PROFESSIONAL INFORMATION

VESIFIN RANGE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

VESIFIN 5 mg Film coated tablet.

VESIFIN 10 mg Film coated tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each VESIFIN 5 mg film coated tablet contains 5 mg solifenacin succinate.

Contains sugar (lactose monohydrate 137,50 mg per tablet).

Each VESIFIN 10 mg film coated tablet contains 10 mg solifenacin succinate.

Contains sugar (lactose monohydrate 132,50 mg per tablet).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film coated tablets

VESIFIN 5 mg is a white to brown white, round, slightly convex film-coated tablet with bevelled edges.

VESIFIN 10 mg is a pinkish white, round, slightly convex film-coated tablet with bevelled edges.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VESIFIN 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.

Potent inhibitors of cytochrome P450 3A4

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

Paediatric population

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

Method of administration

VESIFIN 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 VESIFIN (see section 6.1)
- 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 section 4.5)
- Patients with moderate hepatic impairment and on treatment with a strong CYP3A4 inhibitor, e.g. ketoconazole (see section 4.5)
- Patients with a prolonged QT interval, either congenital or acquired
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

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

VESIFIN 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 ≤ 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 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 (see section 4.3).

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

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

Lactose

VESIFIN 5 mg and VESIFIN 10 mg contain 137,50 mg and 132,50 mg lactose monohydrate per tablet, respectively. This should be taken into account in patients with diabetes mellitus. Patients with the rare hereditary conditions of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take VESIFIN.

4.5 Interaction with other medicines and other forms of interaction

Pharmacological Interactions

Concomitant administration 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 VESIFIN, before commencing other anticholinergic therapy. The therapeutic effect of VESIFIN may be reduced by concomitant administration of cholinergic receptor agonists.

VESIFIN 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 CYP1A1/2, 2C9, 2C19, 2D6 or 3A4 derived from human liver microsomes. Therefore, VESIFIN is unlikely to alter the clearance of medicines metabolised by these CYP enzymes.

Effects of other medicines on the pharmacokinetics of solifenacin

Since solifenacin is metabolised by CYP3A4, pharmacokinetics interactions are possible with other CYP3A4 substrates, inhibitors and inducers.

Ketoconazole and other CYP3A4 inhibitors

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 VESIFIN 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 VESIFIN and strong CYP3A4 inhibitors is contraindicated in patients with severe renal impairment or moderate hepatic impairment (see section 4.3).

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 medicines

Oral contraceptives:

Intake of solifenacin showed no pharmacokinetic interaction between solifenacin and combined oral contraceptives (ethinyl oestradiol/levonorgestrel), as both are CYP3A4 substrates.

Warfarin:

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

4.6 Fertility, pregnancy and lactation

Pregnancy

VESIFIN is contraindicated during pregnancy (see section 4.3).

Foetal toxicity has been shown in rodents.

Breastfeeding

Solifenacin, as in VESIFIN is excreted into breast milk. It is contraindicated during lactation (see section 4.3), therefore women taking VESIFIN should not breastfeed their infants.

Fertility

Animal studies do not indicate direct harmful effects on fertility, embryonal / foetal development or parturition. The potential risk for humans is unknown.

4.7 Effects on ability to drive and use machines

Since VESIFIN may cause blurred vision, somnolence and fatigue (see section 4.8), the ability to drive and use machinery may be negatively affected.

4.8 Undesirable effects

a). Summary of the safety profile

Due to the pharmacological effect of solifenacin, VESIFIN may cause anticholinergic undesirable effects of mild or moderate severity in general.

The frequency of anticholinergic undesirable effects is dose related.

The most frequently reported adverse reaction with VESIFIN was dry mouth, the severity of which was generally mild.

b). Tabulated summary of adverse reactions

System Organ Class	Frequency	Side effects
Infections and Infestations	Less frequent	Urinary tract infection, cystitis
Nervous system disorders	Less frequent	Somnolence, dysgeusia
Eye disorders	Frequent Less frequent	Blurred vision Dry eyes
Respiratory, thoracic and mediastinal disorders	Less frequent	Nasal dryness
Gastrointestinal disorders	Frequent Less frequent	Dry mouth, constipation, nausea, dyspepsia, abdominal pain Gastro-oesophageal reflux disease, dry throat Colonic obstruction, faecal impaction
Skin and subcutaneous tissue disorders	Less frequent	Dry skin
Renal and urinary disorders	Less frequent	Difficulty in micturition, urinary retention
General disorders and administrative site conditions	Less Frequent	Fatigue, peripheral oedema

Post-marketing data:

System Organ Class	Frequency	Side effects
Immune system disorders	Frequency unknown	Anaphylactic reaction
Metabolism and nutrition disorders	Frequency unknown	Decreased appetite, hyperkalaemia
Psychiatric disorders	Less frequent	Hallucinations, confusional state Delirium

	Frequency unknown	
Nervous system disorders	Less frequent	Dizziness, headache
Eye disorders	Frequency unknown	Glaucoma
Cardiac disorders	Frequency unknown	*Torsade de Pointes*, electrocardiogram QT prolonged, atrial fibrillation, palpitations, tachycardia
Respiratory, thoracic and mediastinal disorders	Frequency unknown	Dysphonia
Gastrointestinal disorders	Less frequent Frequency unknown	Vomiting Ileus, abdominal discomfort
Hepato-biliary disorders	Frequency unknown	Liver disorder, liver function test abnormal
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Pruritus, rash, erythema multiforme, urticaria, angioedema Exfoliative dermatitis
Musculoskeletal, connective tissue and bone disorders	Frequency unknown	Muscular weakness
Renal and urinary disorders	Frequency unknown	Renal impairment

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”,

found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

4.9 OVERDOSE

Symptoms

Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects. In the event of overdose with VESIFIN, the patient should be treated with activated charcoal.

Standard supportive treatment should be applied, as necessary.

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 medicines known to prolong QT-interval) and relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, dysrhythmia, congestive heart failure).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics

ATC code: G04BD08

Pharmacological classification: A 5.4 Cholinolytics (anticholinergics).

Solifenacin is a competitive specific cholinergic-receptor antagonist. In vitro studies demonstrated that solifenacin binds to muscarinic receptors, with high affinity.

5.2 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) increased 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 α1-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 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.

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 4*R*-hydroxy-N-oxide metabolite and 8 % as the 4*R*-hydroxy metabolite (active metabolite).

Linearity/non-linearity

Pharmacokinetics are linear in the therapeutic dose range.

Special populations

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 have not been established in children.

Gender

The pharmacokinetics of solifenacin are 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 ≤ 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 have not been studied.

Hepatic impairment

In patients with moderate hepatic impairment 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.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility, embryofoetal 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

Ferric oxide red E172

Hypromellose

Lactose monohydrate

Magnesium stearate

Povidone K25

Talc

Titanium dioxide E171

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 30 °C in original container.

Protect from light and moisture.

Keep the blisters in the outer carton until required for use.

6.5 Nature and contents of container

VESIFIN tablets are supplied in PVC/PVDC - Aluminium blister packs of 30 tablets each. Each blister strip contains 10 tablets, with three blisters per pack.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

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8. REGISTRATION NUMBER(S)

VESIFIN 5 mg: A48/5.4/0671

VESIFIN 10 mg: A48/5.4/0672

9. DATE OF FIRST AUTHORISATION

October 2021

10. DATE OF REVISION OF THE TEXT

October 2021