Solifen™

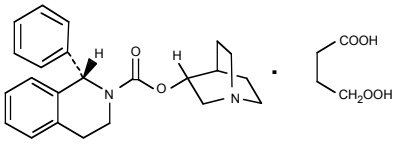
(Solifenacin Succinate)

سوليفن

5mg, 10mg Film-Coated Tablets

DESCRIPTION

SOLIFEN (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*)-isoquinolinecarboxylate (1:1) having molecular formula of $C_{23}H_{26}N_2O_2 .C_4H_6O_4$. The structural formula of Solifenacin Succinate is:



Solifenacin Succinate

QUALITATIVE & QUANTITATIVE COMPOSITION

SOLIFEN (Solifenacin Succinate) is available for oral administration as:

1. SOLIFEN Tablets 5mg
   Each film-coated tablet contains:
   Solifenacin Succinate ... 5mg

2. SOLIFEN Tablets 10mg
   Each film-coated tablet contains:
   Solifenacin Succinate ... 10mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Solifenacin is a competitive, specific cholinergic-receptor antagonist.The urinary bladder is innervated by parasympathetic cholinergic nerves. Acetylcholine contracts the detrusor smooth muscle through muscarinic receptors of which the M_3 subtype is predominantly involved. Solifenacin is a competitive inhibitor of the muscarinic M_3 subtype receptor.

Pharmacokinetics

Absorption

After oral administration of Solifenacin, maximum solifenacin plasma concentrations (C_{max}) are reached after 3 to 8 hours. The t_{max} is independent of the dose. The C_{max} and area under the curve (AUC) increase in proportion to the dose between 5mg to 40 mg. Absolute bioavailability is approximately 90%. There is no significant effect of food on the pharmacokinetics of solifenacin.

Distribution

Solifenacin is approximately 98% bound to plasma proteins, primarily •$_1$-acid glycoprotein.

Metabolism

Solifenacin is extensively metabolised by the liver, primarily by cytochrome P450 3A4 (CYP3A4). However, alternative metabolic pathways exist, that can contribute to the metabolism of solifenacin. The systemic clearance of solifenacin is about 9.5 L/h and the terminal half-life of solifenacin is 45 to 68 hours. After oral dosing, one pharmacologically active (4R-hydroxy solifenacin) and three inactive metabolites (N-glucuronide, N-oxide and 4R- hydroxy-N-oxide of solifenacin) are identified in plasma in addition to solifenacin.

Excretion

Solifenacin has a terminal half-life of 45 to 68 hours. Solifenacin is excreted mainly as metabolites in urine and feces.

Special population

Renal insufficiency

In patients with severe renal insufficiency (Cl_{cr} 30mL/min), with increases in C_{max} of about 30%, AUC of more than 100% and terminal half-life of more than 60%.

Hepatic insufficiency

In patients with moderate hepatic insufficiency (Child-Pugh class B), AUC increased by 60% and terminal half- life doubled.

THERAPEUTIC INDICATIONS

SOLIFEN (Solifenacin Succinate) is indicated for the symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

DOSAGE & ADMINISTRATION

SOLIFEN (Solifenacin Succinate) should be taken with liquids and swallowed whole. SOLIFEN (Solifenacin Succinate) can be administered with or without food.

Adults

The recommended dose of SOLIFEN (Solifenacin Succinate) is 5mg once daily. If needed, the dose may be increased to 10mg once daily.

Patients with renal insufficiency

Patients with severe renal insufficiency ($Cl_{cr} \leq 30$mL/min) should be treated with caution and receive no more than 5mg once daily.

Patients with hepatic insufficiency

Patients with moderate hepatic insufficiency (Child-Pugh class B) should be treated with caution and receive no more than 5mg once daily.

Potent Inhibitors of Cytochrome P450 3A4

The maximum dose of SOLIFEN (Solifenacin Succinate) should be limited to 5mg when treated simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors e.g., ritonavir, nelfinavir, itraconazole.

ADVERSE REACTIONS

Very common

Dry mouth.

Common

Constipation, nausea, dyspepsia, abdominal pain, blurred vision.

Uncommon

Gastroesophageal reflux diseases, dry throat, urinary tract infection, cystitis, somnolence, dysgeusia, dry eyes, fatigue, peripheral edema, nasal dryness, dry skin, difficulty in micturation.

Rare

Colonic obstruction, fecal impaction, urinary retention.

CONTRAINDICATIONS

Solifenacin Succinate is contraindicated in patients with:

- Hypersensitivity to the active substance or to any of the excipients.
- Urinary retention.
- Gastric retention.
- Uncontrolled narrow-angle glaucoma.
- Patients undergoing hemodialysis.
- Patients with severe hepatic insufficiency and renal insufficiency.

Solifenacin Succinate should not be used in children as safety and efficacy in children have not yet been established.

WARNINGS & PRECAUTIONS
Angioedema of the face, lips, tongue, and/or larynx may occur after the first dose. 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. Other causes of frequent urination (heart failure or renal disease) should be assessed before treatment with Solifenacin Succinate. If urinary tract infection is present, an appropriate antibacterial therapy should be started. Solifenacin Succinate should be used with caution in patients with:
- clinically significant bladder outflow obstruction at risk of urinary retention.
- gastrointestinal obstructive disorders.
- risk of decreased gastrointestinal motility.
- severe renal impairment (Cl_{cr} 30 mL/min and doses should not exceed 5mg for these patients.
- moderate hepatic insufficiency and doses should not exceed 5mg for these patients.
- concomitant use of a potent CYP3A4 inhibitor, e.g., ketoconazole.
- hiatus hernia/gastroesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.
- autonomic neuropathy.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
The maximum effect of Solifenacin Succinate can be determined after 4 weeks at the earliest.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Solifenacin Succinate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether Solifenacin Succinate is excreted in human milk. Because many drugs are excreted in human milk, Solifenacin Succinate should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue Solifenacin Succinate in nursing mothers.

Drug Interactions
Pharmacological Interactions
Concomitant administration with other drugs having anticholinergic properties may result in more pronounced therapeutic and side effects. An interval of approximately one week should be allowed after stopping the treatment with Solifenacin Succinate before commencing other cholinergic therapy.
The therapeutic effect of Solifenacin Succinate may be reduced by concomitant administration of cholinergic receptor agonists. Solifenacin Succinate can reduce the effect of the drugs that stimulate the motility of gastrointestinal tract, such as metoclopramide and cisapride.

Ketoconazole and other CYP3A4 Inhibitors
Simultaneous administration of Solifenacin Succinate and ketoconazole (200mg/day) resulted in a two-fold increase of the AUC of Solifenacin Succinate while ketoconazole at a dose of 400mg/day resulted in a three-fold increase of the AUC of Solifenacin Succinate. Therefore, the maximum dose of Solifenacin Succinate should be restricted to 5mg, when used simultaneously with ketoconazole or therapeutic doses of other strong CYP3A4 inhibitors.

Since Solifenacin Succinate is metabolized by CYP3A4, pharmacokinetic interactions are possible with other CYP3A4 substrates with higher affinity (e.g., verapamil, diltiazem) and CYP3A4 inducers (e.g., rifampacin, phenytoin, carbamazepin).

OVERDOSAGE
Overdosage with Solifenacin Succinate can potentially result in severe anticholinergic effects and should be treated accordingly.
In the event of overdosage with Solifenacin Succinate the patient should be treated with activated charcoal. Gastric lavage may be performed within 1 hour, but vomiting should not be induced. ECG monitoring is also recommended.

HOW SUPPLIED
SOLIFEN (Solifenacin Succinate) Tablets 5mg are available in blister packs of 10's.
SOLIFEN (Solifenacin Succinate) Tablets 10mg are available in blister packs of 10's.

STORAGE
Store at 25°C (Excursions permitted between 15°C to 30°C).
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

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.

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