Front

Mirabet™

(Mirabegron)

Tablet

میرابیٹ

COMPOSITION:

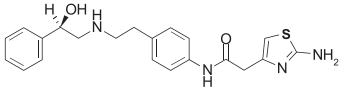
Mirabet Tablet 25 mg:
Each extended release tablet contains:
Mirabegron ..... 25 mg.

Product Specs.: Innovator

Mirabet Tablet 50 mg:
Each extended release tablet contains:
Mirabegron ..... 50 mg.

Product Specs.: Innovator

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



CLINICAL PHARMACOLOGY:
Mechanism of Action: Mirabegron is an agonist of the human beta-3 adrenergic receptor (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.
Pharmacodynamics: Administration of Mirabet once daily for 12 weeks not adversely affect the mean maximum flow rate or mean detrusor pressure at maximum flow rate. Mirabet should be administered with caution to patients with clinically significant BOO (bladder outlet obstruction).
Mirabet increases heart rate on ECG in a dose dependent manner.
Mirabet also increases blood pressure in a dose dependent manner.
Pharmacokinetics:
Absorption: After oral administration 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. 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: 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 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.
Metabolism: Mirabegron is metabolized via multiple pathways involving dealkylation, oxidation, (direct) glucuronidation, and amide hydrolysis. Two major metabolites were are phase 2 glucuronides representing 16% and 11% of total exposure, respectively. These metabolites are not pharmacologically active. Mirabegron is transported and metabolized through multiple pathways.
Excretion: The terminal elimination half-life ($t_{1/2}$) is approximately 50 hours. Renal clearance (CLR) is approximately 13 L/h. 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.
Specific Populations:
Geriatric Patients: The C_{max} and AUC of mirabegron following multiple oral doses in elderly volunteers (≥ 65 years) are similar to those in younger volunteers (18 to 45 years).
Pediatric Patients: The pharmacokinetics of mirabegron in pediatric patients have not been evaluated.
Gender. The C_{max} and AUC of mirabegron are approximately 40% to 50% higher in females than in males. When corrected for differences in body weight, the mirabegron systemic exposure is 20% - 30% higher in females compared to males.
Renal Impairment: In mild renal impairment (eGFR 60 to 89 mL/min/1.73 m^2 as estimated by MDRD), mean mirabegron C_{max} and AUC increase by 6% and 31% relative to normal renal function. In moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m^2), C_{max} and AUC increase by 23% and 66%, respectively. In severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), mean C_{max} and AUC values are 92% and 118% higher compared to normal renal function.
Hepatic Impairment: In mild hepatic impairment (Child-Pugh Class A), mean mirabegron C_{max} and AUC are increased by 9% and 19% relative to normal hepatic function. In moderate hepatic impairment (Child-Pugh Class B), mean C_{max} and AUC values may be 175% and 65% higher.

DRUG INTERACTIONS:
Effect of Other Drugs on Mirabegron: Mirabegron is transported and metabolized through multiple pathways. Sulfonylurea hypoglycemic agents glibenclamide, gliclazide and tolbutamide do not affect the metabolism of mirabegron.
Effect of Mirabegron on Other Drugs: Mirabegron is a moderate and time-dependent inhibitor of CYP2D6 and a weak inhibitor of CYP3A4. Mirabegron did not induce CYP1A2 or CYP3A4.

INDICATIONS AND USAGE:
Mirabet is a beta-3 adrenergic agonist indicated for the:
- Treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.

DOSAGE AND ADMINISTRATION:
The recommended starting dose of Mirabet is 25 mg once daily with or without food. Mirabet 25 mg is effective within 8 weeks. Based on individual patient efficacy and tolerability the dose may be increased to 50 mg once daily.
Administration: Mirabet should be taken with water, swallowed whole and should not be chewed, divided, or crushed.

DOSE MODIFICATION RECOMMENDATIONS:
The daily dose of Mirabet should not exceed 25 mg once daily in the following populations:
- Patients with severe renal impairment (CLCr 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m^2).
- Patients with moderate hepatic impairment (Child-Pugh Class B).
- Mirabet is not recommended for use in patients with end stage renal disease (ESRD), or in patients with severe hepatic impairment (Child-Pugh Class C)

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CONTRAINDICATIONS:
Mirabet is contraindicated in patients who have known hypersensitivity reactions to mirabegron or any component of the tablet.

WARNINGS AND PRECAUTIONS:
Increase in Blood Pressure: Mirabet can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients. Mirabet 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).
Urinary Retention in Patients with Bladder Outlet Obstruction and in Patients Taking Antimuscarinic Medications for OAB: Mirabet should be administered with caution to patients with clinically significant BOO. Mirabet should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB.
Allergic reactions (Angioedema): Angioedema of the face, lips, tongue, and/or larynx can occur with Mirabet. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, promptly discontinue Mirabet and initiate appropriate therapy and/or measures necessary to ensure a patent airway.

DRUG INTERACTIONS:
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. No dose adjustment is recommended when ketoconazole, rifampin, solifenacin, tamsulosin, and oral contraceptives drugs are co-administered with mirabegron.
The following are drug interactions for which monitoring is recommended:
Digoxin: When given in combination, mirabegron may increase 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%). 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 increase 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 has no effect on the warfarin pharmacodynamic endpoints such as International Normalized Ratio (INR) and prothrombin time.
Use in Specific Populations:
Pregnancy Category C: Mirabet 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 Mirabet treatment are encouraged to contact their physician
Nursing Mothers: 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.
Pediatric Use: The safety and effectiveness of Mirabet in pediatric patients have not been established.
Geriatric Use: No dose adjustment is necessary for the elderly. The pharmacokinetics of Mirabet is not significantly influenced by age.
Patients with Renal Impairment: Mirabet is not recommended for use in these patient populations with end stage renal disease (CLCr < 15 mL/min or eGFR <15 mL/min/1.73 m^2 or patients requiring hemodialysis) In patients with severe renal impairment (CLCr 15 to 29 mL/min or eGFR 15 to 29 mL/min/1.73 m^2), the daily dose of Mirabet should not exceed 25 mg.
No dose adjustment is necessary in patients with mild or moderate renal impairment (CLCr 30 to 89 mL/min or eGFR 30 to 89 mL/min/1.73 m^2)
Patients with Hepatic Impairment: Mirabet is not recommended for use in in patients with severe hepatic impairment (Child-Pugh Class C)
In patients with moderate hepatic impairment (Child-Pugh Class B), the daily dose of Mirabet 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.

ADVERSE REACTIONS:
The most frequent adverse events include:
- Nausea
- Common cold symptoms (nasopharyngitis)
- Urinary tract infection
- Headache
- Hypertension
- Diarrhea
- Constipation
- Dizziness
- tachcardia

Specific:
- Hypertension increased blood pressure.
- ***Urologic:*** Urinary retention
- ***Dermatologic:*** angioedema of the face, lips, tongue, and larynx, with or without respiratory symptoms.

OVERDOSAGE: Mirabegron overdose can cause palpitation, increased pulse rate exceeding 100 bpm, increases in pulse rate and systolic blood pressure. Treatment for over dosage should be symptomatic and supportive. In the event of over dosage, pulse rate, blood pressure and ECG monitoring is recommended.

INSTRUCTIONS:
Store below 30°C. Protect from heat, sunlight & moisture. Keep out of the reach of children. Swallow whole do not break, chew or crush the tablets. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:
Mirabet Tablet 25 mg : Pack of 2 x 10 tablets.
Mirabet Tablet 50 mg : Pack of 2 x 10 tablets.

ہدایات:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
گولی کو توڑے یا چبائے بغیر پانی سے نگل لیں۔
صرف ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

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