Mibega™

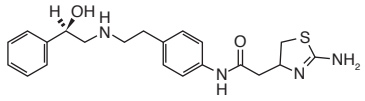
[M i r a b e g r o n]

میبیگا

25mg & 50mg Tablets

DESCRIPTION

Mibega contains Mirabegron which 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. Its molecular formula is $C_{21}H_{24}N_4O_2S$ and the structural formula is:



Mirabegron

QUALITATIVE AND QUANTITATIVE COMPOSITION

Mibega (Mirabegron) is available for oral aministration as:

Mibega Tablets 25mg
Each extended release tablet contains:
Mirabegron...25mg

Mibega Tablets 50mg
Each extended release tablet contains:
Mirabegron...50mg

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.

Pharmacokinetic

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 25mg to 35% at a dose of 50mg. 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 50mg to 100mg mirabegron increased C_{max} and AUC_{tau} by approximately 2.9-fold and 2.6-fold, respectively, whereas a 4-fold increase in dose from 50mg to 200mg 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 50mg 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. 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_{ss}) is approximately 1670L 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. Mirabegron is the major circulating component following a single dose of ^{14}C-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 receptor. 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. 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

Total body clearance (CL_{tot}) from plasma is approximately 57L/h following intravenous administration. The terminal elimination half-life ($t_{1/2}$) is approximately 50 hours. 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 25mg to 12.2% after a daily dose of 100mg. Approximately 25% of unchanged mirabegron was recovered in urine and 0% in feces.

Special Population

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

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 is 20% - 30% higher in females compared to males.

Renal impairment

Following single dose administration of 100mg mirabegron with mild renal impairment (eGFR-MDRD 60 to 89 mL/min/1.73 m^2), mean mirabegron C_{max} and AUC were increased by 6% and 31%. With moderate renal impairment (eGFR-MDRD 30 to 59 mL/min/1.73 m^2), C_{max} and AUC were increased by 23% and 66%, respectively. With severe renal impairment (eGFR-MDRD 15 to 29 mL/min/1.73 m^2), mean C_{max} and AUC values were 92% and 118% higher.

Hepatic impairment

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

THERAPEUTIC INDICATIONS

Mibega (Mirabegron) is indicated for the symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

DOSAGE & ADMINISTRATION

Adults (including elderly patients)

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

Special populations

The following table provides the daily dosing recommendations for patients with renal or hepatic impairment in the absence and presence of strong CYP3A inhibitors.

		Strong CYP3A inhibitors	
		Without inhibitor	With inhibitor
Renal impairment	Mild	50mg	25mg
	Moderate	50mg	25mg
	Severe	25mg	Not recommended
Hepatic impairment	Mild	50mg	25mg
	Moderate	25mg	Not recommended

Mibega (Mirabegron) is not recommended for use in patients with end stage renal disease (ESRD) or in patients with severe hepatic impairment (Child-Pugh Class C).

Pediatric population
The safety and efficacy of Mibega (Mirabegron) in children below 18 years of age have not yet been established.

ADVERSE REACTIONS
Common
Urinary tract infection, tachycardia, nausea, constipation, diarrhea, headache and dizziness.

Uncommon
Vaginal infection, cystitis, palpitation, atrial fibrillation, dyspepsia, gastritis, urticaria, rash, rash macular, rash popular, pruritis, joint swelling, vulvovaginal pruritus, blood pressure increased, GGT increased, AST increased and ALT increased.

Rare
Eyelid edema, lip edema, leukocytoclastic vasculitis, purpura, angioedema and urinary retention.

CONTRAINDICATIONS
Mirabegron is contraindicated;
- In patients with known hypersensitivity to mirabegron or to any excipient of the product.
- Severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg.

PRECAUTIONS
- Mirabegron can increase blood pressure. Periodic blood pressure determinations are recommended, especially in hypertensive patients.
- Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in patients taking mirabegron. 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 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.
- Caution should be exercised when administering mirabegron in patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval.

Pregnancy
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
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.

DRUG INTERACTIONS
Digoxin
When given in combination, 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%). 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 25mg after multiple doses of 100mg mirabegron. Following a single dose administration of 25mg warfarin, mirabegron had no effect on the warfarin pharmacodynamic endpoints such as International Normalized Ratio (INR) and prothrombin time.

Drugs Metabolized by CYP2D6
Since mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure of drugs metabolized by CYP2D6 enzyme such as metoprolol and desipramine is increased when co-administered with mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary when mirabegron is co-administered with these drugs, especially with narrow therapeutic index CYP2D6 substrates, such as thioridazine, flecainide and propafenone.

Effect of mirabegron on CYP2D6 substrates
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.

OVERDOSAGE:
Mirabegron has been administered at single doses up to 400mg. At this dose, adverse events reported included palpitations and increased pulse rate exceeding 100 bpm. Multiple doses of mirabegron up to 300mg daily for 10 days showed increases in pulse rate and systolic blood pressure.

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

STORAGE
Do not store above 30°C.
Protect from sunlight and moisture.
The expiry date refers to the product stored at the required conditions.

HOW SUPPLIED
Mibega (Mirabegron) Tablets 25mg are available in pack of 10's.
Mibega (Mirabegron) Tablets 50mg are available in pack of 10's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan
200009861