Solifen Film Coated Tablets 5mg

(Solifenacin succinate)

5mg Film-Coated Tablets

DESCRIPTION

Solifen Tablet 5mg is available as white oblong, biconvex shaped film coated tablet plain on both sides.

QUALITATIVE & QUANTITATIVE COMPOSITIONS

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

SOLIFEN Tablets 5mg

Each film-coated tablet contains:

Solifenacin succinate ... 5mg

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 M3 subtype is predominantly involved. Reported 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.

Pharmacokinetics

After oral administration of solifenacin succinate, it is absorbed from the gastrointestinal tract, with the peak plasma concentrations reaching after 3 to 8 hours and a bioavailability of about 90%. There is no effect of food on the pharmacokinetics of solifenacin. Solifenacin succinate is about 98% bound to plasma proteins principally to (alpha1)-acid glycoprotein. It is highly distributed to non-CNS tissues, having a mean steady-state volume of distribution of 600L. Solifenacin succinate is extensively metabolised in the liver mainly by the cytochrome P450 isoenzyme CYP3A4, and has a terminal half-life of 45-68hours. Solifenacin succinate is excreted mainly as metabolites in urine and feces.

THERAPEUTIC INDICATIONS

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

DOSAGE AND ADMINISTRATION

Adults, including the elderly

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

Paediatric population

The safety and efficacy of Solifen in children have not yet been established. Therefore, Solifen 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 5 mg 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 5 mg once daily.

Potent inhibitors of cytochrome P450 3A4

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

Method of administration

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

ADVERSE REACTIONS

Due to the pharmacological effect of solifenacin, solifenacin 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 was dry mouth.

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 micturition.

Rare: Dizziness, headache, colonic obstruction, fecal impaction, vomiting, urinary retention, pruritus, rash.

Very rare: Hallucinations, confusional state, Erythema multiforme, urticarial, angioedema.

Not Known: Anaphylactic reaction, decreased appetite, hyperkalaemia, delirium, glaucoma, Torsade de Pointes, electrocardiogram QT prolonged, atrial fibrillation, palpitations, tachycardia. dysphonia, ileus, abdominal discomfort, liver disorder, liver function test abnormal, exfoliative dermatitis, muscular weakness, renal impairment.

CONTRAINDICATIONS

Solifenacin succinate is contraindicated in patients with:

- Urinary retention, severe gastrointestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions.
- Hypersensitivity to the active substance or to any of the excipients.
- Undergoing haemodialysis.
- Severe hepatic impairment.
- Severe renal impairment or moderate hepatic impairment and who are on treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole.

PRECAUTIONS

Other causes of frequent urination (heart failure or renal disease) should be assessed before treatment with Solifen. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Solifen 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 5 mg for these patients.

• moderate hepatic impairment (Child-Pugh score of 7 to 9) and doses should not exceed 5 mg 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.

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 Solifen can be determined after 4 weeks at the earliest. QT prolongation and Torsade de Pointes have been observed in patients with risk factors. As with other drugs in this class, caution is advised in patients with known risk factors for QT-prolongation (i.e. history of QT prolongation, long QT syndrome, hypokalaemia, bradycardia, coadministration of drugs known to prolong the QT interval) and relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure.

Appropriate investigations (e.g. ECG) should be considered in patients with risk factors for QTc prolongation.

DRUG 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 Solifen before commencing other anticholinergic therapy. The therapeutic effect of solifenacin may be reduced by concomitant administration of cholinergic receptor agonists.

Solifenacin can reduce the effect of medicinal products that stimulate the motility of the gastrointestinal tract, such as metoclopramide and cisapride.

Pharmacokinetic interactions

Reported in vitro studies have demonstrated that at therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes. Therefore, solifenacin 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 (200 mg/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 should be restricted to 5 mg 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 contraindicated 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, carbamazepine).

Effect of solifenacin on the pharmacokinetics of other medicinal products

Oral Contraceptives

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

Warfarin

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

Digoxin

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

Drugs which prolong the QT/QTc interval

There is no satisfactory information on the concurrent use of solifenacin succinate with drugs known to prolong the QT/QTc interval. In the absence of such information on these combinations the potential risk of pathological QT/QTc prolongation resulting in arrhythmias cannot be ruled out. Drugs known to prolong the QT/QTc interval include: erythromycin, quinidine, procainamide,

disopyramide, sotalol, amiodarone, cisapride, fluconazole, amitriptyline, haloperidol, chlorpromazine, thioridazine, pimozide and droperidol.

Effects on ability to drive and operate 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.

PREGNANCY AND LACTATION

Pregnancy

No clinical data are available from women who became pregnant while taking solifenacin. 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. The use of solifenacin should be avoided during breast-feeding.

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 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 a 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).

HOW SUPPLIED

Solifen Tablets 5mg are available in blister packs of 30‘s.

STORAGE

Do not store above 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.

NAME AND ADDRESS OF MANUFACTURER

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