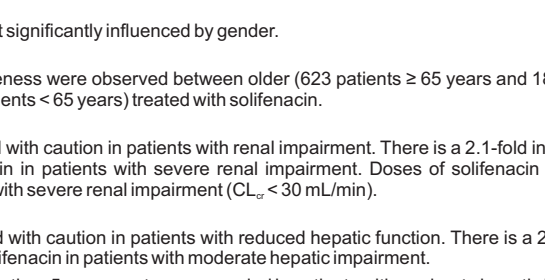
VesiLife वेसिलाइफ़

VesiLife
Solifenacin Succinate Tablets IP 5 mg
Each Film Coated Tablet Contains
Solifenacin Succinate IP 5 mg
Colours : Titanium Dioxide IP Ferric Oxide Yellow USP-NF

Solifenacin Succinate Tablets IP 10 mg
Each Film Coated Tablet Contains
Solifenacin Succinate IP 10 mg
Colours : Titanium Dioxide IP Ferric Oxide Red USP-NF

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 $C_{23}H_{26}N_2O_2C_4H_6O_4$, 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. In addition to the active ingredient solifenacin succinate, each solifenacin tablet also contains the following inert ingredients: lactose monohydrate, hydroxypropyl methylcellulose, magnesium stearate and opadry pink.

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 (see DESCRIPTION).
- 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 a1-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.

PACKAGING INFORMATION
Bottle of 30's
Bottle of 90's
Bottle of 1000's (Bulk Pack)
Blister pack of 10's
Simulated Bulk Pack 200's Count

HANDLING AND DISPOSAL
Care should be exercised in handling of Solefinacin. Solefinacin tablets should not be opened or crushed. If powder from solefinacin contacts the skin, wash the skin immediately and thoroughly with soap and water. If solefinacin contacts the mucous membranes, flush thoroughly with water.

STORAGE
Store below 30°C.

Keep out of reach of children

Manufactured by:
MSN Laboratories Private Limited,
Formulation Division,
Unit-II, Sy.No. 1277, 1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

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