PATIENT INFORMATION LEAFLET

For the use of a Registered Medical Practitioner, or a hospital, or a Laboratory only

Mirabrgron 25/50 mg (ER) And Silodosin 8/8 mg Tablets

SILOTRIF® M 25 सिलोट्रिफ-एम 25 SILOTRIF® M 50 सिलोट्रिफ-एम 50

1. GENERIC NAME

Mirabrgron 25/50 mg (ER) and Silodosin 8/8 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated bilayered tablet contains:
Mirabegron EP 25mg/50mg
(As Extended Release)
Silodosin JP 8mg/8mg
Excipients q.s
Colours: Ferric Oxide Red USP-NF & Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH

Oral dosage form, Tablet
Mirabrgron 25/50 mg (ER) and Silodosin 8/8 mg Tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

It is indicated for the treatment of Benign Prostatic Hyperplasia complicated by overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

4.2 Posology and method of administration

Mirabegron

Recommended Dosage for Adult Patients with OAB

Mirabegron Monotherapy

The recommended starting dosage of Mirabegron is 25 mg orally once daily. If needed, increase to the maximum dosage of Mirabegron 50 mg orally once daily after 4 to 8 weeks.

Recommended Dosage in Adult Patients with Renal or Hepatic Impairment

Dosage in Adults with Renal Impairment

The recommended dosage of Mirabegron (administered orally once daily) in adult patients with renal impairment is described in Table 1

Table 1: Mirabegron Recommended Dosage in Adult Patients with Renal Impairment (Administered Orally Once Daily)

Estimated GFR[1]	Starting Dose	Maximum Dose
eGFR 30 to 89 mL/min/1.73 m^2	25 mg	50 mg
eGFR 15 to 29 mL/min/1.73 m^2	25 mg	25 mg
eGFR < 15 mL/min/1.73 m^2 or requiring dialysis	Not recommended	

1. Estimated GFR using the modification of diet in renal disease (MDRD) formula

Dosage in Adults with Hepatic Impairment

The recommended dosage of Mirabegron (administered orally once daily) in adult patients with hepatic impairment is described in Table 2

Table 2: Mirabegron Recommended Dosage in Adult Patients with Hepatic Impairment (Administered Orally Once Daily)

Hepatic Impairment Classification	Starting Dose	Maximum Dose
Child-Pugh Class A (Mild hepatic impairment)	25 mg	50 mg
Child-Pugh Class B (Moderate hepatic impairment)	25 mg	25 mg
Child-Pugh Class C (Severe hepatic impairment)	Not Recommended	

Administration Instructions

Administration instructions for Mirabegron differ based on the patient population. Mirabegron Adult patients: Swallow Mirabegron whole with water. Do not chew, divide, or crush. Take with or without food.

Missed Dose

Instruct patients to take any missed doses as soon as they remember, unless more than 12 hours have passed since the missed dose. If more than 12 hours have passed, the missed dose can be skipped, and the next dose should be taken at the usual time.

Silodosin

Dosing Information

The recommended dose is 8 mg orally once daily with a meal.

Patients who have difficulty swallowing pills and tablets may carefully open the Silodosin tablet and sprinkle the powder inside on a tablespoonful of applesauce. The applesauce should be swallowed immediately (within 5 minutes) without chewing and followed with an 8 oz glass of cool water to ensure complete swallowing of the powder. The applesauce used should not be hot, and it should be soft enough to be swallowed without chewing. Any powder/applesauce mixture should be used immediately (within 5 minutes) and not stored for future use. Subdividing the contents of a Silodosin tablet is not recommended.

Dosage Adjustment in Special Populations

Renal impairment

Silodosin is contraindicated in patients with severe renal impairment (CCr < 30 mL/min). In patients with moderate renal impairment (CCr 30-50 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 50-80 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.

4.3 Contraindications

Mirabegron

Mirabegron is contraindicated in patients with known hypersensitivity reactions to mirabegron or any inactive ingredients of the tablet.

Silodosin

- Severe renal impairment (CCr < 30 mL/min)
- Severe hepatic impairment (Child-Pugh score ≥ 10)
- Concomitant administration with strong Cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ketoconazole, clarithromycin, itraconazole, ritonavir)
- Patients with a history of hypersensitivity to silodosin or any of the ingredients of Silodosin.

4.4 Special warnings and precautions for use

Mirabegron

Increases in Blood Pressure

Increases in Blood Pressure in Adults

Mirabegron can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. Mirabegron is not recommended for use in patients with severe uncontrolled hypertension (defined as systolic blood pressure greater than or equal to 180 mm Hg and/or diastolic blood pressure greater than or equal to 110 mm Hg).

In two, randomized, placebo-controlled, healthy adult volunteer studies, Mirabegron was associated with dose-related increases in supine blood pressure. In these studies, at the maximum recommended dose of 50 mg, the mean maximum increase in systolic/diastolic blood pressure was approximately 3.5/1.5 mm Hg greater than placebo.

In contrast, in adult OAB patients in clinical trials, Mirabegron , taken as monotherapy or in combination, the mean increase in systolic and diastolic blood pressure at the maximum recommended mirabegron dose of 50 mg was approximately 0.5 to 1 mm Hg greater than placebo. Worsening of pre-existing hypertension was reported infrequently in patients taking Mirabegron.

Urinary Retention in Patients with Bladder Outlet Obstruction and in Patients Taking Muscarinic Antagonist Medications for OAB

In patients taking Mirabegron, urinary retention has been reported to occur in patients with bladder outlet obstruction (BOO) and in patients taking muscarinic antagonist medications for the treatment of OAB. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with mirabegron; however, Mirabegron should still be administered with caution to patients with clinically significant BOO. For example, monitor these patients for signs and symptoms of urinary retention. Mirabegron should also be administered with caution to patients taking muscarinic antagonist medications for the treatment of OAB.

Angioedema

Angioedema of the face, lips, tongue, and/or larynx has been reported with Mirabegron. In some cases, angioedema occurred after the first dose, however, cases have been reported to occur hours after the first dose or after multiple doses. Angioedema, associated with upper airway swelling, may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, promptly discontinue Mirabegron and provide appropriate therapy and/or measures necessary to ensure a patent airway.

Patients Taking Drugs Metabolized by CYP2D6

Since Mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates is increased when coadministered with Mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6.

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 C_{max}) 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).

4.5 Drug Interactions

Mirabegron

Drug interaction studies were conducted in adult patients to investigate the effect of coadministered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of coadministered drugs (e.g., ketoconazole, rifampin, solifenacin succinate, tamsulosin, and oral contraceptives). No dose adjustment is recommended when these drugs are coadministered with mirabegron.

The following are drug interactions for which monitoring is recommended:

Drugs Metabolized by CYP2D6

Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure of drugs metabolized by CYP2D6 enzyme is increased when coadministered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary when Mirabegron is coadministered with these drugs, especially with narrow therapeutic index CYP2D6 substrates.

Digoxin

When given in combination, 100 mg mirabegron increased mean digoxin C_{max} from 1.01 to 1.3 ng/mL (29%) and AUC from 16.7 to 19.3 ng.h/mL (27%). Concomitant administration of 0.25 mg digoxin with a combination of 5 mg solifenacin and 50 mg mirabegron increased digoxin AUC_{tau} and C_{max} by approximately 10% and 14%, respectively. For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be considered. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect.

Warfarin

The mean C_{max} of S- and R-warfarin was increased by approximately 4% and AUC by approximately 9% when administered as a single dose of 25 mg after multiple doses of 100 mg mirabegron. Following a single dose administration of 25 mg warfarin, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as International Normalized Ratio (INR) and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated.

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 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 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 (C_{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.

4.6 Use in special populations

Mirabegron

Pregnancy

Risk Summary

There are no studies with the use of Mirabegron in pregnant women or adolescents to inform a drug-associated risk of major birth defects, miscarriages, or adverse maternal or fetal outcomes. Mirabegron administration to pregnant animals during organogenesis resulted in reversible skeletal variations (in rats) at 22-fold (via AUC) the maximum recommended human dose (MRHD) of 50 mg/day and decreased fetal body weights (in rabbits) at 14-fold the MRHD. At maternally toxic exposures in rats (96-fold), decreased fetal weight and increased fetal mortality were observed and, in rabbits (36-fold), cardiac findings (fetal cardiomegaly and fetal dilated aortae) were observed.

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. In the U.S. general population, the estimated background risk of major birth defects or miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

No embryo-fetal lethality or morphological fetal developmental abnormalities were produced in pregnant rats following daily oral administration of mirabegron during the period of organogenesis (Days 7 to 17 of gestation) at 0, 10, 30, 100, or 300 mg/kg, doses which were associated with systemic exposures (AUC) 0, 1, 6, 22, and 96-fold the MRHD. Skeletal variations (wavy ribs, delayed ossification) were observed in fetuses at doses 22-fold the systemic exposure at the MRHD and were reversible during development. Exposures 96-fold the MRHD were maternally-toxic (mortality, decreased body weight gain) and associated with fetal growth reduction.

Pregnant rabbits were treated with daily oral doses of mirabegron at 0, 3, 10, or 30 mg/kg/day during the period of organogenesis (Days 6 to 20 of gestation), which resulted in plasma exposures that were 0, 1, 14, or 36-fold the MRHD based on AUC. At 10 mg/kg/day (14-fold the MRHD) and higher, fetal body weights were reduced. At 30 mg/kg/day, maternal toxicity (increased heart rate, mortality, reduced body weight gain, reduced food consumption) occurred, and fetal deaths, fetal cardiomegaly and fetal dilated aortae were observed at systemic exposure levels (AUC) 36-fold the MRHD.

In a pre- and postnatal developmental study, rats were treated with daily oral doses of mirabegron at 0, 10, 30, or 100 mg/kg/day (0, 1, 6, or 22-fold the MRHD) from day 7 of gestation until day 20 after birth. Decreased maternal body weight was observed along with decreased pup survival in the first few days after birth (92.7% survival) compared to the control group (98.8% survival), at 100 mg/kg/day (22-fold the MRHD). Pup body weight gain was reduced until postnatal day 7 but not further affected throughout the remainder of the lactation period. In utero and lactational exposure did not affect developmental milestones, behavior, or fertility of offspring. No effects were observed at 30 mg/kg/day.

Lactation

Risk Summary

There are no data on the presence of mirabegron in human milk, the effects on the breastfed child, or the effects on milk production. Mirabegron related material was present in rat milk and in the stomach of nursing pups following administrations of a single 10 mg/kg oral dose of ^{14}C-labeled mirabegron to lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Mirabegron and any potential adverse effects on the breastfed child from mirabegron or from the underlying maternal condition.

Geriatric Use

Of 5648 patients who received Mirabegron monotherapy in the phase 2 and 3 studies for OAB, 2029 (35.9%) were 65 years of age or older, and 557 (9.9%) were 75 years of age or older. No overall differences in safety or effectiveness were observed between patients younger than 65 years of age and those 65 years of age or older in these studies.

Renal Impairment

Mirabegron have not been studied in patients with End-Stage Renal Disease (eGFR < 15 mL/min/1.73 m^2) or patients requiring hemodialysis and, therefore, is not recommended for use in these patient populations. No dose adjustment is necessary in patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2).

In adult patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), the daily dose of Mirabegron should not exceed 25 mg.

Hepatic Impairment

Mirabegron have not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, is not recommended for use in this patient population. No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A).

In adult patients with moderate hepatic impairment (Child-Pugh Class B), the daily dose of Mirabegron should not exceed 25 mg.

Silodosin

Pregnancy

Risk Summary

Silodosin is not indicated for use in females.

Lactation

Silodosin is not indicated for use in females.

Females and Males of Reproductive Potential

Infertility

Males

Possible effects on male fertility could be observed based on findings in rats at exposures that were at least two times higher than at the MRHD (based on AUC). These findings may be reversible, and the clinical relevance is unknown.

Geriatric Use

In double-blind, placebo-controlled, 12-week clinical studies of Silodosin, 259 (55.6%) were under 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 < 65 years of age (1.2% for placebo), 2.9% of Silodosin patients ≥ 65 years of age (1.9% for placebo), and 5.0% of patients ≥ 75 years of age (0% for placebo). There were otherwise no significant differences in safety or effectiveness between older and younger patients.

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.

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.

4.7 Effects on ability to drive and use machines

Mirabegron

Mirabegron has no or negligible influence on the ability to drive and use machines

Silodosin

Silodosin has minor or moderate influence on the ability to drive and use machines. Patients should be informed about the possible occurrence of symptoms related to postural hypotension (such as dizziness) and should be cautioned about driving or operating machines until they know how silodosin will affect them.

4.8 Undesirable effects

Mirabegron

The following adverse reactions

- Hypertension
- Urinary Retention
- Angioedema

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.

Mirabegron Monotherapy for Adult OAB

In three, 12-week, double-blind, placebo-controlled, safety and efficacy studies in patients with OAB (Studies 1, 2, and 3), Mirabegron was evaluated for safety in 2736 patients [see Clinical Studies (14.1)]. Study 1 also included an active control. For the combined Studies 1, 2, and 3, 432 patients received Mirabegron 25 mg, 1375 received Mirabegron 50 mg, and 929 received Mirabegron 100 mg once daily. In these studies, the majority of the patients were Caucasian (94%) and female (72%) with a mean age of 59 years (range 18 to 95 years).

Mirabegron was also evaluated for safety in 1632 patients who received Mirabegron 50 mg once daily (n=812 patients) or Mirabegron 100 mg (n=820 patients) in a 1-year, randomized, fixed-dose, double-blind, active controlled, safety study in patients with OAB (Study 4). Of these patients, 731 received Mirabegron in a previous 12- week study. In Study 4, 1385 patients received Mirabegron continuously for at least 6 months, 1311 patients received Mirabegron for at least 9 months, and 564 patients received Mirabegron for at least 1 year.

The most frequent adverse events (0.2%) leading to discontinuation in Studies 1, 2, and 3 for the 25 mg or 50 mg dose were nausea, headache, hypertension, diarrhea, constipation, dizziness, and tachycardia.

Atrial fibrillation (0.2%) and prostate cancer (0.1%) were reported as serious adverse events by more than 1 patient and at a rate greater than placebo.

Table 3 lists the adverse reactions, derived from all adverse events, that were reported in Studies 1, 2, and 3 at an incidence greater than placebo and in 1% or more of patients treated with Mirabegron 25 mg or 50 mg once daily for up to 12 weeks. The most commonly reported adverse reactions (greater than 2% of Mirabegron patients and greater than placebo) were hypertension, nasopharyngitis, urinary tract infection, and headache.

Table 3: Percentages of Patients with Adverse Reactions, Derived from All Adverse Events, Exceeding Placebo Rate and Reported ≥1% of OAB Patients Treated with Mirabegron 25 mg or 50 mg Once Daily in Studies 1, 2, and 3.

Adverse Reaction	Placebo (%)	Mirabegron 25 mg(%)	Mirabegron 50 mg(%)
Number of Patients	**1380**	**432**	**1375**
Hypertension[1]	7.6	11.3	7.5
Nasopharyngitis	2.5	3.5	3.9
Urinary Tract Infection	1.8	4.2	2.9
Headache	3.0	2.1	3.2
Constipation	1.4	1.6	1.6
Upper Respiratory TractInfection	1.7	2.1	1.5
Arthralgia	1.1	1.6	1.3
Diarrhea	1.3	1.2	1.5
Tachycardia	0.6	1.6	1.2
Abdominal Pain	0.7	1.4	0.6
Fatigue	1.0	1.4	1.2

1. Includes reports of blood pressure above the normal range, and BP increased from baseline, occurring predominantly in subjects with baseline hypertension.

Other adverse reactions reported by less than 1% of patients treated with Mirabegron in Studies 1, 2, or 3 included:

Cardiac disorders: palpitations, blood pressure increased.
Eye disorders: glaucoma
Gastrointestinal disorders: dyspepsia, gastritis, abdominal distension
Infections and Infestations: sinusitis, rhinitis
Investigations: GGT increased, AST increased, ALT increased, LDH increased
Renal and urinary disorders: nephrolithiasis, bladder pain
Reproductive system and breast disorders: vulvovaginal pruritus, vaginal infection
Skin and subcutaneous tissue disorders: urticaria, leukocytoclastic vasculitis, rash, pruritus, purpura, lip edema

Table 4 lists the rates of the most commonly reported adverse reactions, derived from all adverse events in patients treated with Mirabegron 50 mg for up to 52 weeks in Study 4. The most commonly reported adverse reactions (> 3% of Mirabegron patients) were hypertension, urinary tract infection, headache, and nasopharyngitis.

Table 4: Percentages of Patients with Adverse Reactions, Derived from All Adverse Events, Reported in > 2% of OAB Patients Treated with Mirabegron 50 mg Once Daily in Study 4

Adverse Reaction	Mirabegron 50 mg(%)	Active Control(%)
Number of Patients	**812**	**812**
Hypertension	9.2	9.6
Urinary Tract Infection	5.9	6.4
Headache	4.1	2.5
Nasopharyngitis	3.9	3.1
Back Pain	2.8	1.6
Constipation	2.8	2.7
Dry Mouth	2.8	8.6
Dizziness	2.7	2.6
Sinusitis	2.7	1.5
Influenza	2.6	3.4
Arthralgia	2.1	2.0
Cystitis	2.1	2.3

In Study 4, in patients treated with Mirabegron 50 mg once daily, adverse reactions leading to discontinuation reported by more than 2 patients and at a rate greater than active control included: constipation (0.9%), headache (0.6%), dizziness (0.5%), hypertension (0.5%), dry eyes (0.4%), nausea (0.4%), vision blurred (0.4%), and urinary tract infection (0.4%). Serious adverse events reported by at least 2 patients and exceeding active control included cerebrovascular accident (0.4%) and osteoarthritis (0.2%). Serum ALT/AST increased from baseline by greater than 10-fold in 2 patients (0.3%) taking Mirabegron 50 mg; and these markers subsequently returned to baseline while both patients continued Mirabegron.

In Study 4, serious adverse events of neoplasm were reported by 0.1%, 1.3%, and 0.5% of patients treated with Mirabegron 50 mg, Mirabegron 100 mg, and active control once daily, respectively. Neoplasms reported by 2 patients treated with Mirabegron 100 mg included breast cancer, lung neoplasm malignant, and prostate cancer. A causal relationship between mirabegron and these reported neoplasms has not been established.

In a separate clinical study in Japan, a single case was reported as Stevens-Johnson syndrome with increased serum ALT, AST, and bilirubin in a patient taking Mirabegron 100 mg as well as an herbal medication (Kyufu Gold).

The most commonly reported adverse reactions were UTI, nasopharyngitis, constipation, and headache.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Mirabegron. 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. The following events have been reported in association with mirabegron use in worldwide postmarketing experience:

Cardiac disorders: atrial fibrillation
Gastrointestinal disorders: nausea, constipation, diarrhea
Nervous system disorders: dizziness, headache

There have been postmarketing reports of confusion, hallucinations, insomnia, and anxiety in patients taking mirabegron. The majority of these patients had pre-existing medical conditions or concomitant medications that may cause confusion, hallucinations, insomnia, and anxiety. A causal relationship between mirabegron and these disorders has not been established.

Skin and subcutaneous tissue disorders: angioedema of the face, lips, tongue, and larynx, with or without respiratory symptoms; pruritus

Renal and urinary disorders: urinary retention

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, multicenter, 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 5.

Table 5: 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)
Diarrhea	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 two 12-week, placebo-controlled clinical trials, the following adverse events were 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 (IFIS) 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.

4.9 Overdose

Mirabegron

Mirabegron has been administered to healthy volunteers at single doses up to 400 mg. At this dose, adverse events reported included palpitations (1 of 6 subjects) and increased pulse rate exceeding 100 beats per minute (bpm) (3 of 6 subjects). Multiple doses of mirabegron up to 300 mg daily for 10 days showed increases in pulse rate and systolic blood pressure when administered to healthy volunteers. Treatment for overdosage should be symptomatic and supportive. In the event of overdosage, pulse rate, blood pressure and ECG monitoring is recommended.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action

Mirabegron

Mirabegron is an agonist of the human beta-3 adrenergic receptor (AR) as demonstrated by in vitro laboratory experiments using the cloned human beta-3 AR. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR which increases bladder capacity. Although mirabegron showed very low intrinsic activity for cloned human beta-1 AR and beta-2 AR, results in humans indicate that beta-1 AR stimulation occurred at a mirabegron dose of 200 mg.

Silodosin

Silodosin is a selective antagonist of post-synaptic alpha-1 adrenoreceptors, which are located in the human prostate, bladder base, bladder neck, prostatic Tablets, and prostatic urethra. Blockade of these alpha-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 binding affinity of silodosin to the three subtypes of the alpha-1 adrenoreceptors (alpha-1A, alpha-1B, and alpha-1D) was conducted. The results of the study demonstrated that silodosin binds with high affinity to the alpha-1A subtype.

5.2 Pharmacodynamic properties

Mirabegron

Urodynamics

The effects of mirabegron on maximum urinary flow rate and detrusor pressure at maximum flow rate were assessed in a urodynamic study consisting of 200 male patients with lower urinary tract symptoms (LUTS) and BOO. Administration of mirabegron once daily for 12 weeks did not adversely affect the mean maximum flow rate or mean detrusor pressure at maximum flow rate in this study. Nonetheless, mirabegron should be administered with caution to patients with clinically significant BOO.

Cardiac Electrophysiology

The effect of multiple doses of mirabegron 50 mg, 100 mg, and 200 mg (four times the maximum recommended dose) once daily on QTc interval was evaluated in a randomized, placebo- and active-controlled (moxifloxacin 400 mg), four treatment arm, parallel crossover study in 352 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 msec. For the 50 mg mirabegron dose group (the maximum approved dosage), the mean difference from placebo on QTcI interval at 4 to 5 hours post-dose was 3.7 msec (upper bound of the 95% CI 5.1 msec).

For the mirabegron 100 mg and 200 mg dose groups (dosages greater than the maximum approved dose and resulting in substantial multiples of the anticipated maximum blood levels at 50 mg), the mean differences from placebo in QTcI interval at 4 to 5 hours post dose were 6.1 msec (upper bound of the 95% CI 7.6 msec) and 8.1 msec (upper bound of the 95% CI 9.8 msec), respectively. At the mirabegron 200 mg dose, in females, the mean effect was 10.4 msec (upper bound of the 95% CI 13.4 msec).

In this thorough QT study, mirabegron increased heart rate on ECG in a dose-dependent manner. Maximum mean increases from baseline in heart rate for the 50 mg, 100 mg, and 200 mg dose groups compared to placebo were 6.7 bpm, 11 bpm, and 17 bpm, respectively. In the clinical efficacy and safety studies, the change from baseline in mean pulse rate for mirabegron 50 mg was approximately 1 bpm. In this thorough QT study, mirabegron also increased blood pressure in a dose-dependent manner.

Effects on Blood Pressure

In a study of 352 healthy subjects assessing the effect of multiple daily doses of 50 mg, 100 mg, and 200 mg (four times the maximum recommended dose) of mirabegron for 10 days on the QTc interval, the maximum mean increase in supine systolic blood pressure (SBP)/diastolic blood pressure (DBP) at the maximum recommended dose of 50 mg was approximately 4.0/1.6 mm Hg greater than placebo. The 24-hour average increases in SBP compared to placebo were 3.0, 5.5, and 9.7 mm Hg at mirabegron doses of 50 mg, 100 mg, and 200 mg, respectively. Increases in DBP were also dose-dependent, but were smaller than SBP.

In another study in 96 healthy subjects to assess the impact of age on pharmacokinetics of multiple daily doses of 50 mg, 100 mg, 200 mg, and 300 mg (six times the maximum recommended dose) of mirabegron for 10 days, SBP also increased in a dose-dependent manner. The mean maximum increases in SBP were approximately 2.5, 4.5, 5.5, and 6.5 mm Hg for mirabegron exposures associated with doses of 50 mg, 100 mg, 200 mg, and 300 mg, respectively.

In three, 12-week, double-blind, placebo-controlled, safety and efficacy studies (Studies 1, 2, and 3) in patients with OAB receiving mirabegron 25 mg, 50 mg, or 100 mg (two times the maximum recommended dose) once daily, mean increases in SBP/DBP compared to placebo of approximately 0.5 – 1 mm Hg were observed. Morning SBP increased by at least 15 mm Hg from baseline in 5.3%, 5.1%, and 6.7% of placebo, mirabegron 25 mg and mirabegron 50 mg patients, respectively. Morning DBP increased by at least 10 mm Hg in 4.6%, 4.1%, and 6.6% of placebo, mirabegron 25 mg, and mirabegron 50 mg patients, respectively. Both SBP and DBP increases were reversible upon discontinuation of treatment.

Effect on Intraocular Pressure (IOP)

Mirabegron 100 mg once daily did not increase IOP in healthy subjects after 56 days of treatment. In a phase 1 study assessing the effect of mirabegron on IOP using Goldmann applanation tonometry in 310 healthy subjects, a dose of mirabegron 100 mg was non-inferior to placebo for the primary endpoint of the treatment difference in mean change from baseline to day 56 in subject average IOP; the upper bound of the two-sided 95% CI of the treatment difference between mirabegron 100 mg and placebo was 0.3 mm Hg.

Silodosin

Orthostatic Effects

A test for postural hypotension was conducted 2 to 6 hours after the first dose in the 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 mmHg decrease in systolic blood pressure, or a > 20 mmHg decrease in diastolic blood pressure, or a > 20 bpm increase in heart rate.

Table 6: Summary of Orthostatic Test Results in 12-week, Placebo-Controlled Clinical Trials

Time of Measurement	Test Result	Silodosin N = 466 n (%)	Placebo N = 457 n (%)
1 Minute After Standing	Negative	459 (98.7)	454 (99.6)
	Positive	6 (1.3)	2 (0.4)
3 Minutes After Standing	Negative	456 (98.1)	454 (99.6)
	Positive	9 (1.9)	2 (0.4)

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 either Silodosin 8 mg, Silodosin 24 mg, or placebo once daily for five 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 CYP3A4 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.

5.3 Pharmacokinetic Properties

Mirabegron

Absorption

Mirabegron Monotherapy for Adult OAB

After oral administration of mirabegron in healthy volunteers, mirabegron was absorbed to reach maximum plasma concentrations (C_{max}) at approximately 3.5 hours. The absolute bioavailability increased from 29% at a dose of 25 mg to 35% at a dose of 50 mg. Mean C_{max} and AUC increased more than dose proportionally. This relationship was more apparent at doses above 50 mg. In the overall population of males and females, a 2-fold increase in dose from 50 mg to 100 mg mirabegron increased C_{max} and AUC_{tau} by approximately 2.9- and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50 to 200 mg mirabegron increased C_{max} and AUC_{tau} by approximately 8.4- and 6.5-fold. Steady-state concentrations were achieved within 7 days of once daily dosing with mirabegron. After once daily administration, plasma exposure of mirabegron at steady state was approximately double that seen after a single dose.

Effect of Food

Mirabegron Monotherapy for Adult OAB

There were no clinically significant differences in mirabegron pharmacokinetics when administered with or without food in adult patients.

Distribution

Mirabegron for Adult OAB

Mirabegron is extensively distributed in the body. The volume of distribution at steady state (V_{ss}) is approximately 1670 L following intravenous administration. Mirabegron is bound (approximately 71%) to human plasma proteins and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes. Based on an in vitro study, erythrocyte concentrations of ^{14}C-mirabegron were about 2-fold higher than in plasma.

Elimination

Mirabegron Monotherapy for Adult OAB

The terminal elimination half-life ($t_{1/2}$) of mirabegron is approximately 50 hours in patients.

Metabolism

Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Mirabegron is the major circulating component following a single dose of ^{14}C-mirabegron. Two major metabolites were observed in human plasma and phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active toward beta-3 adrenergic receptor. Although in vitro studies suggest a role for CYP2D6 and CYP3A4 in the oxidative metabolism of mirabegron, in vivo results indicate that these isozymes play a limited role in the overall elimination. In healthy subjects who were genotypically poor metabolizers of CYP2D6, mean C_{max} and AUC_{tau} were approximately 16% and 17% higher than in

extensive metabolizers of CYP2D6, respectively. In vitro and ex vivo studies have shown the involvement of butylcholinesterase, uridine diphospho-glucuronosyltransferases (UGT), and possibly alcohol dehydrogenase in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

Excretion

Mirabegron Monotherapy for Adult OAB

Total body clearance (CL_{tot}) from plasma is approximately 57 L/h following intravenous administration. Renal clearance (CL_R) is approximately 13 L/h, which corresponds to nearly 25% of CL_{tot}. Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary elimination of unchanged mirabegron is dose-dependent and ranges from approximately 6.0% after a daily dose of 25 mg to 12.2% after a daily dose of 100 mg. Following the administration of 160 mg ^{14}C-mirabegron solution to healthy volunteers, approximately 55% of the radioactivity dose was recovered in the urine and 34% in the feces. Approximately 25% of unchanged mirabegron was recovered in urine and 0% in feces.

Specific Populations

Geriatric Patients

The C_{max} and AUC of mirabegron following multiple oral doses in elderly volunteers (≥65 years) were similar to those in younger volunteers (18 to 45 years).

Gender

Mirabegron Monotherapy for Adult OAB

The C_{max} and AUC of mirabegron were approximately 40% to 50% higher in females than in males. When corrected for differences in body weight, the mirabegron systemic exposure was 20%-30% higher in females compared to males.

Race

The pharmacokinetics of mirabegron were comparable between Caucasians and African American Blacks. Cross studies comparison showed that the exposure in Japanese subjects were higher than that in North American subjects. However, when the C_{max} and AUC were normalized for dose and body weight, the difference was smaller.

Patients with Renal Impairment

Following single-dose administration of 100 mg mirabegron in adult volunteers with mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2 as estimated by MDRD), mean mirabegron C_{max} and AUC were increased by 6% and 31% relative to adult volunteers with normal renal function. In adult volunteers with moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2), C_{max} and AUC were increased by 23% and 66%, respectively. In adult volunteers with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), mean C_{max} and AUC values were 92% and 118% higher compared to healthy subjects with normal renal function. Mirabegron has not been studied in adult patients with End-Stage Renal Disease (ESRD) (eGFR less than 15 mL/min/1.73 m^2) or adult patients requiring dialysis.

Patients with Hepatic Impairment

Following single-dose administration of 100 mg mirabegron in adult volunteers with mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC were increased by 9% and 19%, relative to adult volunteers with normal hepatic function. In adult volunteers with moderate hepatic impairment (Child-Pugh Class B), mean Cmax and AUC values were 175% and 65% higher. Mirabegron has not been studied in adult patients with severe hepatic impairment (Child-Pugh Class C).

Drug Interaction Studies

In Vitro Studies

Effect of Other Drugs on Mirabegron

Mirabegron is transported and metabolized through multiple pathways. Mirabegron is a substrate for CYP3A4, CYP2D6, butyrylcholinesterase, UGT, the efflux transporter P-glycoprotein (P-gp), and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. Sulfonylurea hypoglycemic agents glibenclamide (a CYP3A4 substrate), gliclazide (a CYP2C9 and CYP3A4 substrate), and tolbutamide (a CYP2C9 substrate) did not affect the in vitro metabolism of mirabegron.

Effect of Mirabegron on Other Drugs

Studies of mirabegron using human liver microsomes and recombinant human CYP enzymes showed that mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A. Mirabegron is unlikely to inhibit the metabolism of coadministered drugs metabolized by the following cytochrome P450 enzymes: CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1 because mirabegron did not inhibit the activity of these enzymes at clinically relevant concentrations. Mirabegron did not induce CYP1A2 or CYP3A. Mirabegron inhibited P-gp-mediated drug transport at high concentrations. Mirabegron is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport. Mirabegron did not affect the metabolism of glibenclamide or tolbutamide.

Effect of Alcohol on Mirabegron

The addition of alcohol (5, 10, 20, and 40%) increases the dissolution rate of mirabegron from Mirabegron at pH 6.8. The clinical impact on the systemic exposure of mirabegron has not been evaluated. The addition of alcohol does not increase the dissolution rate of Mirabegron at pH 1.0 regardless of pH.

In Vivo Studies

Mirabegron for Adult OAB

The effect of coadministered drugs on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of coadministered drugs was studied after single and multiple doses of mirabegron. Most drug-drug interactions (DDI) were studied using mirabegron 100 mg extended-release tablets. However, interaction studies of mirabegron with metoprolol and with metformin were studied using mirabegron 160 mg immediate-release (IR) tablets.

The effect of ketoconazole, rifampicin, solifenacin succinate, tamsulosin, and metformin on systemic mirabegron exposure is shown in Figure 1.

The effect of mirabegron on metoprolol, desipramine, combined oral contraceptive-COC (ethinyl estradiol-EE, levonorgestrel-LNG), solifenacin succinate, digoxin, warfarin, tamsulosin, and metformin is shown in Figure 2.

In these studies, the largest increase in mirabegron systemic exposure was seen in the ketoconazole DDI study. As a potent CYP3A4 inhibitor, ketoconazole increased mirabegron C_{max} by 45% and mirabegron AUC by 80% after multiple dose administration of 400 mg of ketoconazole for 9 days prior to the administration of a single dose of 100 mg mirabegron in 23 male and female healthy subjects.

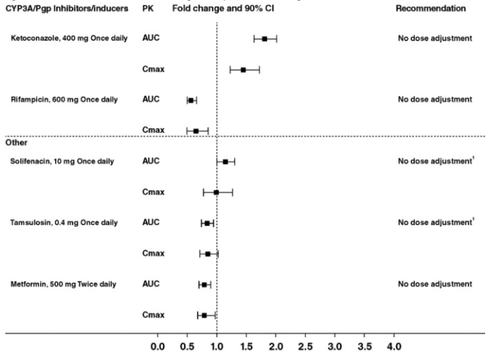
As a moderate CYP2D6 inhibitor, mirabegron increased the systemic exposure to metoprolol and desipramine:

Mirabegron increased the Cmax of metoprolol by 90% and metoprolol AUC by 229% after multiple doses of 160 mg mirabegron IR tablets once daily for 5 days and a single dose of 100 mg metoprolol tablet in 12 healthy male subjects administered before and concomitantly with mirabegron.

Mirabegron increased the Cmax of desipramine by 79% and desipramine AUC by 241% after multiple dose administration of 100 mg mirabegron once daily for 18 days and a single dose of 50 mg desipramine before and concomitantly with mirabegron in 28 male and female healthy subjects.

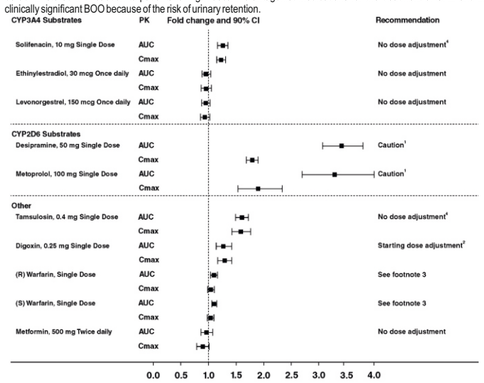
Figures 1 and 2 show the magnitude of these interactions on the pharmacokinetic parameters and the recommendations for dose adjustment, if any:

Figure 1: The Effect of Coadministered Drugs on Exposure of Mirabegron and Dose Recommendation



Mean change relative to mirabegron alone

Although no dose adjustment is recommended with tamsulosin based on the lack of pharmacokinetic interaction, Mirabegron should be administered with caution to patients taking muscarinic antagonist medications for the treatment of OAB and in patients with clinically significant BOO because of the risk of urinary retention.



Mean change relative to substrate alone

(1) Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when coadministered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide, and propafenone.

(2) For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should initially be prescribed. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. The same approach for the dose of digoxin should be followed when digoxin is coadministered with mirabegron and tamsulosin.

(3) Warfarin was administered as a single 25 mg dose of the racemate (a mixture of R-warfarin and S-warfarin). Based on this single-dose study, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as INR and prothrombin time. However, the effect of mirabegron on multiple doses of warfarin and on warfarin pharmacodynamic end points such as INR and prothrombin time has not been fully investigated.

(4) Although no dose adjustment is recommended with tamsulosin based on the lack of pharmacokinetic interaction, Mirabegron should be administered with caution to patients taking muscarinic antagonist medications for the treatment of OAB and in BOO because of the risk of urinary retention.

Based on the lack of relevant pharmacokinetic interaction, no dose adjustment for tamsulosin is recommended when coadministered with mirabegron.

Silodosin

The pharmacokinetics of silodosin have been evaluated in adult male subjects with doses ranging from 0.1 mg to 24 mg per day. The pharmacokinetics of silodosin are linear throughout this dosage range.

Absorption

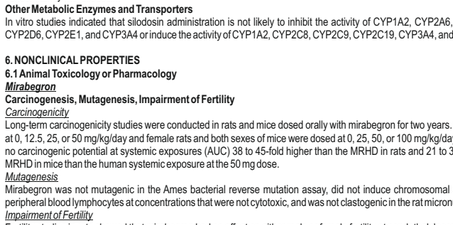
The pharmacokinetic characteristics of silodosin 8 mg once daily were determined in a multi-dose, open-label, 7-day pharmacokinetic study completed in 19 healthy, target-aged (≥ 45 years of age) male subjects. Table 7 presents the steady state pharmacokinetics of this study.

Table 7: Mean (±SD) Steady State Pharmacokinetic Parameters in Healthy Males Following Silodosin 8 mg Once Daily with Food

C_{max} (ng/mL)	t_{max} (hours)	t1/2 (hours)	AUC_{ss} (ng•hr/mL)
61.6 ± 27.54	2.6 ± 0.90	13.3 ± 8.07	373.4 ± 164.94

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

Figure 3 Mean (±SD) Silodosin Steady State Plasma Concentration-Time Profile in Healthy Target-Aged Subjects Following Silodosin 8 mg Once Daily with Food



The absolute bioavailability is approximately 32%.

Food Effect

The maximum effect of food (i.e., co-administration with a high fat, high calorie meal) on the PK 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 AUC by 4 to 49% across three different studies.

In a single-center, open-label, single-dose, randomized, two-period crossover study in twenty healthy male subjects age 21 to 43 years under fed conditions, a study was conducted to evaluate the relative bioavailability of the contents of an 8 mg tablets (size #1) of silodosin sprinkled on applesauce compared to the product administered as an intact tablets. Based on AUC_{0-24} and C_{max}, silodosin administered by sprinkling the contents of a Silodosin tablets onto a tablespoonful of applesauce was found to be bioequivalent to administering the tablets whole.

Distribution

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

Elimination

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 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-labeled silodosin, the recovery of radioactivity after 10 days was approximately 33.5% in urine and 54.9% in feces. After intravenous administration, the plasma clearance of silodosin was approximately 10 L/hour.

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.

Renal Impairment

In a study with six subjects with moderate renal impairment, the total silodosin (bound and unbound) AUC, C_{max}, and elimination half-life were 3.2-, 3.1-, and 2-fold higher, respectively, compared to seven subjects with normal renal function. The unbound silodosin AUC and C_{max} were 2.0- and 1.5-fold higher, respectively, in subjects with moderate renal impairment compared to 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 nine male patients with moderate hepatic impairment (Child-Pugh scores 7 to 9), to nine 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 have not been studied.

Drug Interactions

Cytochrome P450 (CYP) 3A4 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 3.8-fold increase in silodosin C_{max} and 3.2-fold increase in AUC. Co-administration of 4 mg silodosin with 200 mg ketoconazole led to similar increases: 3.7- and 2.9-fold in silodosin C_{max} and AUC, respectively. Silodosin is contraindicated with strong CYP3A4 inhibitors.

The effect of moderate CYP3A4 inhibitors on the pharmacokinetics of silodosin has not been evaluated.

Due to the potential for increased exposure to silodosin, caution should be exercised when co- administering silodosin with moderate CYP3A4 inhibitors, particularly those that also inhibit P glycoprotein (e.g., verapamil, erythromycin).

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 (e.g., cyclosporine).

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 seven days and then concomitantly with silodosin 4 mg twice a day for the next seven days. No significant differences in digoxin AUC and C_{max} were observed when digoxin was administered alone or concomitantly with silodosin.

Other Metabolic Enzymes and Transporters

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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Mirabegron

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Long-term carcinogenicity studies were conducted in rats and mice dosed orally with mirabegron for two years. Male rats were dosed at 0, 12.5, 25, or 50 mg/kg/day and female rats and both sexes of mice were dosed at 0, 25, 50, or 100 mg/kg/day. Mirabegron showed no carcinogenic potential at systemic exposures (AUC) 38 to 45-fold higher than the MRHD in rats and 21 to 38-fold higher than the MRHD in mice than the human systemic exposure at the 50 mg dose.

Mutagenesis

Mirabegron was not mutagenic in the Ames bacterial reverse mutation assay, did not induce chromosomal aberrations in human peripheral blood lymphocytes at concentrations that were not cytotoxic, and was not clastogenic in the rat micronucleus assay.

Impairment of Fertility

Fertility studies in rats showed that mirabegron had no effect on either male or female fertility at non-lethal doses up to 100 mg/kg/day. Systemic exposures (AUC) at 100 mg/kg in female rats was estimated to be 22-fold the MRHD in women and 93-fold the MRHD in men.

Silodosin

Carcinogenesis, Mutagenesis, and Impairment of Fertility

In a 2-year oral carcinogenicity study in rats administered doses up to 150 mg/kg/day [about 8 times the exposure at the MRHD based on AUC of silodosin], an increase in thyroid follicular cell tumor incidence was seen in male rats receiving doses of 150 mg/kg/day. Silodosin induced stimulation of thyroid stimulating hormone (TSH) secretion in the male rat as a result of increased metabolism and decreased circulating levels of thyroxine (T_4). These changes are believed to produce specific morphological and functional changes in the rat thyroid including hypertrophy, hyperplasia, and neoplasia. Silodosin did not alter TSH or T_4 levels in clinical trials and no effects based on thyroid examinations were noted. The relevance to human risk of these thyroid tumors in rats is not known.

In a 2-year oral carcinogenicity study in mice administered doses up to 100 mg/kg/day in males (about 9 times the exposure at the MRHD based on AUC of silodosin) and 400 mg/kg/day in females (about 72 times the exposure at the MRHD based on AUC), there were no significant tumor findings in male mice. Female mice treated for 2 years with doses of 150 mg/kg/day (about 29 times the exposure at the MRHD based on AUC) or greater had statistically significant increases in the incidence of mammary gland adenoacanthomas and adenocarcinomas. The increased incidence of mammary gland neoplasms in female mice was considered secondary to silodosin-induced hyperprolactinemia measured in the treated mice. Elevated prolactin levels were not observed in clinical trials. The relevance to human risk of prolactin-mediated endocrine tumors in mice is not known. Rats and mice do not produce glucuronidated silodosin, which is present in human serum at approximately four times the level of circulating silodosin and which has similar pharmacological activity to silodosin.

Silodosin produced no evidence of mutagenic or genotoxic potential in the in vitro Ames assay, mouse lymphoma assay, unscheduled DNA synthesis assay and the in vivo mouse micronucleus assay. A weakly positive response was obtained in two in vitro Chinese Hamster Lung (CHL) tests for chromosomal aberration assays at high, cytotoxic concentrations.

Treatment of male rats with silodosin for 15 days resulted in decreased fertility at the high dose of 20 mg/kg/day (about 2 times the exposure at the MRHD based on AUC) which was reversible following a two-week recovery period. No effect was observed at 6 mg/kg/day. The clinical relevance of this finding is not known.

In a fertility study in female rats, the high dose of 20 mg/kg/day (about 1 to 4 times the exposure at the MRHD based on AUC) resulted in estrus cycle changes, but no effect on fertility. No effect on the estrus cycle was observed at 6 mg/kg/day.

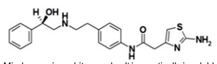
In a male rat fertility study, sperm viability and count were significantly lower after administration of 600 mg/kg/day (about 65 times the exposure at the MRHD based on AUC) for one month.

Histopathological examination of infertile males revealed changes in the testes and epididymides at 200 mg/kg/day (about 30 times the exposure at the MRHD based on AUC).

7. DESCRIPTION

Mirabegron

Mirabegron is a beta-3 adrenergic agonist. The chemical name is 2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy2-phenylethyl]amino}ethyl)phenyl]acetamide having an empirical formula of $C_{21}H_{24}N_4O_2S$ and a molecular weight of 396.51 g/mol. The structural formula of Mirabegron is:

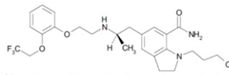


Mirabegron is a white powder. It is practically insoluble in water (0.082 mg/mL). It is soluble in methanol and dimethyl sulfoxide.

Silodosin

Silodosin is a selective antagonist of alpha-1 adrenoreceptors.

The chemical name of silodosin is 1-(3-Hydroxypropyl)-5-[(2R)-2-{[2-[2-(2,2,2 trifluoroethoxy)phenoxy]ethyl]amino}propyl]-2,3-dihydro-1H-indole-7-carboxamide and the molecular formula is $C_{25}H_{32}F_3N_3O_4$ with a molecular weight of 495.53. The structural formula of silodosin is:



Silodosin is a white to pale yellowish white powder that melts at approximately 105 to 109°C. It is very soluble in acetic acid, freely soluble in alcohol, and very slightly soluble in water.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

NA

8.2 Shelf life:

Please refer details on blister/carton.

8.3 Packaging information

Alu-Alu blister of 10 tablets

8.4 Storage & Handling Instructions:

Store at a temperature not exceeding 30°C. Protected from light & moisture.

9. PATIENT COUNSELLING INFORMATION

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What Mirabegron & Silodosin Tablet is and what it is used for

Mirabegron

Mirabegron contains the active substance mirabegron. It is a bladder muscle relaxant (a so-called beta 3-adrenoceptor agonist), which reduces the activity of an overactive bladder and treats the related symptoms.

Mirabegron is used to treat the symptoms of an overactive bladder in adults such as:

- suddenly needing to empty your bladder (called urgency)
- having to empty your bladder more than usual (called increased urinary frequency)
- not being able to control when to empty your bladder (called urgency incontinence)

Silodosin

Silodyx belongs to a group of medicines called alpha1A-adrenoreceptor blockers. By blocking these receptors, it causes smooth muscle in these tissues to relax. This makes it easier for you to pass water and relieves your symptoms.

Silodyx is used in adult men to treat the urinary symptoms associated with benign enlargement of the prostate (prostatic hyperplasia), such as:

- difficulty in starting to pass water,
- a feeling of not completely emptying the bladder,
- a more frequent need to pass water, even at night.

What you need to know before you take Mirabegron & Silodosin Tablet

Do not take Mirabegron & Silodosin Tablet

If you are allergic to Mirabegron & Silodosin or any of the other ingredients of this medicine

Warnings and precautions

- if you have trouble emptying your bladder or you have a weak urine stream or if you take other medicines for the treatment of overactive bladder such as anticholinergic medicines.
- if you have kidney or liver problems.
- if you have an ECG (heart tracing) abnormality known as QT prolongation
- If you have ever fainted or felt dizzy when suddenly standing up.

Children and adolescents

Do not give Mirabegron & Silodosin Tablet to children and adolescents below 18 years since there is no relevant indication for this age group.

Other medicines and Mirabegron & Silodosin Tablet

Tell your doctor or pharmacist if you are taking/using, have recently taken/used or might take/use any other medicines. It is especially important to inform your doctor if you are taking:

- Tell your doctor if you use thioridazine (a medicine for mental illness), propafenone or flecainide (medicines for abnormal heart rhythm), imipramine or desipramine (medicines used for depression).
- if you use dabigatran etexilate (a medicine which is used to reduce the risk of brain or body vessel obstruction by blood clot formation in adult patients with an abnormal heart beat (atrial fibrillation) and additional risk factors).
- medicines which lower blood pressure (in particular, medicines called alpha1-blockers, such as prazosin or doxazosin)
- antifungal medicines (such as ketoconazole or itraconazole), medicines used for HIV-AIDS (such as ritonavir) or medicines used after transplants to prevent organ rejection (such as cyclosporin)

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not use Mirabegron & Silodosin Tablet if you are pregnant unless clearly necessary. Do not use Mirabegron & Silodosin Tablet if you are breast-feeding as Mirabegron & Silodosin may get into your breast milk.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most serious side effects may include irregular heartbeat (atrial fibrillation). If you get headaches, especially sudden, migraine-like (throbbing) headaches, tell your doctor. These may be signs of severely elevated blood pressure. Dizziness, including dizziness when standing up, and occasionally fainting, may occur.

Mirabegron & Silodosin may cause the following other side effects:

Very common (may affect more than 1 in 10 people)

- Abnormal ejaculation (less or no noticeable semen is released during sex.

Common (may affect up to 1 in 10 people)

- Increased heart rate (tachycardia)
- Infection of the structures that carry urine (urinary tract infections)
- Dizziness, including dizziness when standing up
- Runny or blocked nose
- constipation, nausea

Uncommon (may affect up to 1 in 100 people)

- Bladder infection (cystitis)
- Feeling your heartbeat (palpitations)
- Vaginal infection
- Indigestion (dyspepsia)
- Infection of the stomach (gastritis)
- Swelling of the joints
- Itching of the vulva or vagina (vulvovaginal pruritus)
- Increased blood pressure
- Increase in liver enzymes (GGT, AST and ALT)
- Itching, rash or hives (urticaria, rash, rash macular, rash papular, pruritus)
- Nausea
- Decreased sexual drive
- Dry mouth

Rare (may affect up to 1 in 1,000 people)

- Fast or irregular heart beats (called palpitations)
- Fainting/ Loss of consciousness
- Swelling of the eyelid (eyelid oedema)
- Swelling of the lip (lip oedema)
- Swelling of the deeper layers of the skin caused by a build-up of fluid
- Small purple spots on the skin (purpura)
- Inflammation of small blood vessels mainly affecting the skin (leukocytoclastic vasculitis)
- Inability to completely empty the bladder (urinary retention)

Very rare (may affect up to 1 in 10,000 people)

- Hypertensive crisis.
- Other allergic reactions with swelling of the face or throat

Not known (frequency cannot be estimated from the available data)

- Floppy pupil during cataract surgery, increased pressure in the eyes
- Insomnia
- Confusion

10. DETAILS OF MANUFACTURER

Windlas Biotech Limited (Plant-2),
Khasra No. 141 to 143 & 145, Mohabewala Indl. Area, Dehradun-248110 (U.K.)
R.O.: 40/1, Mohabewala Indl. Area, Dehradun.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Licence No.: 34/UA/2013 **Dated:** 16/11/2023

12. DATE OF REVISION

November 2023

MFLL0042-00