

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Solifen (Solifenacin succinate) Tablets 5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Solifenacin succinate...5mg

Excipient(s) with known effect: Pharmatose DCL 11 [lactose monohydrate (75.42mg)]

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

White, oblong biconvex shaped film-coated tablet plain on both sides.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

4.2. Posology and method of administration

Posology

Adults, including the elderly

The recommended dose is 5mg solifenacin succinate once daily. If needed, the dose may be increased to 10mg solifenacin succinate once daily.

Paediatric population

The safety and efficacy of Solifen (Solifenacin succinate) in children have not yet been established. Therefore, Solifen (Solifenacin succinate) should not be used in children.

Patients with renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment (creatinine clearance > 30 ml/min). Patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) should

be treated with caution and receive no more than 5mg once daily.

Patients with hepatic impairment

No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) 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.

Method of administration

Solifen (Solifenacin succinate) should be taken orally and should be swallowed whole with liquids. It can be taken with or without food.

4.3. Contraindications

Solifenacin succinate 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 of the product.
- 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.

4.4. Special warnings and special precautions for use

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 (creatinine clearance ≤ 30 ml/min), and doses should not exceed 5mg for these patients.

- moderate hepatic impairment (Child-Pugh score of 7 to 9), and doses should not exceed 5mg for these patients.
- concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole.
- hiatus hernia/gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.
- autonomic neuropathy.

QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia.

Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Angioedema with airway obstruction has been reported in some patients on solifenacin succinate.

If angioedema occurs, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken.

Anaphylactic reaction has been reported in some patients treated with solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken.

The maximum effect of Solifenacin succinate can be determined after 4 weeks at the earliest.

4.5. Interaction with other medicinal products and other forms of Interactions

Pharmacological interactions

Concomitant medication with other medicinal products with anticholinergic properties may result in more pronounced therapeutic effects and undesirable effects. An interval of approximately one week should be allowed after stopping treatment with solifenacin succinate, before commencing other anticholinergic therapy. The therapeutic effect of solifenacin succinate may be reduced by concomitant administration of cholinergic receptor agonists.

Solifenacin succinate can reduce the effect of medicinal products that

stimulate the motility of the gastro-intestinal tract, such as metoclopramide and cisapride.

Pharmacokinetic interactions

In vitro studies have demonstrated that at therapeutic concentrations, solifenacin succinate does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes. Therefore, solifenacin succinate is unlikely to alter the clearance of drugs metabolised by these CYP enzymes.

Effect of other medicinal products on the pharmacokinetics of solifenacin

Solifenacin is metabolised by CYP3A4. Simultaneous administration of ketoconazole (200mg/day), a potent CYP3A4 inhibitor, resulted in a two-fold increase of the AUC of solifenacin, while ketoconazole at a dose of 400 mg/day resulted in a three-fold increase of the AUC of solifenacin. Therefore, the maximum dose of solifenacin succinate should be restricted to 5mg, when used simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole).

Simultaneous treatment of solifenacin and a potent CYP3A4 inhibitor is contra-indicated in patients with severe renal impairment or moderate hepatic impairment. The effects of enzyme induction on the pharmacokinetics of solifenacin and its metabolites have not been studied as well as the effect of higher affinity CYP3A4 substrates on solifenacin exposure. Since solifenacin is metabolised by CYP3A4, pharmacokinetic interactions are possible with other CYP3A4 substrates with higher affinity (e.g. verapamil, diltiazem) and CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepin).

Effect of solifenacin on the pharmacokinetics of other medicinal products

Oral Contraceptives

Intake of solifenacin succinate showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel).

Warfarin

Intake of solifenacin succinate did not alter the pharmacokinetics of R-warfarin or S-warfarin or their effect on prothrombin time.

Digoxin

Intake of solifenacin succinate showed no effect on the pharmacokinetics of digoxin.

4.6. Fertility, pregnancy and lactation

Pregnancy

No clinical data are available from women who became pregnant while taking solifenacin. Animal studies do not indicate direct harmful effects on fertility, embryonal / foetal development or parturition. The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women.

Breast-feeding

No data on the excretion of solifenacin in human milk are available. In mice, solifenacin and/or its metabolites was excreted in milk, and caused a dose dependent failure to thrive in neonatal mice. The use of solifenacin succinate should therefore be avoided during breast-feeding.

4.7. Effects on ability to drive and use machines

Since solifenacin, like other anticholinergics may cause blurred vision, and, uncommonly, somnolence and fatigue, the ability to drive and use machines may be negatively affected.

4.8. Undesirable effects

Summary of the safety profile

Due to the pharmacological effect of solifenacin, solifenacin succinate may cause anticholinergic undesirable effects of (in general) mild or moderate severity. The frequency of anticholinergic undesirable effects is dose related.

The most commonly reported adverse reaction with solifenacin succinate was dry mouth. It occurred in 11% of patients treated with 5mg once daily, in 22% of patients treated with 10mg once daily and in 4% of placebo-treated patients. The severity of dry mouth was generally mild and did only occasionally lead to discontinuation of treatment. In general, medicinal product compliance was very high (approximately 99%) and approximately 90% of the patients treated with Vesicare completed the full study period of 12 weeks treatment.

Infections and infestations

Uncommon

Urinary tract infection, cystitis.

Immune system disorders

Not known
Anaphylactic reaction.

Metabolism and nutrition disorders

Not known
Decreased appetite, hyperkalaemia.

Psychiatric disorders

Very rare
Hallucinations, confusional state.
Not known
Delirium.

Nervous system disorders

Uncommon
Somnolence, dysgeusia.
Rare
Dizziness, headache.

Eye disorders

Common
Blurred vision.
Uncommon
Dry eyes.
Not known
Glaucoma.

Cardiac disorders

Not known
Torsade de Pointes, electrocardiogram, QT prolonged, atrial fibrillation, palpitations, tachycardia.

Respiratory, thoracic and mediastinal disorders

Uncommon
Nasal dryness.
Not known
Dysphonia.

Gastrointestinal disorders

Very common
Dry mouth.
Common
Constipation, nausea, dyspepsia, abdominal pain.
Uncommon
Gastro-oesophageal reflux diseases, dry throat.

Rare

Colonic obstruction, faecal impaction, vomiting.

Not known

Ileus, abdominal discomfort.

Hepatobiliary disorders

Not known

Liver disorder, Liver function test abnormal.

Skin and subcutaneous tissue disorders

Uncommon

Dry skin.

Rare

Pruritus, rash.

Very rare

Erythema multiforme, urticaria, angioedema.

Not known

Exfoliative dermatitis.

Musculoskeletal and connective tissue disorders

Not known

Muscular weakness.

Renal and urinary disorders

Uncommon

Difficulty in micturition.

Rare

Urinary retention.

Not known

Renal impairment.

General disorders and administration site conditions

Uncommon

Fatigue, peripheral oedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the National Regulatory Authority.

4.9. Overdose

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 280mg 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).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics, ATC code: G04B D08. 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 M3 subtype is predominantly involved. In vitro and in vivo pharmacological studies indicate that solifenacin is a competitive inhibitor of the muscarinic M3 subtype receptor. In addition, solifenacin showed to be a specific antagonist for muscarinic receptors by displaying low or no affinity for various other receptors and ion channels tested.

5.2. Pharmacokinetic properties

Absorption

After intake of solifenacin succinate tablets, 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 5 to 40mg.

Absolute bioavailability is approximately 90%.

Food intake does not affect the C_{max} and AUC of solifenacin.

Distribution

The apparent volume of distribution of solifenacin following intravenous administration is about 600 L. Solifenacin is to a great extent (approximately 98%) bound to plasma proteins, primarily α 1-acid glycoprotein.

Biotransformation

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 - 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) have been identified in plasma in addition to solifenacin.

Elimination

After a single administration of 10mg [¹⁴C-labelled]-solifenacin, about 70% of the radioactivity was detected in urine and 23% in faeces over 26 days. In urine, approximately 11% of the radioactivity is recovered as unchanged active substance; about 18% as the N-oxide metabolite, 9% as the 4R-hydroxy-N-oxide metabolite and 8% as the 4R-hydroxy metabolite (active metabolite).

Linearity/non-linearity

Pharmacokinetics are linear in the therapeutic dose range.

Other special populations

Elderly

No dosage adjustment based on patient age is required. Studies in elderly have shown that the exposure to solifenacin, expressed as the AUC, after administration of solifenacin succinate (5mg and 10mg once daily) was similar in healthy elderly subjects (aged 65

through 80 years) and healthy young subjects (aged less than 55 years). The mean rate of absorption expressed as t_{max} was slightly slower in the elderly and the terminal half-life was approximately 20% longer in elderly subjects.

These modest differences were considered not clinically significant. The pharmacokinetics of solifenacin have not been established in children and adolescents.

Gender

The pharmacokinetics of solifenacin are not influenced by gender.

Race

The pharmacokinetics of solifenacin are not influenced by race.

Renal impairment

The AUC and C_{max} of solifenacin in mild and moderate renally impaired patients, was not significantly different from that found in healthy volunteers. In patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) exposure to solifenacin was significantly greater than in the controls with increases in C_{max} of about 30%, AUC of more than 100% and $t_{1/2}$ of more than 60%. A statistically significant relationship was observed between creatinine clearance and solifenacin clearance. Pharmacokinetics in patients undergoing haemodialysis have not been studied.

5.3. Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility, embryofetal development, genotoxicity, and carcinogenic potential. In the pre- and postnatal development study in mice, solifenacin treatment of the mother during lactation caused dose-dependent lower postpartum survival rate, decreased pup weight and slower physical development at clinically relevant levels. Dose related increased mortality without preceding clinical signs occurred in juvenile mice treated from day 10 or 21 after birth with doses that achieved a pharmacological effect and both groups had higher mortality compared to adult mice. In juvenile mice treated from postnatal day 10, plasma exposure was higher than in adult mice; from postnatal day 21 onwards, the systemic exposure was comparable to adult mice. The clinical implications of the increased mortality in juvenile mice are not known.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Pharmatose DCL 11 (Lactose Monohydrate)
- Microcrystalline Cellulose (Avicel PH-102)
- Pregelatinized Starch
- Magnesium Stearate
- Opadry White YS-1-7027

6.2. Incompatibilities

None

6.3. Shelf-life

2 years

The expiration date refers to the product correctly stored at the required conditions.

6.4. Special precautions for storage

- Store below 30°C.
- Protect from sunlight and moisture.
- Keep out of the reach of children.

6.5. Nature and contents of container

Solifen (Solifenacin succinate) Tablets 5mg are available in Alu-Alu Blister packs of 10's (1 × 10 Tablets) packed in a printed unit carton along with a package insert.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area
Karachi 74900, Pakistan Tel: (92-21)
111 111 511
Fax: (92-21) 5057592

8. MARKETING AUTHORIZATION NUMBER

H2012/CTD378/054

**9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE
AUTHORIZATION**

2026 May 18

10. DATE OF REVISION OF THE TEXT

2026 May 18