

Summary of Product Characteristics

1. Name of the Medical Product

S-MIRAH® 50/5 MG

Mirabegron (Extended Release) 50mg & Solifenacin Succinate 5 mg Tablets

2. Qualitative & Quantitative Composition:

Each Film coated Bilayered tablet contains:

Mirabegron (As Extended Release)50 mg

Solifenacin Succinate EP.....5 mg

Excipient of known effect

Lactose Monohydrate USP

Aspartame

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form:

Film coated Bilayered Tablets

Visual description

Pink colour round shape Slightly Biconvex Plain on both side Film coated bilayer Tablets.

4. Clinical Particulars

4.1 Therapeutic Indications:

Mirabegron in combination with the muscarinic antagonist solifenacin succinate, is indicated for the treatment of OAB with symptoms of urge urinary incontinence, urgency, and urinary frequency.

4.2 Posology and Method of administration:

The recommended adult oral dose is Mirabegron (ER) & Solifenacin Tablets (25 mg/5 mg) once daily or as directed by the Physician.

The recommended starting dose for Mirabegron (ER) & Solifenacin Tablets (25 mg/5 mg) is once daily. Based on individual patient efficacy and tolerability, the dose may be increased to Mirabegron/Solifenacin succinate (50 mg + 5 mg) tablet once daily after 4 to 8 weeks or as directed by the Physician.

Dose Adjustments in Specific Populations

The daily dose of Mirabegron/Solifenacin tablets should not exceed 1 tablet (Mirabegron/Solifenacin succinate 25 mg + 5 mg tablets) once daily in the following populations:

- Patients with severe renal impairment.
- Patients with moderate hepatic impairment (Child-Pugh Class B).
- Mirabegron/Solifenacin tablet is not recommended for use in patients with End-Stage Renal Disease (ESRD), or in patients with severe hepatic impairment (Child-Pugh Class C).

Method of administration For oral use only.

The Mirabegron/Solifenacin tablets should be taken with water, swallowed whole and should not be chewed, divided, or crushed. It can be taken together with or without food.

4.3 Contraindications:

It is contraindicated in patients with known hypersensitivity to mirabegron or solifenacin or to any of the excipients.

Mirabegron is contraindicated in:

- Severe uncontrolled hypertension (defined as systolic blood pressure $\geq$ 180 mm Hg and/or diastolic blood pressure $\geq$ 110 mm Hg). Solifenacin is contraindicated in:
- Patients with urinary retention, severe gastrointestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions.
- Patients at high risk of QT prolongation, including patients with a known history of QT prolongation and patients taking medications known to prolong the QT interval.
- Patients undergoing haemodialysis.
- Patients with severe hepatic impairment.
- Patients with severe renal impairment or moderate hepatic impairment and who are on treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole.

4.4 Special warnings & precautions for use

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) [see Clinical Pharmacology].

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 Mirabegron, patients; 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, including solifenacin succinate .

Angioedema

Angioedema of the face, lips, tongue, and/or larynx has been reported with Mirabegron. In some cases, angioedema occurred after the first dose. Cases of angioedema 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 initiate appropriate therapy and/or measures necessary to ensure a patent airway. In two, randomized, placebo-controlled, healthy 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 OAB patients in clinical trials, Mirabegron taken as monotherapy or in combination with solifenacin succinate 5 mg, 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 Mirabegron patients.

Patients Taking Drugs Metabolized by CYP2D6

Since Mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with Mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6, such as asthioridazine, flecainide, and propafenone and Clinical Pharmacology.

Renal impairment

Mirabegron has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m² or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73m²); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. This medicinal product is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²) concomitantly receiving strong CYP3A inhibitors.

Hepatic impairment

Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. This medicinal product is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors.

Hypertension

Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with mirabegron, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg).

Patients with congenital or acquired QT prolongation

Mirabegron, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients.

Solifenacin Succinate

Other causes of frequent urination (heart failure or renal disease) should be assessed before treatment with Solifenacin succinate. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Solifenacin succinate should be used with caution in patients with:

- Clinically significant bladder outflow obstruction at risk of urinary retention.
- Gastrointestinal obstructive disorders.
- Risk of decreased gastrointestinal motility.
- Severe renal impairment (creatinine clearance ≤ 30 mL/min) and doses should not exceed 5 mg for these patients.
- Moderate hepatic impairment (Child-Pugh score of 7 to 9) and doses should not exceed 5 mg for these patients.
- Concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole.

- Hiatus hernia/gastro-esophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.
- Autonomic neuropathy.

QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia.

Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity.

Angioedema with airway obstruction has been reported in some patients on solifenacin succinate. If angioedema occurs, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken.

Anaphylactic reaction has been reported in some patients treated with solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken.

The maximum effect of Solifenacin succinate can be determined after 4 weeks at the earliest.

4.5 Interactions with other medicinal products and other forms of Interactions

Drug interaction studies were conducted to investigate the effect of co-administered 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 co-administered with Mirabegron. The following are drug interactions for which monitoring is recommended:

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Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. This medicinal product is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors.

Hypertension

Mirabegron can increase blood pressure. Blood pressure can be measured at baseline & periodically during treatment with mirabegron, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg).

Patients with congenital or acquired QT prolongation

Mirabegron, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies. However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these

patients is unknown. Caution should be exercised when administering mirabegron in these patients.

In vitro data

Mirabegron is transported and metabolised through multiple pathways. Mirabegron is a substrate for cytochrome P450 (CYP) 3A4, CYP2D6, butyrylcholinesterase, uridine diphospho glucuronosyl transferases (UGT), the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3. 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 inhibited P-gp-mediated drug transport at high concentrations.

In vivo data

Drug-drug interactions

The effect of co-administered medicinal products on the pharmacokinetics of mirabegron and the effect of mirabegron on the pharmacokinetics of other medicinal products was studied in single and multiple dose studies. Most drug-drug interactions were studied using a dose of 100 mg mirabegron given as oral controlled absorption system (OCAS) tablets. Interaction studies of mirabegron with metoprolol and with metformin used mirabegron immediate-release (IR) 160 mg. Clinically relevant drug interactions between mirabegron and medicinal products that inhibit; induce or are a substrate for one of the CYP isozymes or transporters are not expected except for the inhibitory effect of mirabegron on the metabolism of CYP2D6 substrates.

Effect of enzyme inhibitors

Mirabegron exposure (AUC) was increased 1.8-fold in the presence of the strong inhibitor of CYP3A/P-gp ketoconazole in healthy volunteers. No dose-adjustment is needed when Mirabegron is combined with inhibitors of CYP3A and/or P-gp. However, in patients with mild to moderate renal impairment (GFR 30 to 89 mL/min/1.73 m²) or mild hepatic impairment (Child-Pugh Class A) concomitantly receiving strong CYP3A inhibitors, such as itraconazole, ketoconazole, ritonavir and clarithromycin, the recommended dose is 25 mg once daily with or without food. Mirabegron is not recommended in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m²) or patients with moderate hepatic impairment (Child-Pugh Class B) concomitantly receiving strong CYP3A inhibitors.

Effect of enzyme inducers

Substances that are inducers of CYP3A or P-gp decrease the plasma concentrations of mirabegron. No dose adjustment is needed for mirabegron when administered with therapeutic doses of rifampicin or other CYP3A or P-gp inducers.

Effect of CYP2D6 polymorphism

CYP2D6 genetic polymorphism has minimal impact on the mean plasma exposure to mirabegron. Interaction of mirabegron with a known CYP2D6 inhibitor is not expected and was not studied. No dose adjustment is needed for mirabegron when administered with CYP2D6 inhibitors or in patients who are CYP2D6 poor metabolisers. Effect of mirabegron on CYP2D6 substrates

In healthy volunteers, the inhibitory potency of mirabegron towards CYP2D6 is moderate and the CYP2D6 activity recovers within 15 days after discontinuation of mirabegron. Multiple once daily dosing of mirabegron IR resulted in a 90% increase in C_{max} and a 229% increase in AUC of a single dose of metoprolol. Multiple once

daily dosing of mirabegron resulted in a 79% increase in C_{max} and a 241% increase in AUC of a single dose of desipramine.

Caution is advised if mirabegron is co-administered with medicinal products with a narrow therapeutic index and significantly metabolised by CYP2D6, such as thioridazine, Type 1C antiarrhythmics (e.g., flecainide, propafenone) and tricyclic antidepressants (e.g., imipramine, desipramine). Caution is also advised if mirabegron is co-administered with CYP2D6 substrates that are individually dose titrated. Effect of mirabegron on transporters

Mirabegron is a weak inhibitor of P-gp. Mirabegron increased C_{max} and AUC by 29% and 27%, respectively, of the P-gp substrate digoxin in healthy volunteers. For patients who are initiating a combination of mirabegron and digoxin, the lowest dose for digoxin should be prescribed initially. Serum digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect. The potential for inhibition of P-gp by mirabegron should be considered when Mirabegron is combined with sensitive P-gp substrates e.g. dabigatran.

Other interactions

No clinically relevant interactions have been observed when mirabegron was co-administered with therapeutic doses of solifenacin, tamsulosin, warfarin, metformin or a combined oral contraceptive medicinal product containing ethinylestradiol and levonorgestrel. Dose-adjustment is not recommended. Increases in mirabegron exposure due to drug-drug interactions may be associated with increases in pulse rate.

Solifenacin Succinate

Pharmacological interactions

Concomitant medication with other medicinal products with anticholinergic properties may result in more pronounced therapeutic effects and undesirable effects. An interval of approximately one week should be allowed after stopping treatment with Solifenacin succinate film-coated tablets, before commencing other anticholinergic therapy. The therapeutic effect of solifenacin may be reduced by concomitant administration of cholinergic receptor agonists.

Solifenacin can reduce the effect of medicinal products that stimulate the motility of the gastrointestinal tract, such as metoclopramide and cisapride.

Pharmacokinetic interactions

In vitro studies have demonstrated that at therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes. Therefore, solifenacin is unlikely to alter the clearance of drugs metabolised by these CYP enzymes.

Effect of other medicinal products on the pharmacokinetics of solifenacin

Solifenacin is metabolised by CYP3A4. Simultaneous administration of ketoconazole (200 mg/day), a potent CYP3A4 inhibitor, resulted in a two-fold increase of the AUC of solifenacin, while ketoconazole at a dose of 400 mg/day resulted in a three-fold increase of the AUC of solifenacin. Therefore, the maximum dose of Solifenacin succinate film-coated tablets should be restricted to 5mg, when used simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole).

Simultaneous treatment of solifenacin and a potent CYP3A4 inhibitor is contraindicated in patients with severe renal impairment or moderate hepatic impairment.

The effects of enzyme induction on the pharmacokinetics of solifenacin and its metabolites have not been studied as well as the effect of higher affinity CYP3A4 substrates on solifenacin exposure. Since solifenacin is metabolised by CYP3A4, pharmacokinetic interactions are possible with other CYP3A4 substrates with

higher affinity (e.g. verapamil, diltiazem) and CYP3A4 inducers (e.g. rifampicin, phenytoin, and carbamazepine).

Effect of solifenacin on the pharmacokinetics of other medicinal products

Oral Contraceptives

Intake of solifenacin showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel).

Warfarin

Intake of solifenacin did not alter the pharmacokinetics of R-warfarin or S-warfarin or their effect on prothrombin time.

Digoxin

Intake of solifenacin showed no effect on the pharmacokinetics of digoxin.

4.6 Pregnancy and Lactation

Pregnancy :

Mirabegron : -

Risk Summary : There are no studies with the use of Mirabegron in pregnant women to inform drug-associated risk for birth defects or miscarriage. 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 risks of major birth defects and 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.

Solifenacin Succinate :

There are no adequate and well-controlled studies in pregnant women.

No clinical data are available from women who became pregnant while taking solifenacin. Animal studies do not indicate direct harmful effects on fertility, embryonal / foetal development or parturition. The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women.

Labour and Delivery

The effect of solifenacin succinate on labour and delivery in humans has not been studied.

Lactation :

Mirabegron

Risk Summary: There is no information 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 ¹⁴C-labeled Mirabegron to lactating rats. 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.

Solifenacin

No data on the excretion of solifenacin in human milk are available. In mice, solifenacin and/or its metabolites was excreted in milk and caused a dose dependent failure to thrive in neonatal mice. The use of Solifenacin succinate should therefore be avoided during breast-feeding.

Paediatric Patients

The safety and effectiveness of mirabegron and solifenacin combination in paediatric patients have not been established.

4.7 Effects on ability to drive and use machine*:

Mirabegron has no or negligible influence on the ability to drive and use machines. Since solifenacin, like other anticholinergics may cause blurred vision, and, uncommonly, somnolence and fatigue, the ability to drive and use machines may be negatively affected.

4.8 Undesirable Effects*:

Mirabegron

The following adverse reactions are discussed in more detail in other sections of the labeling.

- Hypertension (see Warnings and Precautions).
- Urinary retention (see Warnings and Precautions).
- Angioedema (see Warnings and Precautions)

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>.

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 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.

Solifenacin

Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects. The highest dose of solifenacin succinate accidentally given to a single patient was 280 mg in a 5 hour period, resulting in mental status changes not requiring hospitalization.

In the event of overdose with solifenacin succinate the patient should be treated with activated charcoal. Gastric lavage is useful if performed within 1 hour, but vomiting should not be induced. As for other anticholinergics, symptoms can be treated as follows:

- Severe central anticholinergic effects such as hallucinations or pronounced excitation: treat with physostigmine or carbachol.
- Convulsions or pronounced excitation: treat with benzodiazepines.
- Respiratory insufficiency: treat with artificial respiration.
- Tachycardia: treat with beta-blockers.

5. Pharmacological properties:

5.1 Pharmacodynamic Properties:

Pharmacotherapeutic group: Urological; Drugs for urinary frequency and incontinence.

ATC Code : G04B D08 (Mirabegron) & A06AX05 (Solifenacin Succinate) **Mechanism of Action**

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

Solifenacin Succinate : Solifenacin is a competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of urinary bladder smooth muscle.

Pharmacodynamic effects

Mirabegron

Mirabegron has little effect on the mean maximum flow rate or mean detrusor pressure at maximum flow rate in patients with lower urinary tract symptoms and bladder outlet obstruction. Furthermore, mirabegron increases blood pressure in a dose dependent manner. However, this effect is reversible when mirabegron is

discontinued. Mirabegron also increases heart rate in a dose dependent manner. The dose in which half-maximal efficacy is demonstrated is 25 mg. comparatively, the dose in which maximal efficacy is demonstrated is 100 mg.

Solifenacin

The urinary bladder is innervated by parasympathetic cholinergic nerves. Acetylcholine contracts the detrusor smooth muscle through muscarinic receptors of which the M3 subtype is predominantly involved. In vitro and in vivo pharmacological studies indicate that solifenacin is a competitive inhibitor of the muscarinic M3 subtype receptor. In addition, solifenacin showed to be a specific antagonist for muscarinic receptors by displaying low or no affinity for various other receptors and ion channels tested.

5.2 Pharmacokinetics Properties*:

Mirabegron

Absorption

After oral administration of mirabegron in healthy volunteers, mirabegron is absorbed to reach maximum plasma concentrations (C_{max}) at approximately 3.5 hours. The absolute bioavailability increases from 29% at a dose of 25 mg to 35% at a dose of 50 mg. Mean C_{max} and AUC increase more than dose proportionally. This relationship is 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 are achieved within 7 days of once-daily dosing with mirabegron. After once-daily administration, plasma exposure of mirabegron at steady state is approximately double that seen after a single dose.

Effect of Food: Co-administration of a 50 mg tablet with a high-fat meal reduced mirabegron C_{max} and AUC by 45% and 17%, respectively. A low-fat meal decreased mirabegron C_{max} and AUC by 75% and 51%, respectively. In the phase 3 studies, mirabegron was administered irrespective of food contents and intake (e.g., with or without food) and demonstrated both safety and efficacy. Therefore, mirabegron can be taken with or without food at the recommended dose.

Distribution

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 ¹⁴C-mirabegron were about 2-fold higher than in plasma.

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 ¹⁴C-mirabegron. Two major metabolites were observed in human plasma and are Phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active toward beta-3 adrenergic receptors. Although in vitro studies suggest a role for cytochrome (CY) P2D6 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 are 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 diphosphoglucuronosyltransferases (UGT) and, possibly, alcohol dehydrogenase in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

Excretion.

Total body clearance (CL_{tot}) from plasma is approximately 57 L/h following intravenous administration. The terminal elimination half-life (t_{1/2}) is approximately 50 hours. Renal clearance (CLR) 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 ¹⁴C-mirabegron solution to healthy volunteers, approximately 55% of the radioactivity dose was recovered in the urine and 34% in the faeces. Approximately 25% of unchanged mirabegron was recovered in urine and 0% in faeces.

Solifenacin

Absorption : After intake of solifenacin, maximum solifenacin plasma concentrations (C_{max}) are reached after 3 to 8 hours. The t_{max} is independent of the dose. The C_{max} and area under the curve (AUC) increase in proportion to the dose between 5 to 40 mg. Absolute bioavailability is approximately 90%. Food intake does not affect the C_{max} and AUC of solifenacin.

Distribution : The apparent volume of distribution of solifenacin following intravenous administration is about 600L. Solifenacin is to a great extent (approximately 98%) bound to plasma proteins, primarily α₁acid glycoprotein.

Biotransformation: Solifenacin is extensively metabolised by the liver, primarily by cytochrome P450 3A4 (CYP3A4). However, alternative metabolic pathways exist, that can contribute to the metabolism of solifenacin. The systemic clearance of solifenacin is about 9.5 L/h and the terminal half-life of solifenacin is 45-68 hours. After oral dosing, one pharmacologically active (4R-hydroxy solifenacin) and three inactive metabolites (N-glucuronide, N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been identified in plasma in addition to solifenacin.

Elimination

After a single administration of 10 mg [¹⁴C-labelled]-solifenacin, about 70% of the radioactivity was detected in urine and 23% in faeces over 26 days. In urine, approximately 11% of the radioactivity is recovered as unchanged active substance; about 18% as the N-oxide metabolite, 9% as the 4Rhydroxy-N-oxide metabolite and 8% as the 4R-hydroxy metabolite (active metabolite).

5.3 Preclinical safety data

Mirabegron:

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.

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.

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.

Solifenacin:

No increase in tumors was found following the administration of solifenacin succinate to male and female mice for 104 weeks at doses up to 200 mg/kg/day (5 and 9 times, respectively, of the exposure at the maximum recommended human dose [MRHD] of 10 mg), and male and female rats for 104 weeks at doses up to 20 and 15 mg/kg/day, respectively (< 1 times the exposure at the MRHD).

Solifenacin succinate was not mutagenic in the in vitro Salmonella typhimurium or Escherichia coli microbial mutagenicity test or chromosomal aberration test in human peripheral blood lymphocytes with or without metabolic activation or in the in vivo micronucleus test in rats. Solifenacin succinate had no effect on reproductive function, fertility, or early embryonic development of the fetus in male and female mice treated with 250 mg/kg/day (13 times the exposure at the MRHD) of solifenacin succinate, and in male rats treated with 50 mg/kg/day (< 1 times the exposure at the MRHD) and female rats treated with 100 mg/kg/day (1.7 times the exposure at the MRHD) of solifenacin succinate.

Solifenacin

Juvenile Animal Toxicology Data:

Dose-related increased mortality without preceding clinical signs occurred in juvenile mice treated before weaning for a duration of 12 weeks, from day 10 after birth, with doses that achieved a pharmacological effect. Animals dosed from postnatal day 10 onwards had higher mortality compared to the mortality in adult mice. No increased frequency in mortality was observed in juvenile mice that were treated after weaning for a duration of 4 weeks, from day 21 after birth onwards. Plasma exposure at postnatal day 10 was higher than in adult mice; the systemic exposure at postnatal day 21 was comparable to the systemic exposure in adult mice.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Layer- 1
Corn Starch USP
Microcrystalline Cellulose Powder USP
Hydrocel CW -4000 –CR USP
Povidone (K-30) USP
Isopropyl Alcohol USP
Magnesium stearate USP
Layer- 2
Lactose Monohydrate USP
Butylated Hydroxytoluene USP
Hydrophobic Colloidal Silica USP
Hypromellose (E -5)

Aspartame USP
Magnesium stearate USP
Erythrosine IHS
Coating Material (Layer I&II)
Drcoat Seal IHS
Hypromellose (E-15) USP
Aspartame USP
Titanium Dioxide USP
Talc USP
Erythrosine Lake IHS
Methylene Chloride USP

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

24 months

6.4 Special Precautions for storage:

Store below 30°C. Protect from light & moisture.

6.5 Nature and contents of container:

3x10 Alu-Alu Blister packed in a carton with Product leaflet.

6.6 Special precautions for disposal:

none

7. Marketing Authorization Holder:

Javia International Limited

Manufacturing Site Address:

LOGOS PHARMA

Village Maissa Tibba, Tehsil Nalagarh,

District Solan, Himachal Pradesh (INDIA)-174101

8. Marketing Authorization Numbers:

H2025/CTD11219/24369

9. Date of first registration /renewal of the registration:

2025 August 04

10. Date of revision of text:

2025 August 04