dutasteride s. The following statements reflect the information available on the individual components.

Silodosin

Moderate and Strong CYP3A4 Inhibitors

In a clinical metabolic inhibition study, a 3.8-fold increase in silodosin maximum plasma concentrations and 3.2-fold increase in silodosin exposure were observed with concurrent administration of a strong CYP3A4 inhibitor, 400 mg ketoconazole. 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 concentration of silodosin. Exercise caution and monitor patients for adverse events when co-administering silodosin with moderate CYP3A4 inhibitors.

Strong P-glycoprotein (P-gp) Inhibitors

In vitro studies indicated that silodosin is a P-gp substrate. Ketoconazole, a CYP3A4 inhibitor that also inhibits P-gp, caused significant increase in exposure to silodosin. Inhibition of P-gp may lead to increased silodosin concentration. Silodosin is therefore 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 co-administration of silodosin and digoxin 0.25 mg/day for 7 days was evaluated in a clinical trial in 16 healthy males, aged 18 years to 45 years. Concomitant administration of silodosin and digoxin did not significantly alter the steady state pharmacokinetics of digoxin. No dose adjustment is required.

PDE5 Inhibitors

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 years 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). Exercise caution during concomitant use with antihypertensives and monitor patients for possible adverse events.

Metabolic Interactions: In vitro data indicate that silodosin does not have the potential to inhibit or induce cytochrome P450 enzyme systems.

Food Interactions

The effect of a moderate fat, moderate calorie meal on silodosin pharmacokinetics was variable and decreased silodosin maximum plasma concentration (Cmax) 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

For information on the decrease of serum PSA levels during treatment with dutasteride and guidance concerning prostate cancer detection.

Effects of other drugs on the pharmacokinetics of dutasteride:

Use together with CYP3A4 and/or P-glycoprotein-inhibitors: Dutasteride is mainly eliminated via metabolism. In vitro studies indicate that this metabolism is catalysed by CYP3A4 and CYP3A5. No formal interaction studies have been performed with potent CYP3A4 inhibitors. However, in a population pharmacokinetic study, dutasteride serum concentrations were on average 1.6 to 1.8 times greater, respectively, in a small number of patients treated concurrently with verapamil or diltiazem (moderate inhibitors of CYP3A4 and inhibitors of P-glycoprotein) than in other patients. 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. Administration of 12 g cholestyramine one hour after a 5 mg single dose of dutasteride did not affect the pharmacokinetics of dutasteride.

Effects of dutasteride on the pharmacokinetics of other drugs:

Dutasteride has no effect on the pharmacokinetics of warfarin or digoxin. This indicates that dutasteride does not inhibit/induce CYP2C9 or the transporter P-glycoprotein. In vitro interaction studies indicate that dutasteride does not inhibit the enzymes CYP1A2, CYP2D6, CYP2C9, CYP2C19 or CYP3A4.

In a small study (n=24) of two weeks' duration in healthy men, dutasteride (0.5 mg daily) had no effect on the pharmacokinetics of tamsulosin or terazosin. There was also no indication of a pharmacodynamic interaction in this study.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Silodosin

Pregnancy Category B. Silodosin is not indicated for use in women. An embryo/fetal study in rabbits showed decreased maternal body weight at 200 mg/kg/day (approximately 13 to 25 times the maximum recommended human exposure or MRHE of silodosin via AUC). No statistically significant teratogenicity was observed at this dose. Silodosin was not teratogenic when administered to pregnant rats during organogenesis at 1000 mg/kg/day (estimated to be approximately 20 times the MRHE). No maternal or fetal effects were observed at this dose. Rats and rabbits do not produce glucuronidated silodosin, which is present in human serum at approximately 4 times the level of circulating silodosin and which has similar pharmacological activity to silodosin. No effects on physical or behavioral development of offspring were observed when rats were treated during pregnancy and lactation at up to 300 mg/kg/day.

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. It is not known whether 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). 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.

Lactation

Silodosin is not indicated for use in lactating women It is not known whether dutasteride is excreted in human milk.

Paediatric Use

Silodosin/Dutasteride are not indicated for use in paediatric patients. Safety and effectiveness in paediatric patients have not been established.

Geriatric Use

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. No dose adjustment of dutasteride is necessary in the elderly.

Renal impairment

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.

The effect of renal impairment on dutasteride pharmacokinetics has not been studied. No adjustment in dosage is anticipated for patients with renal impairment.

Hepatic impairment

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.

The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied so caution should be used in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the use of dutasteride is contraindicated.

4.7. Effects on ability to drive and use machines

No studies on the effects of Silodosin/Dutasteride on the ability to drive and use machines have been performed. However, patients should be informed about the possible occurrence of symptoms related to orthostatic hypotension such as dizziness when taking Silodosin/Dutasteride s.

4.8. 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 cannot 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.

Table: Adverse Reactions Occurring in ≥2% of Patients in 12-week, Placebo-Controlled Clinical Trials

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

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 rhinorrhoea. 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 edema resulting in serious outcomes.

Dutasteride

The adverse reactions frequency is defined using the following conventions: very common (≥ 1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Approximately 19% of the 2167 patients who received dutasteride in the 2-year Phase III placebo-controlled trials developed adverse reactions during the first year of treatment. The majority of events were mild to moderate and occurred in the reproductive system. No change to the adverse event profile was apparent over a further 2 years in open-label extension studies.

The following table shows adverse reactions from controlled clinical trials and post-marketing experience. The listed adverse events from clinical trials are investigator-judged drug-related events (with incidence more than or equal to 1%) reported with a higher incidence in patients treated with dutasteride compared with placebo during the first year of treatment. Adverse events from post-marketing experience were identified from spontaneous post-marketing reports; therefore, the true incidence is not known:

Reproductive system and breast disorders (Incidence from clinical trial data): Impotence*, Altered (decreased) libido*, Ejaculation disorders*, Breast disorders+.

Immune system disorders: Not known: Allergic reactions including rash, pruritus, urticaria, localised oedema, and angioedema.

Psychiatric disorders: Not known: Depressed mood.

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

Reproductive system and breast disorders: Not known: Testicular pain and swelling.

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

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 edema, serious skin reactions, and angioedema.

Neoplasms: Male breast cancer.

Psychiatric Disorders: Depressed mood.

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

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

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 daily doses of dutasteride up to 40 mg/day (80 times the therapeutic dose) have been administered for 7 days without significant safety concerns. In clinical studies, doses of 5 mg daily have been administered to subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg. There is no specific antidote for dutasteride, therefore, in suspected overdosage symptomatic and supportive treatment should be given as appropriate.

5. Pharmacological properties

5.1. Mechanism of Action

Silodosin

Silodosin is a selective antagonist of post-synaptic alpha1-adrenoreceptors, which are located in the human prostate, bladder base, bladder neck, prostatic and prostatic urethra. Blockade of these alpha1-adrenoreceptors can cause smooth muscle in these tissues to relax, resulting in an improvement in urine flow and a reduction in benign prostatic hyperplasia (BPH) symptoms. An in vitro study examining the binding affinity of silodosin to the three subtypes of the alpha1-adrenoreceptors (alpha1A, alpha1B, and alpha1D) was conducted. The results of the study demonstrated that silodosin binds with high affinity to the alpha1A subtype.

Dutasteride

Dutasteride inhibits the conversion of testosterone to 5 alpha-dihydrotestosterone (DHT) by a competitive and specific inhibition of both the type I and type II isoforms of steroid 5 alpha-reductase (5AR). Testosterone is converted to DHT by the enzyme 5 alpha-reductase, which exists as 2 isoforms, type I and type II. The type II isoenzyme is primarily active in the reproductive tissues, while the type I isoenzyme is also responsible for testosterone conversion in the skin and liver. DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland.

5.2. Pharmacodynamic properties

Silodosin

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.

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

Effect on 5 Alpha-Dihydrotestosterone 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, estradiol, 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, 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.

5.3. Pharmacokinetic properties

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 presents the steady state pharmacokinetics of this study.

Table: Mean (±SD) Steady-State Pharmacokinetic Parameters in Healthy Males Following Silodosin 8 mg Once Daily with Food

Cmax (ng/mL)	**tmax (hours)**	**t1/2 (hours)**	**AUCss (ng•hr/mL)**
61.6 ± 27.54	2.6 ± 0.90	13.3 ± 8.07	373.4 ± 164.94

The absolute bioavailability is approximately 32%.

Following oral administration of a single 0.5 mg dutasteride dose, the time to peak serum concentrations of dutasteride is 1 to 3 hours. The absolute bioavailability is approximately 60%. The bioavailability of dutasteride is not affected by food.

Distribution

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

Dutasteride has a large volume of distribution (300 to 500 L) and is highly bound to plasma proteins (>99.5%). Following daily dosing, dutasteride serum concentrations achieve 65% of steady state concentration after 1 month and approximately 90% after 3 months. Steady state serum concentrations (Css) of approximately 40 ng/mL are achieved after 6 months of dosing 0.5 mg once a day. Dutasteride partitioning from serum into semen averaged 11.5%.

Metabolism

Silodosin undergoes extensive metabolism through glucuronidation, alcohol and aldehyde dehydrogenase, and cytochrome P450 3A4 (CYP3A4) 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.

Dutasteride is extensively metabolised in vivo. In vitro, dutasteride is metabolised by the cytochrome P450 3A4 and 3A5 to three monohydroxylated metabolites and one dihydroxylated metabolite. Following oral dosing of dutasteride 0.5 mg/day to steady state, 1.0% to 15.4% (mean of 5.4%) of the administered dose is excreted as unchanged dutasteride in the faeces. The remainder is excreted in the faeces as 4 major metabolites comprising 39%, 21%, 7%, and 7% each of 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.

Excretion

Following oral administration of 14C-labeled 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.

The elimination of dutasteride is dose dependent and the process appears to be described by two elimination pathways in parallel, one that is saturable at clinically relevant concentrations and one that is non saturable. At low serum concentrations (less than 3 ng/mL), dutasteride is cleared 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 3-9 days. At therapeutic concentrations, following repeat dosing of 0.5 mg/day, the slower, linear elimination pathway is dominating and the half-life is approx. 3-5 weeks.

6. Nonclinical properties

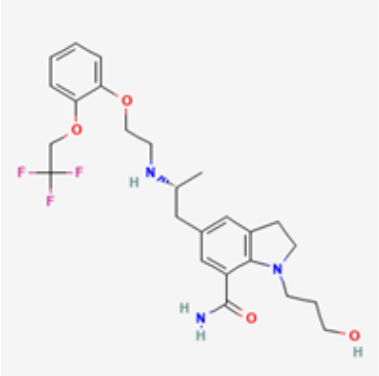
6.1. Animal Toxicology or Pharmacology

Current studies of general toxicity, genotoxicity and carcinogenicity did not show any particular risk to humans. Reproduction toxicity studies in male rats have shown a decreased weight of the prostate and seminal vesicles, decreased secretion from accessory genital glands and a reduction in fertility indices (caused by the pharmacological effect of dutasteride).The clinical relevance of these findings is unknown. As with other 5 alpha reductase inhibitors, feminisation of male foetuses in rats and rabbits has been noted when dutasteride was administered during gestation. Dutasteride has been found in blood from female rats after mating with dutasteride treated males. When dutasteride was administered during gestation to primates, no feminisation of male foetuses was seen at blood exposures sufficiently in excess of those likely to occur via human semen. It is unlikely that a male foetus will be adversely affected following seminal transfer of dutasteride.

7. Description

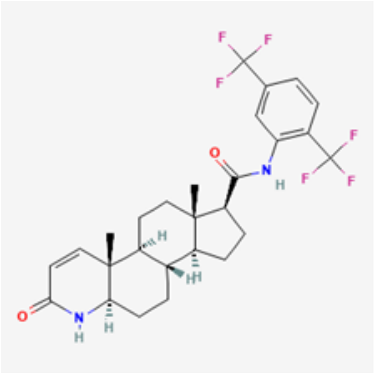
SILODOSIN

Silodosin is 1-(3-hydroxypropyl)-5-[(2R)-2-[2-[2-(2,2,2 trifluoroethoxy) phenoxy]ethylamino] propyl]-2,3-dihydroindole-7-carboxamide The empiric formula of $C_{25}H_{32}F_3N_3O_4$ and its molecular weight is 495.5 g/mol. Its structural formula is:



DUTASTERIDE

Dutasteride is (1S,3aS,3bS,5aR,9aR,9bS,11aS)-N-[2,5-bis(trifluoromethyl)phenyl]-9a,11a-dimethyl-7-oxo-1,2,3,3a,3b,4,5,5a,6,9b,10,11-dodecahydroindeno[5,4-f]quinoline-1-carboxamide The empiric formula of $C_{27}H_{30}F_6N_2O_2$ and its molecular weight is 528.5 g/mol. Its structural formula is:



SILOXIO D 8

SILOXIO D 8 is red cap & white body size "2" hard gelatin capsule shell containing one tablet of white, round, biconvex both side plain & film coated tablet (Silodosin) & one tablet of yellow coloured, round, biconvex both side plain & film coated tablet (Dutasteride).

The excipients used are Akoat-512, Sodium lauryl sulphate (S.L.S.), magnesium stearate I.P., Colloidal silicon Dioxide, Col. Iron Oxide (Ferric Oxide USPNF) Yellow, Croscarmellose sodium I.P., Lactose I.P., Microcrystalline cellulose I.P., Povidone I.P., Starch IP (Maize), Pearlitol SD 200, Pregelatinised starch I.P., sodium starch glycolate

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

SILOXIO D 8 is packed in Strip of 10 Capsules.

8.4. Storage and handing instructions

Store below 30°C.

Keep the medicine out of reach of children.

Capsule should be swallowed whole and not to be opened chewed or crushed.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. **Details of manufacturer**

    M/s Akums Drugs & Pharmaceuticals Ltd.

    AT: Plot No. 16, Vardhman Industrial Estate,

    Village-Bahadarpur Saini, NH-58,

    Haridwar-247667 (Uttarakhand)

11. **Details of permission or licence number with date**

    Mfg Lic No. 7/UA/LL/SC/P-2014 issued on 22.10.2011.

12. **Date of revision**

    NA

    MARKETED BY

    TORRENT PHARMACEUTICALS LTD.

    IN/SILOXIO D 8/SEP-2025/01/PI