Professional Information for SOLIFENACIN UNICORN

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SOLIFENACIN UNICORN 5 Film-coated tablets

SOLIFENACIN UNICORN 10 Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SOLIFENACIN UNICORN 5 film-coated tablet contains 5 mg solifenacin succinate.

Contains sugar: lactose monohydrate 50,00 mg.

Each SOLIFENACIN UNICORN 10 film-coated tablet contains 10 mg solifenacin succinate.

Contains sugar: lactose monohydrate 100,00 mg.

For the full list of excipients, **see section 6.1**

3. PHARMACEUTICAL FORM

Film-coated tablets

SOLIFENACIN UNICORN 5: Light yellow coloured, round, biconvex, film coated tablet, debossed with ‘D5’ on the one side and plain on the other side.

SOLIFENACIN UNICORN 10: Light pink coloured, round, biconvex, film coated tablet, debossed with ‘D6’ on the one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SOLIFENACIN UNICORN 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 received not more than 5 mg once daily.

Potent inhibitors of cytochrome P450 3A4:

The maximum dose of SOLIFENACIN UNICORN 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 SOLIFENACIN UNICORN in children have not yet been established. Therefore, SOLIFENACIN UNICORN is not recommended for children.

Method of administration

SOLIFENACIN UNICORN 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 or to any of the excipients of SOLIFENACIN UNICORN (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 SOLIFENACIN UNICORN. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

SOLIFENACIN UNICORN 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 a potent CYP3A4 inhibitor, e.g. ketoconazole.
- 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 (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, SOLIFENACIN UNICORN should be discontinued and appropriate therapy and/or measures should be taken.

Anaphylactic reaction has been reported in some patients treated with solifenacin. In patients who develop anaphylactic reactions, SOLIFENACIN UNICORN 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 monohydrate

SOLIFENACIN UNICORN contains lactose monohydrate.

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

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

SOLIFENACIN UNICORN 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, SOLIFENACIN UNICORN 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, 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 SOLIFENACIN UNICORN 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 UNICORN 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

SOLIFENACIN UNICORN is contraindicated during pregnancy (see **section 4.3**).

Foetal toxicity has been shown in rodents.

Breastfeeding

Solifenacin, as in SOLIFENACIN UNICORN is excreted into breast milk. It is contraindicated during lactation (see **section 4.3**), therefore women taking SOLIFENACIN UNICORN 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 SOLIFENACIN UNICORN may cause blurred vision, somnolence and fatigue (see **section 4.8**), the ability to drive and use machines may be negatively affected.

4.8 Undesirable effects

Due to the pharmacological effect of solifenacin, SOLIFENACIN UNICORN may cause anticholinergic side effects of mild or moderate severity in general. The frequency of anticholinergic side effects is dose related.

The most frequently reported adverse reaction SOLIFENACIN UNICORN was dry mouth. The severity of dry mouth was generally mild.

Infectious and infestations:

Less frequent: Urinary tract infection, cystitis.

Nervous system disorders:

Less frequent: Somnolence, dysgeusia.

Eye disorders:

Frequent: Blurred vision.

Less frequent: Dry eyes.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Nasal dryness.

Gastrointestinal disorders:

Frequent: Dry mouth, constipation, nausea, dyspepsia, abdominal pain.

Less frequent: Gastro-oesophageal reflux diseases, 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 administration site conditions:

Less frequent: Fatigue, peripheral oedema.

Post-marketing data:

Immune system disorders:

Frequency unknown: Anaphylactic reaction.

Metabolism and nutrition disorders:

Frequency unknown: Decreased appetite, hyperkalaemia.

Psychiatric disorders:

Less frequent: Hallucinations, confusional state.

Frequency unknown: Delirium.

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: Vomiting.

Frequency unknown: Ileus, abdominal discomfort.

Hepatobiliary disorders:

Frequency unknown: Liver disorder, liver function test abnormal.

Skin and subcutaneous tissue disorder:

Less frequent: Pruritus, rash, erythema multiforme, urticaria, angioedema.

Frequency unknown: Exfoliative dermatitis.

Musculoskeletal, connective tissue and bone disorders:

Frequency unknown: Muscular weakness.

Renal and urinary disorders:

Frequency unknown: Renal impairment.

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. 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 SOLIFENACIN UNICORN**,** 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

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 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 radioactivity is recovered as unchanged medicine 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 is 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 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 renal 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 has not been studied.

Hepatic impairment

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SOLIFENACIN UNICORN 5: Hypromellose, lactose monohydrate, magnesium stearate, maize starch and Opadry Yellow (containing hypromellose, iron oxide yellow, macrogol, talc and titanium dioxide).

SOLIFENACIN UNICORN 10: Hypromellose, lactose monohydrate, magnesium stearate, maize starch and Opadry Pink (containing hypromellose, iron oxide red, iron oxide yellow, macrogol, talc and titanium dioxide).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 ºC.

Store in the original packaging.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Blister pack: Silver aluminium/Colourless transparent PVC blisters containing 10 tablets. 3 blister strips are packed into an outer carton. Pack size is 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unicorn Pharmaceuticals (Pty) Ltd

Corner of Searle & Pontac Streets

Cape Town

South Africa

8001

8. REGISTRATION NUMBER(S)

Solifenacin Unicorn 5: A 48/5.4/0612

Solifenacin Unicorn 10: A 48/5.4/0613

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 March 2022

10. DATE OF REVISION OF THE TEXT

Not applicable.