

Solifenacin

Core Safety profile

4.3 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 (see Section 5.2).
- Patients with severe hepatic impairment (see Section 5.2).
- Patients with severe renal impairment or moderate hepatic impairment and who are on treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole (see Section 4.5).

4.4 Special warnings and precautions for use

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

Vesicare 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 \leq 30 ml/min; see Section 4.2 and 5.2), and doses should not exceed 5 mg for these patients.
- moderate hepatic impairment (Child-Pugh score of 7 to 9; see Section 4.2 and 5.2), and doses should not exceed 5 mg for these patients.
- concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole (see 4.2 and 4.5).
- 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 Vesicare can be determined after 4 weeks at the earliest.

4.5 Interaction with other medicinal products and other forms of interaction

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 Vesicare, 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 gastro-intestinal tract, such as metoclopramide and cisapride.

Pharmacokinetic interactions

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 Vesicare should be restricted to 5 mg, when used simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole) (see Section 4.2). 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 Vesicare showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel).

Warfarin

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

Digoxin

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

4.6 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 (see Section 5.3). The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women.

Lactation

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 (see Section 5.3). The use of Vesicare 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 (see section 4.8. undesirable effects), the ability to drive and use machines may be negatively affected.

4.8 Undesirable effects

Due to the pharmacological effect of solifenacin, Vesicare 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 Vesicare was dry mouth. It occurred in 11% of patients treated with 5 mg once daily, in 22% of patients treated with 10 mg 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.

MedDRA system organ class	Very common ≥1/10	Common >1/100, <1/10	Uncommon >1/1000, <1/100	Rare > 1/10000, <1/1000	Very rare <1/10,000	Not known (cannot be estimated from the available data)
Infections and infestations			Urinary tract infection Cystitis			
Immune system disorders						Anaphylactic reaction*
Metabolism and nutrition disorders						Decreased appetite* Hyperkalaemia*
Psychiatric disorders					Hallucinations* Confusional state*	Delirium*
Nervous system disorders			Somnolence Dysgeusia	Dizziness*, Headache*		
Eye disorders		Blurred vision	Dry eyes			Glaucoma*
Cardiac disorders						Torsade de Pointes* Electrocardiogram QT prolonged
Respiratory, thoracic and mediastinal disorders			Nasal dryness			Dysphonia*
Gastrointestinal disorders	Dry mouth	Constipation Nausea Dyspepsia Abdominal pain	Gastro-oesophageal reflux diseases Dry throat	Colonic obstruction Faecal impaction, Vomiting*		Ileus* Abdominal discomfort*
Hepatobiliary disorders						Liver disorder* Liver function test abnormal*
Skin and subcutaneous tissue disorders			Dry skin	Pruritus*, Rash*,	Erythema multiforme*, Urticaria* Angioedema*	Exfoliative dermatitis*
Musculoskeletal and connective tissue disorders						Muscular weakness*
Renal and urinary disorders			Difficulty in micturition	Urinary retention		Renal impairment*

General disorders and administration site conditions			Fatigue Peripheral oedema			
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*observed post-marketing

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 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).