Caution: To be sold by retail on the prescription of a Registered Medical Practitioner (RMP) only.

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Combikit of Mirabegron Extended-Release tablets and Solifenacin Succinate Tablets IP

MSN **Mirabig®-S** एम एस एन मिराबिग-एस

Each combi pack contains:
Each Co-Packaged Drug Products (Blister packing) contains:-

1) **Mirabegron ER Tablet (A) & Solifenacin Succinate Tablet (B)**

(A) **Mirabegron ER Tablet 25 mg**
Each film coated extended release tablet contains:
Mirabegron 25 mg
Excipients q.s.
Colours: Ferric Oxide Red USP-NF, Ferric Oxide Yellow USP-NF and Titanium Dioxide IP

(B) **Solifenacin Succinate Tablets IP 5 mg**
Each film coated tablet contains:
Solifenacin Succinate IP 5 mg
Excipients q.s.
Colours: Ferric Oxide Yellow USP-NF and Titanium Dioxide IP

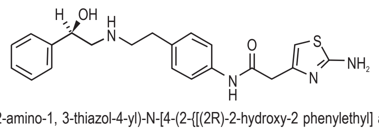
2) **Mirabegron ER Tablet (A) & Solifenacin Succinate Tablet (B)**

(A) **Mirabegron ER Tablet 50 mg**
Each film coated extended release tablet contains:
Mirabegron 50 mg
Excipients q.s.
Colours: Ferric Oxide Red USP-NF, Ferric Oxide Yellow USP-NF and Titanium Dioxide IP

(B) **Solifenacin Succinate Tablets IP 5 mg**
Each film coated tablet contains:
Solifenacin Succinate IP 5 mg
Excipients q.s.
Colours: Ferric Oxide Yellow USP-NF and Titanium Dioxide IP

A) Mirabegron

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: $C_{21}H_{24}N_4O_2S$

DESCRIPTION

Mirabegron is white to off-white crystals or powder. It is freely soluble in dimethyl sulfoxide, soluble in methanol and 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

INDICATIONS

Mirabegron is used for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence in patients with overactive bladder (OAB) syndrome.
Mirabegron in combination with muscarinic antagonist Solifenacin is indicated for the treatment of OAB with symptoms of urge urinary incontinence, urgency and urinary frequency.

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.

Combination therapy with Muscarinic antagonist Solifenacin Succinate
The recommended starting dose of Mirabegron is 25 mg once daily and Solifenacin succinate 5 mg once daily. Based on individual patient efficacy and tolerability, the mirabegron dose may be increased to 50 mg once daily after 4 to 8 weeks.
Mirabegron and Solifenacin succinate can be taken together with or without food

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 m^2 as estimated by MDRD). In patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), 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 m^2 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 m^2 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 m^2), 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 m^2)

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 ≥180mmHg and /or diastolic ≥110mmHg).

WARNINGS AND PRECAUTIONS

Renal impairment
Mirabegron has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 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 m^2); 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 m^2) 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 ≥ 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.

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 metabolised through multiple pathways. Mirabegron is a substrate for cytochrome P450 (CYP) 3A4, CYP2D6, butyrylcholinesterase, uridine diphospho-glucuronosyltransferases (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), gliclazide (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 m^2) 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 m^2) 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,0 Haemorrhagic 00 to <1/100); rare (≥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.

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*	
Gastrointestinal disorders	Nausea* Constipation* Diarrhoea*	Dyspepsia Gastritis	Lip oedema		
Skin and subcutaneous tissue disorders		Urticaria Rash Rash macular Rash papular Pruritus	Leukocytoclastic vasculitis Purpura Angioedema*		
Musculoskeletal 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	Headache* Dizziness*				

*observed during post-marketing experience

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 (QTcI 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_{ss}) 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 14C-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 ^{14}C-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.

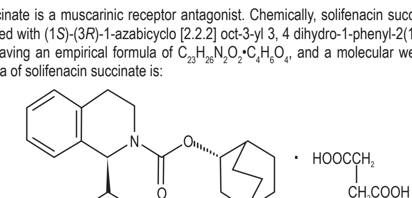
CYP2D6 polymorphism
In healthy subjects who are genotypically poor metabolisers of CYP2D6 substrates (used as a surrogate for CYP2D6 inhibition), mean C_{max} and AUC_{inf} of a single 160 mg dose of a mirabegron IR formulation were 14% and 19% higher than in extensive metabolisers, indicating that CYP2D6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

B) Solifenacin

DESCRIPTION

Solifenacin succinate is a muscarinic receptor antagonist. Chemically, solifenacin succinate is butanedioic acid, compounded with (1*S*)-(3*R*)-1-azabicyclo [2.2.2] oct-3-yl 3, 4 dihydro-1-phenyl-2(1*H*)-iso-quinolinecarboxylate (1:1) having an empirical formula of $C_{23}H_{26}N_2O_2 \cdot C_4H_6O_4$, and a molecular weight of 480.55. The structural formula of solifenacin succinate is:



Solifenacin succinate is a white to pale-yellowish-white crystal or crystalline powder. It is freely soluble at room temperature in water, glacial acetic acid, dimethyl sulfoxide, and methanol. Each tablet contains 5 or 10 mg of solifenacin succinate and is formulated for oral administration.

DOSAGE FORM AND STRENGTHS

Tablets: 5 mg and 10 mg.

INDICATIONS

Solifenacin is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency.

DOSAGE AND METHOD OF ADMINISTRATION

Dosing Information
The recommended dose of Solifenacin is 5 mg once daily. If the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily.
Solifenacin should be taken with liquids and swallowed whole. Solifenacin can be administered with or without food.

Dose Adjustment in Renal Impairment
For patients with severe renal impairment (CLcr <30 mL/min), a daily dose of solifenacin greater than 5 mg is not recommended.

Dose Adjustment in Hepatic Impairment
For patients with moderate hepatic impairment (Child-Pugh B), a daily dose of solifenacin greater than 5 mg is not recommended. Use of Solifenacin in patients with severe hepatic impairment (Child-Pugh C) is not recommended.

Dose Adjustment CYP3A4 Inhibitors
When administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors, a daily dose of solifenacin greater than 5 mg is not recommended.

USE IN SPECIAL POPULATIONS

Pregnancy
Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women.
Reproduction studies have been performed in mice, rats and rabbits. After oral administration of 14C-solifenacin succinate to pregnant mice, drug-related material was shown to cross the placental barrier. No embryotoxicity or teratogenicity was observed in mice treated with 1.2 times (30 mg/kg/day) the expected exposure at the maximum recommended human dose [MRHD] of 10 mg. Administration of solifenacin succinate to pregnant mice at 3.6 times and greater (100 mg/kg/day and greater) the exposure at the MRHD, during the major period of organ development resulted in reduced fetal body weights.
Administration of 7.9 times (250 mg/kg/day) the MRHD to pregnant mice resulted in an increased incidence of cleft palate. In utero and lactational exposures to maternal doses of solifenacin succinate of 3.6 times (100 mg/kg/day) the MRHD resulted in reduced peripartum and postnatal survival, reductions in body weight gain, and delayed physical development (eye opening and vaginal patency). An increase in the percentage of male offspring was also observed in litters from offspring exposed to maternal doses of 250 mg/kg/day. No embryotoxic effects were observed in rats at up to 50 mg/kg/day (< 1 times the exposure at the MRHD) or in rabbits at up to 1.8 times (50 mg/kg/day) the exposure at the MRHD. Because animal reproduction studies are not always predictive of human response, solifenacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery
The effect of solifenacin on labor and delivery in humans has not been studied.
There were no effects on natural delivery in mice treated with 1.2 times (30 mg/kg/day) the expected exposure at the maximum recommended human dose [MRHD] of 10 mg. Administration of solifenacin succinate at 3.6 times (100 mg/kg/day) the exposure at the MRHD or greater increased peripartum pup mortality.

Nursing Mothers
After oral administration of ^{14}C-solifenacin succinate to lactating mice, radioactivity was detected in maternal milk. There were no adverse observations in mice treated with 1.2 times (30 mg/kg/day) the expected exposure at the maximum recommended human dose [MRHD]. Pups of female mice treated with 3.6 times (100 mg/kg/day) the exposure at the MRHD or greater revealed reduced body weights, postpartum pup mortality or delays in the onset of reflex and physical development during the lactation period.
It is not known whether solifenacin is excreted in human milk. Because many drugs are excreted in human milk, solifenacin should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue solifenacin in nursing mothers.

Pediatric Use
The safety and effectiveness of solifenacin in pediatric patients have not been established.

Gender
The use of solifenacin is not significantly influenced by gender.

Geriatric Use
Similar safety and effectiveness were observed between older (623 patients ≥ 65 years and 189 patients ≥ 75 years) and younger patients (1188 patients < 65 years) treated with solifenacin.

Renal Impairment
Solifenacin should be used with caution in patients with renal impairment. There is a 2.1-fold increase in AUC and 1.6-fold increase in $t_{1/2}$ of solifenacin in patients with severe renal impairment. Doses of solifenacin greater than 5 mg are not recommended in patients with severe renal impairment (CL_{cr} < 30 mL/min).

Hepatic Impairment
Solifenacin should be used with caution in patients with reduced hepatic function. There is a 2-fold increase in the $t_{1/2}$ and 35% increase in AUC of solifenacin in patients with moderate hepatic impairment.
Doses of solifenacin greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). Solifenacin is not recommended for patients with severe hepatic impairment (Child-Pugh C).

Race
No adequate information is present to make any conclusions on use of solifenacin.

CONTRAINDICATIONS

Solifenacin is contraindicated in patients with urinary retention, severe gastro-intestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions.
- Patients hypersensitive to the active substance or to any of the excipients
- 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.

WARNINGS AND PRECAUTIONS

Angioedema and Anaphylactic Reactions
Angioedema of the face, lips, tongue, and/or larynx have been reported with solifenacin. 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, solifenacin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided. Anaphylactic reactions have been reported rarely in patients treated with solifenacin succinate. Solifenacin succinate should not be used in patients with a known or suspected hypersensitivity to solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken.

Urinary Retention
Solifenacin like other anticholinergic drugs should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

Gastrointestinal Disorders
Solifenacin, like other anticholinergics, should be used with caution in patients with decreased gastrointestinal motility.

Central Nervous System Effects
Solifenacin is associated with anticholinergic central nervous system (CNS) effects. A variety of CNS anticholinergic effects have been reported, including headache, confusion, hallucinations and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how solifenacin affects them. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

Controlled Narrow-Angle Glaucoma
Solifenacin should be used with caution in patients being treated for narrow-angle glaucoma.

Hepatic Impairment
Solifenacin should be used with caution in patients with hepatic impairment. Doses of Solifenacin greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). Solifenacin is not recommended for patients with severe hepatic impairment (Child-Pugh C).

Renal Impairment
Solifenacin should be used with caution in patients with renal impairment. Doses of solifenacin greater than 5 mg are not recommended in patients with severe renal impairment (CLcr < 30 mL/min).

Patients with Congenital or Acquired QT Prolongation
The QT prolonging effect appeared less with solifenacin 10 mg than with 30 mg (three times the maximum recommended dose), and the effect of solifenacin 30 mg did not appear as large as that of the positive control moxifloxacin at its therapeutic dose. This observation should be considered in clinical decisions to prescribe solifenacin for patients with a known history of QT prolongation or patients who are taking medications known to prolong the QT interval.

DRUG-DRUG INTERACTIONS

Potent CYP3A4 Inhibitors
Following the administration of 10 mg of solifenacin in the presence of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, the mean Cmax and AUC of solifenacin increased by 1.5 and 2.7-fold, respectively. Therefore, it is recommended not to exceed a 5 mg daily dose of solifenacin when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors. The effects of weak or moderate CYP3A4 inhibitors were not examined.

CYP3A4 Inducers
There were no *in vivo* studies conducted to evaluate the effect of CYP3A4 inducers on solifenacin. *In vitro* drug metabolism studies have shown that solifenacin is a substrate of CYP3A4. Therefore, inducers of CYP3A4 may decrease the concentration of solifenacin.

Drugs Metabolized by Cytochrome P450
At therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes.

Warfarin
Solifenacin has no significant effect on the pharmacokinetics of R-warfarin or S-warfarin.

Oral Contraceptives
In the presence of solifenacin there are no significant changes in the plasma concentrations of combined oral contraceptives (ethinyl estradiol/ levonorgestrel).

Digoxin
Solifenacin had no significant effect on the pharmacokinetics of digoxin (0.125 mg/day) in healthy subjects.

UNDESIRABLE EFFECTS

Post-Marketing Experience
Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events and the role of solifenacin in their causation cannot be reliably determined. The following events have been reported in association with solifenacin use in worldwide postmarketing experience:

General: peripheral edema, hypersensitivity reactions, including angioedema with airway obstruction, rash, pruritus, urticaria, and anaphylactic reaction;

Central Nervous: headache, confusion, hallucinations, delirium and somnolence;

Cardiovascular: QT prolongation; Torsade de Pointes, atrial fibrillation, tachycardia, palpitations;

Hepatic: liver disorders mostly characterized by abnormal liver function tests, AST (aspartate aminotransferase), ALT (alanine aminotransferase), GGT (gamma-glutamyl transferase);

Renal: renal impairment;

Metabolism and nutrition disorders: decreased appetite, hyperkalemia;

Dermatologic: exfoliative dermatitis and erythema multiforme;

Eye disorders: glaucoma;

Gastrointestinal disorders: Gastroesophageal reflux disease and ileus;

Respiratory, thoracic and mediastinal disorders: dysphonia;

Musculoskeletal and connective tissue disorders: muscular weakness.

Clinical Trail Experience
Gastrointestinal disorders: Dry mouth, constipation, Nausea, Dyspepsia, Abdominal Pain Upper, Vomiting NOS

Infections and infestations: Urinary Tract Infection NOS, Influenza, Pharyngitis NOS

Nervous system disorders: Dizziness

Eye Disorders: Vision Blurred, Dry Eyes NOS

Renal and urinary disorders: Urinary Retention

General disorders and administration site conditions: Edema Lower Limb, fatigue

Psychiatric disorders: Depression NOS

Respiratory, thoracic and mediastinal disorders: Cough

Vascular disorders: Hypertension NOS

OVERDOSAGE

Symptoms
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.

Treatment
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.
- Urinary retention: treat with catheterisation.
- Mydriasis: treat with pilocarpine eye drops and/or place patient in dark room.

As with other antimuscarinics, in case of overdosing, specific attention should be paid to patients with known risk for QT-prolongation (i.e. hypokalaemia, bradycardia and concurrent administration of medicinal products known to prolong QT-interval) and relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure).

PHARMACODYNAMICS

Mechanism of action
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 and stimulation of salivary secretion.
The effect of 5 mg and 10 mg solifenacin succinate on the QT interval was evaluated at the time of peak plasma concentration of solifenacin. The QT interval prolonging effect appeared greater for the 10 mg compared to the 5 mg dose of solifenacin. Although the effect of the highest solifenacin dose (three times the maximum therapeutic dose) did not appear as large as that of the positive control moxifloxacin at its therapeutic dose.

PHARMACOKINETICS

Absorption
After oral administration of solifenacin to healthy volunteers, peak plasma levels (C_{max}) of solifenacin are reached within 3 to 8 hours after administration, and at steady state ranged from 32.3 to 62.9 ng/mL for the 5 and 10 mg solifenacin tablets, respectively. The absolute bioavailability of solifenacin is approximately 90%, and plasma concentrations of solifenacin are proportional to the dose administered.

Effect of Food
Solifenacin may be administered without regard to meals. A single 10 mg dose administration of solifenacin with food increased Cmax and AUC by 4% and 3%, respectively.

Distribution
Solifenacin is approximately 98% (*in vivo*) bound to human plasma proteins, principally to $\propto$1-acid glycoprotein. Solifenacin is highly distributed to non-CNS tissues, having a mean steady-state volume of distribution of 600L.

Metabolism
Solifenacin is extensively metabolized in the liver. The primary pathway for elimination is by way of CYP3A4; however, alternate metabolic pathways exist. The primary metabolic routes of solifenacin are through N-oxidation of the quinuclidin ring and 4R-hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (4R-hydroxy solifenacin), occurring at low concentrations and unlikely to contribute significantly to clinical activity, and three pharmacologically inactive metabolites (N-glucuronide and the N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after oral dosing.

Excretion
Following the administration of 10 mg of 14C-solifenacin succinate to healthy volunteers, 69.2% of the radioactivity was recovered in the urine and 22.5% in the feces over 26 days. Less than 15% (as mean value) of the dose was recovered in the urine as intact solifenacin. The major metabolites identified in urine were N-oxide of solifenacin, 4R-hydroxy solifenacin and 4R-hydroxy-N-oxide of solifenacin and in feces 4R-hydroxy solifenacin. The elimination half-life of solifenacin following chronic dosing is approximately 45-68 hours.

STORAGE: Store at a temperature not exceeding 30°C.

Keep out of reach of children.

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