SCHEDULING STATUS:
South Africa: S3
Namibia: NS2
Botswana: Schedule 2
Kenya: POM

PROPRIETARY NAME (and dosage form):
VESICARE 5 mg (film-coated tablet)
VESICARE 10 mg (film-coated tablet)

COMPOSITION:
Each VESICARE 5 mg tablet contains 5 mg solifenacin succinate
Each VESICARE 10 mg tablet contains 10 mg solifenacin succinate
Excipients:
Maize starch, lactose monohydrate, hypromellose, magnesium stearate, macrogol 8000, talc, titanium dioxide, yellow ferric oxide (VESICARE 5 mg), red ferric oxide (VESICARE 10 mg)
Contains sugar: Lactose monohydrate (VESICARE 5 mg: 107,5 mg; VESICARE 10 mg: 102,5 mg)

PHARMACOLOGICAL CLASSIFICATION:
A 5.4 Cholinolytics (anticholinergics)

PHARMACOLOGICAL ACTION:
Pharmacodynamic properties
Solifenacin is a competitive, specific cholinergic-receptor antagonist. *In vitro* studies demonstrated that solifenacin binds to muscarinic receptors, with high affinity.
Pharmacokinetic properties
Absorption
Following the oral administration 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 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 largely (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 (4*R*-hydroxy solifenacin) and three inactive metabolites (*N*-glucuronide, *N*-oxide and 4*R*-hydroxy-*N*-oxide of solifenacin) have been identified in plasma in addition to solifenacin.
Excretion
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 drug; about 18 % as the *N*-oxide metabolite, 9 % as the 4*R*-hydroxy-*N*-oxide metabolite and 8 % as the 4*R*-hydroxy metabolite (active metabolite).
Dose Proportionality
Pharmacokinetics is linear in the therapeutic dose range.

Characteristics in patients
Age
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 has not been established in children.

Gender

The pharmacokinetics of solifenacin is not influenced by gender.

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 $\leq$ 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 $t_{½}$ of more than 60 %. A statistically significant relationship was observed between creatinine clearance and solifenacin clearance.
Pharmacokinetics in patients undergoing haemodialysis has not been studied.

Hepatic impairment

In patients with moderate hepatic impairment the C_{max} is not affected, AUC increase with 60 % and $t_{½}$ doubled. Pharmacokinetics of solifenacin in patients with severe hepatic impairment has not been studied.

INDICATIONS

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

CONTRA-INDICATIONS

- Hypersensitivity to the active substance or to any of the excipients.
- Urinary retention.
- Uncontrolled narrow angle glaucoma.
- Myasthenia gravis.
- Toxic megacolon.
- Patients undergoing haemodialysis.
- Patients with severe hepatic impairment.
- Patients with severe renal impairment (Cl_{cr} < 30 ml/min) and on treatment with a strong CYP3A4 inhibitor, e.g. ketoconazole (see Interactions).
- Patients with moderate hepatic impairment and on treatment with a strong CYP3A4 inhibitor, e.g. ketoconazole (see Interactions).
- Patients with a prolonged QT interval, either congenital or acquired.
- Pregnancy and lactation (see Human Reproduction).

WARNINGS AND SPECIAL PRECAUTIONS

Organic reasons for urge and frequent micturition should be excluded before treatment.
VESICARE should be used with caution in patients with:

- Significant decompensated bladder outlet obstruction at risk of urinary retention.
- Gastrointestinal obstructive disorders.
- Risk of decreased gastrointestinal motility.
- Severe renal impairment (creatinine clearance $\leq$ 30 ml/min), and doses should not exceed 5 mg for these patients.
- Moderate hepatic impairment, and doses should not exceed 5 mg for these patients.
- Concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole.
- hiatus hernia/gastro-oesophagal 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.(see Contraindications)

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

VESICARE contains lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp Lactose deficiency or glucose-galactose malabsorption, should not take this medicine.

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

Anaphylactic reaction has been reported in some patients treated with VESICARE. In patients who develop anaphylactic reactions, VESICARE 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.

Effects on ability to drive and use machines
Since VESICARE may cause blurred vision, somnolence and fatigue (see Side Effects), the ability to drive and use machines may be negatively affected.

INTERACTIONS
Pharmacological interactions
Concomitant medication with other medicines with anticholinergic properties may result in more pronounced therapeutic effects and side effects. An interval of approximately one week should be allowed after stopping treatment with VESICARE, before commencing other anticholinergic therapy. The therapeutic effect of VESICARE may be reduced by concomitant administration of cholinergic receptor agonists.
VESICARE can reduce the effect of medicines 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 CYP1A/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes. Therefore, VESICARE is unlikely to alter the clearance of medicines metabolised by these CYP enzymes.
Effect of other medicines on the pharmacokinetics of solifenacin
Since solifenacin is metabolised by CYP3A4, pharmacokinetic interactions are possible with other CYP3A4 substrates, inhibitors and inducers.
Simultaneous administration of ketoconazole (200 mg/day) 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). Simultaneous treatment of VESICARE and strong CYP3A4 inhibitor is contra-indicated in patients with severe renal impairment or moderate hepatic impairment (see Contra-Indications).
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 medications
Oral contraceptives
Intake of VESICARE showed no pharmacokinetic interaction between solifenacin and combined oral contraceptives (ethinyl oestradiol / levonorgestrel),both CYP3A4 substrates.

Warfarin
Intake of VESICARE did not alter the pharmacokinetics of *R*-warfarin (substrate for CYP3A4) or *S*-warfarin (substrate for CYP2C9) or their effect on the INR.
Digoxin
Intake of VESICARE showed no effects on the pharmacokinetics of digoxin.

HUMAN REPRODUCTION
Pregnancy
VESICARE is contraindicated during pregnancy (see Contraindications).

Foetal toxicity has been shown in rodents.

Lactation
Solifenacin is excreted into breast milk. Women taking VESICARE should not breastfeed their infants.

DOSAGE AND DIRECTIONS FOR USE
Adults, including the elderly
The recommended dose is 5 mg once daily. If needed, the dose may be increased to 10 mg once daily.
Children
Safety and effectiveness of VESICARE in children have not yet been established. Therefore, VESICARE is not recommended for children.

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.
Potent inhibitors of cytochrome P450 3A4
The maximum dose of VESICARE 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
VESICARE should be taken orally and should be swallowed whole with liquids. It can be taken with or without food, as is convenient.

SIDE EFFECTS
Due to the pharmacological effect of solifenacin, VESICARE may cause anticholinergic side effects of mild or moderate severity in general**.** The frequency of anticholinergic side 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 and in 22 % of patients treated with 10 mg once daily. The severity of dry mouth was generally mild.
The following data was obtained with VESICARE in clinical trials.

MedDRA organ class system	**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*		Glaucoma*
Eye disorders		Blurred vision	Dry eyes			
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		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			

*observed post-marketing

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Symptoms

Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects. Treatment

In the event of overdose with VESICARE the patient should be treated with activated charcoal.

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.

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).

IDENTIFICATION
VESICARE 5 mg is a round, light yellow film-coated tablet debossed with the Astellas-logo and "150" on the same side, (debossed on one side only).
VESICARE 10 mg is a round, light pink film-coated tablet debossed with the Astellas-logo and "151" on the same side, (debossed on one side only).

PRESENTATION
VESICARE tablets are supplied in PVC/Aluminium blisters packs of 30 tablets. There are ten tablets in each blister strip and three blister strips in each pack.

STORAGE INSTRUCTIONS
Store in the original packs at or below 25 ºC.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

South Africa:	VESICARE 5 mg: A39/5.4/0490
	VESICARE 10 mg: A39/5.4/0491
Namibia:	VESICARE 5 mg: Reg. No. 07/5.4/0084
	VESICARE 10 mg: Reg. No. 10/5.4/0466
Kenya:	VESICARE 5 mg: H2015/CTD 2283/003
	VESICARE 10 mg: H2015/CTD 2150/004
Botswana:	VESICARE 5 mg: BOT1702937
	VESICARE 10 mg: BOT1702938

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
Astellas Pharma (Pty) Ltd, 7 Mirage Road, Bedfordview, 2007, South Africa

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