

MSN Mirabig®

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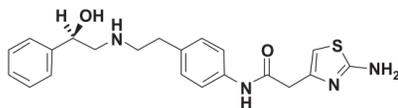
Mirabegron Extended Release Tablets 25 mg

Each Film coated Extended Release Tablet
Contains Mirabegron.....25 mg
Colours: -Ferric Oxide Red-USP-NF, Ferric Oxide Yellow USP-NF and Titanium dioxide IP

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Chemical structure:



Chemical name: 2-(2-amino-1, 3-thiazol-4-yl)-N-[4-(2-((2R)-2-hydroxy-2-phenylethyl) amino) ethyl) phenyl] acetamide.
Molecular formula: C₂₁H₂₆N₄O₂S

DESCRIPTION

Mirabegron is white to yellowish color powder. It is Soluble in Methanol and Dimethyl-sulphoxide and practically insoluble in Water.
The dissociation constant (pKa) is 4.5 and 8.0.
It contains mirabegron 25 mg or 50 mg as the active ingredient

DOSAGE FORM AND STRENGTHS

Mirabegron is available as extended-release film-coated tablets for oral administration.
Strengths: 25 mg and 50 mg

Mirabegron contains the following excipients: Polyethylene glycol 8000/Macrogol 8000 (Carbowax Sentry 8000), Polyethylene Oxide (Polyox WSR N60K-LEO), Hydroxypropyl Cellulose (KLUCEL EXF Pharm), Magenesium Sterate (LIGAMED MF-2-V), Opadry Brown 03B565101, Opadry Yellow 03B520180 and Purified water.

INDICATIONS

Mirabegron is used for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence in patients with overactive bladder (OAB) syndrome.

DOSAGE AND METHOD OF ADMINISTRATION

Adults (including Elderly Patients)

The recommended starting dose of Mirabegron is 25 mg once daily. Based on individual patient efficacy and tolerability the dose may be increased to 50 mg once daily.

Mirabegron can be taken with or without food. The tablet should be taken with liquids, swallowed whole and is not to be chewed, divided, or crushed.

Patients with Renal Impairment:

No dose adjustment is necessary in patients with mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m² as estimated by MDRD). In patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²), the recommended dose is 25 mg once daily with or without food. Mirabegron has not been studied in patients with End Stage Renal Disease (eGFR <15 mL/min/1.73 m² or patients requiring haemodialysis).

Patients with Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A). In patients with moderate hepatic impairment (Child-Pugh Class B) the recommended dose is 25 mg once daily with or without food. Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

USE IN SPECIAL POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies using Mirabegron in pregnant women. Mirabegron should be used during pregnancy only if the potential benefit to the patient outweighs the risk to the patient and fetus. Women who become pregnant during Mirabegron treatment are encouraged to contact their physician.

Nursing Mothers

It is not known whether Mirabegron is excreted in human milk. Mirabegron was found in the milk of rats at concentrations twice the maternal plasma level. Mirabegron was found in the lungs, liver, and kidneys of nursing pups. No studies have been conducted to assess the impact of Mirabegron on milk production in humans, its presence in human breast milk, or its effects on the breast-fed child. Because Mirabegron is predicted to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Paediatric population

The safety and efficacy of mirabegron in children below 18 years of age have not yet been established. No data are available.

Geriatric Use

No dose adjustment is necessary for the elderly. The pharmacokinetics of Mirabegron is not significantly influenced by age.

Renal and hepatic impairment

Mirabegron has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m² or patients requiring haemodialysis) or severe hepatic impairment (Child-Pugh Class C) and it is therefore not recommended for use in these patient populations.

In patients with severe renal impairment (CL 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m²), the daily dose of Mirabegron should not exceed 25 mg. No dose adjustment is necessary in patients with mild or moderate renal impairment (CL 30 to 89 mL/min or eGFR 30 to 89 mL/min/1.73 m²)

Hepatic impairment

Mirabegron has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), and therefore is not recommended

for use in this patient population.

In patients with moderate hepatic impairment (Child-Pugh Class B), the daily dose of Mirabegron should not exceed 25 mg. No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh Class A).

Gender

No dose adjustment is necessary based on gender. When corrected for differences in body weight, the Mirabegron systemic exposure is 20% to 30% higher in females compared to males.

CONTRAINDICATIONS

Mirabegron is contraindicated in patients with:

Hypersensitivity to the active substance or to any of the excipients.

Patients with severe uncontrolled hypertension (systolic \geq 180mmHg and/or diastolic \geq 110mmHg).

WARNINGS AND PRECAUTIONS

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/1.73 m²); based on a pharmacokinetic study a dose reduction to 25 mg is recommended in this population. Mirabegron 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. Mirabegron 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 \geq 160 mm Hg or diastolic blood pressure \geq 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.

Patients with bladder outlet obstruction and patients taking antimuscarinics medications for OAB

Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with Mirabegron; however, Mirabegron should be administered with caution to patients with clinically significant BOO. Mirabegron should also be administered with caution to patients taking antimuscarinic 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. 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.

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 thioridazine, flecainide, and propafenone.

DRUG INTERACTIONS

In vitro data

Mirabegron is transported and metabolized through multiple pathways. Mirabegron is a substrate for cytochrome P450 (CYP) 3A4, CYP2D6, butyrylcholinesterase, uridine diphosphoglucuronosyltransferases (UGT), the efflux transporter P-glycoprotein (P-gp) and the influx organic cation transporters (OCT) OCT1, OCT2, and OCT3.

Sulfonylurea hypoglycaemic agents glibenclamide (a CYP3A4 substrate), glimepiride (a CYP2C9 and CYP3A4 substrate) and tolbutamide (a CYP2C9 substrate) did not affect the *in vitro* metabolism of mirabegron. Mirabegron did not affect the metabolism of glibenclamide or tolbutamide.

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 co-administered 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.

In vivo data

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.

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 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.

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.

Digoxin

When given in combination, mirabegron increased mean digoxin C from 1.01 to 1.3 ng/mL (29%) and AUC from 16.7 to 19.3 ng.h/mL (27%). Therefore, 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.

UNDESIRABLE EFFECTS

Tabulated list of adverse reactions

The frequency of adverse reactions is defined as follows: very common (\geq 1/10); common (\geq 1/100 to <1/10); uncommon (\geq 1/1,000 to <1/100); rare (\geq 1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

*observed during post-marketing experience

MedDRA System organ class	Common	Uncommon	Rare	Very rare	Not known (cannot be estimated from the available data)
Infections and infestations	Urinary tract infection	Vaginal infection Cystitis			
Psychiatric disorders					Insomnia*
Eye disorders			Eyelid oedema		
Cardiac disorders	Tachycardia	Palpitation Atrial fibrillation			
Vascular disorders				Hypertensive crisis*	
Gastro-intestinal disorders	Nausea* Constipation* Diarrhoea*	Dyspepsia Gastritis	Lip oedema		
Skin and subcutaneous tissue disorders		Urticaria Rash macular Rash	Leuko-cytoclastic vasculitis		

		papular Pruritus	Purpura An-gioede-ma*		
Musculo-skeletal and connective tissue disorders		Joint swelling			
Reproductive system and breast disorders		Vulvovaginal pruritus			
Investigations		Blood pressure increased GGT increased AST increased ALT increased			
Renal and urinary disorders			Urinary retention*		
Nervous system disorders	Head-ache* Dizzi-ness*				

OVERDOSE

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 overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure, and ECG monitoring is recommended.

PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Urologicals, Urinary antispasmodics ATC code: G04BD12.

Mechanism of action

Mirabegron is a potent and selective beta 3-adrenoceptor agonist. Mirabegron showed relaxation of bladder smooth muscle in rat and human isolated tissue, increased cyclic adenosine monophosphate (cAMP) concentrations in rat bladder tissue and showed a bladder relaxant effect in rat urinary bladder function models. Mirabegron increased mean voided volume per micturition and decreased the frequency of non-voiding contractions, without affecting voiding pressure, or residual urine in rat models of bladder overactivity. In a monkey model, mirabegron showed decreased voiding frequency. These results indicate that mirabegron enhances urine storage function by stimulating beta 3-adrenoceptors in the bladder.

During the urine storage phase, when urine accumulates in the bladder, sympathetic nerve stimulation predominates. Noradrenaline is released from nerve terminals, leading predominantly to beta adrenoceptor activation in the bladder musculature, and hence bladder smooth muscle relaxation. During the urine voiding phase, the bladder is predominantly under parasympathetic nervous system control. Acetylcholine, released from pelvic nerve terminals, stimulates cholinergic M2 and M3 receptors, inducing bladder contraction. The activation of the M2 pathway also inhibits beta 3-adrenoceptor induced increases in cAMP. Therefore beta 3-adrenoceptor stimulation should not interfere with the voiding process. This was confirmed in rats with partial urethral obstruction, where mirabegron decreased the frequency of non-voiding contractions without affecting the voided volume per micturition, voiding pressure, or residual urine volume.

Pharmacodynamic Effects

Urodynamics

Mirabegron at doses of 50 mg and 100 mg once daily for 12 weeks in men with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO) showed no effect on cystometry parameters and was safe and well tolerated.

Effect on QT Interval

Mirabegron at doses of 50 mg or 100 mg had no effect on the QT interval individually corrected for heart rate (QTc interval) when evaluated either by sex or by the overall group.

Effects on Pulse Rate and Blood Pressure in Patients with Overactive Bladder (OAB)

In OAB patients (mean age of 59 years) across three 12-week phase 3 double blind, placebo controlled studies receiving mirabegron 50 mg once daily, an increase in mean difference from placebo of approximately 1 bpm for pulse rate and approximately 1 mm Hg or less in systolic blood pressure/diastolic blood pressure was observed. Changes in pulse rate and blood pressure are 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.

PHARMACOKINETIC PROPERTIES

Absorption

After oral administration of mirabegron in healthy volunteers mirabegron is absorbed to reach peak plasma concentrations (C_{max}) between 3 and 4 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 over the dose range. 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 mg 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 on absorption

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 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. The volume of distribution at steady state (V_d) is approximately 1670 L. Mirabegron is bound (approximately 71%) to human plasma proteins, and shows moderate affinity for albumin and alpha-1 acid glycoprotein. Mirabegron distributes to erythrocytes. In vitro erythrocyte concentrations of ^{14}C -mirabegron were about 2-fold higher than in plasma.

Biotransformation

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; both are phase 2 glucuronides representing 16% and 11% of total exposure. These metabolites are not pharmacologically active.

Based on in vitro studies, mirabegron is unlikely to inhibit the metabolism of co-administered medicinal products 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 is predicted not to cause clinically relevant inhibition of OCT-mediated drug transport.

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 vitro and ex vivo studies have shown the involvement from butyrylcholinesterase, UGT and possibly alcohol dehydrogenase (ADH) in the metabolism of mirabegron, in addition to CYP3A4 and CYP2D6.

CYP2D6 polymorphism

In healthy subjects who are genotypically poor metabolisers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean C_{max} and AUC $_{0-24}$ of a single 160 mg dose of a mirabegron IR formulation were 14% and 19% higher than in extensive metabolisers, indicating that 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.

Elimination

Total body clearance (CL_{TB}) from plasma is approximately 57 L/h. 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_{TB} . Renal elimination of mirabegron is primarily through active tubular secretion along with glomerular filtration. The urinary excretion 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 to healthy volunteers, approximately 55% of the radiolabel was recovered in the urine and 34% in the faeces. Unchanged mirabegron accounted for 45% of the urinary radioactivity, indicating the presence of metabolites. Unchanged mirabegron accounted for the majority of the faecal radioactivity.

INCOMPATIBILITIES

Not applicable

PACKAGING INFORMATION

Mirabegron Extended Release Tablets 25 mg: Blister pack of 10 Tablets.

Mirabegron Extended Release Tablets 50 mg: Blister pack of 10 Tablets.

STORAGE

Store below 30°C.

KEEP OUT OF REACH OF CHILDREN

Keep away from infants and small children.

Manufactured by:

MSN Laboratories Private Limited
(Formulations Division),
Plot No. 42, Anrich Industrial Estate,
Bollaram, Sangareddy District - 502 325,
Telangana, INDIA.

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