SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

Solirest 5 mg film-coated tablets

Solirest 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 or 10 mg solifenacin succinate respectively.

Excipient with known effect:

Solirest 5: Contains sugar (lactose monohydrate 134,5 mg per tablet).

Solirest 10: Contains sugar (lactose monohydrate 129,5 mg per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated Tablets

Solirest 5: Light yellow round shaped, 7,5 mm, biconvex film coated tablets, debossed with "SOL" on one side and "5" on other side

Solirest 10: Light pink round shaped, 7,5 mm, biconvex film coated tablets, debossed with "SOL" on one side and "10" on other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Solirest is indicated for the symptomatic treatment of overactive bladder syndrome: symptoms of urinary urgency, frequent micturition and/or urge incontinence.

4.2 Posology and method of administration

Posology

Adults, including the elderly

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

Special populations

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 not 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 should be treated with caution and receive not more than 5 mg once daily.

Strong inhibitors of cytochrome P450 3A4

The maximum dose of Solirest should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other strong CYP3A4-inhibitors.

Paediatric population

Safety and effectiveness in children have not yet been established. Therefore, Solirest is not recommended for children.

Method of administration

Solirest should be taken orally and should be swallowed whole with liquids. It can be taken with or without food, as is convenient.

4.3 Contraindications

- Hypersensitivity to solifenacin succinate or to any of the excipients of Solirest.
- 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 undergoing haemodialysis (see section 5.2)
- Patients with severe hepatic impairment (see section 5.2)
- Patients with severe renal impairment (CLcr < 30 mL/ min) 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 Solirest. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Solirest 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; 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 medicines (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.

Angioedema with airway obstruction has been reported in some patients on Solirest. If angioedema occurs, Solirest should be discontinued and appropriate therapy and/or measures should be taken.

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

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

Contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take Solirest.

4.5 Interaction with other medicines and other forms of interaction

Pharmacological interactions

Concomitant medication with other medicines 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 Solirest, before commencing other anticholinergic therapy. The therapeutic effect of

solifenacin succinate as in Solirest may be reduced by concomitant administration of cholinergic receptor agonists.

Solifenacin succinate as in Solirest can reduce the effect of medicines that stimulate the motility of the gastrointestinal 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 succinate as in Solirest is unlikely to alter the clearance of medicines metabolised by these CYP enzymes.

Effect of other medicines 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 Solirest l 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 Solirest 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, carbamazepin).

Effect of solifenacin on the pharmacokinetics of other medicines

Oral Contraceptives

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

Warfarin

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

Digoxin

Intake of Solirest 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 (see section 5.3). The potential risk for humans is unknown.

Safety in pregnancy and lactation has not been established.

Breastfeeding

No data on the excretion of Solirest 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 Solirest should therefore be avoided during breastfeeding.

4.7 Effects on ability to drive and use machines

Solirest may cause blurred vision, and, somnolence and fatigue (see section 4.8.), 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, Solirest may cause anticholinergic undesirable effects of (in general) mild or moderate severity. The frequency of anticholinergic undesirable effects is dose related.

The most frequently reported adverse reaction with Solirest was dry mouth. The severity of dry mouth was generally mild and did only occasionally lead to discontinuation of treatment.

Tabulated list of adverse reactions

MedDRA System Organ Class	Frequency		
	Frequent	**Less frequent**	**Frequency unknown**
Infections and infestations		Urinary tract infection, cystitis	
Immune system disorders		Angioedema*	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*, atrial fibrillation*, palpitations*, tachycardia*
Respiratory, thoracic and mediastinal disorders		Nasal dryness	
Gastrointestinal disorders	Dry mouth, constipation, nausea, dyspepsia, abdominal pain	Gastroesophageal reflux diseases, dry throat, colonic obstruction, faecal impaction, vomiting*	Ileus*, abdominal discomfort*
Hepato-biliary disorders			Liver disorder*, abnormal liver function test*
Skin and subcutaneous tissue disorders		Dry skin, pruritus*, rash*, erythema multiforme*, urticaria*	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	

* Observed post-marketing

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

The highest dose of solifenacin succinate given to human volunteers was 100 mg as a single dose. At this dose, the most frequent adverse events were headache, dry mouth, dizziness, drowsiness and blurred vision.

Treatment

No cases of acute overdosage have been reported. In the event of overdose with Solirest the patient should be treated symptomatically and with activated charcoal. Vomiting should not be induced.

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.

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 medicines 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 Solirest 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 40 mg. 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 10 mg [^{14}C-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.

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 (5 mg and 10 mg 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 Cmax of about 30 %, AUC of more than 100 % and $t_{½}$ 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.

Hepatic impairment

In patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) the C_{max} is not affected, AUC increased with 60 % and $t_{½}$ doubled. Pharmacokinetics of solifenacin in patients with severe hepatic impairment have not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet

Lactose monohydrate

Hydroxypropyl methyl cellulose

Magnesium stearate

Maize starch

Film coating

Hypromellose

Polyethylene glycol 8 000

Talc

Titanium dioxide (E171)

Red iron oxide (E172) – Solirest 10 mg

Yellow iron oxide (E172) – Solirest 5 mg

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C in the original package. Protect from moisture.

Do not remove foil strip from carton until required for use.

6.5 Nature and contents of container

Solirest film-coated tablets are packaged in PVC-Alu strips. 10 tablets per foil strip.

Pack sizes: 30 (3x10) film-coated tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

iPharma (Pty) Ltd

124 Elevation Avenue, Randjesfontein

Midrand, 1683, South Africa

8. REGISTRATION NUMBER

Solirest 5: 55/5.4/0028

Solirest 10: 55/5.4/0029

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28 June 2021

10. DATE OF REVISION OF THE TEXT

13 March 2025