Professional Information for SOLIFENACIN UNICHEM

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SOLIFENACIN 5 mg UNICHEM film-coated tablets

SOLIFENACIN 10 mg UNICHEM film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipients with known effect:

Contains sugar: lactose monohydrate.

SOLIFENACIN 5 mg UNICHEM: Each film-coated tablet contains 124,9 mg lactose monohydrate.

SOLIFENACIN 10 mg UNICHEM: Each film-coated tablet contains 119,9 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

SOLIFENACIN 5 mg UNICHEM: Light yellow, round, biconvex, film-coated tablets, debossed with "U" on one side and "328" on the other side.

SOLIFENACIN 10 mg UNICHEM: Light pink, round, biconvex, film-coated tablets, debossed with "U" on one side and "329" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SOLIFENACIN UNICHEM 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 SOLIFENACIN UNICHEM 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 efficacy of SOLIFENACIN UNICHEM in children have not yet been established. Therefore, SOLIFENACIN UNICHEM is not recommended for children.

Method of administration

SOLIFENACIN UNICHEM should be taken orally and should be swallowed whole with liquids. It can be taken with or without food.

4.3 Contraindications

- Hypersensitivity to solifenacin succinate or to any of the excipients of SOLIFENACIN UNICHEM listed in 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 (see section 4.6).

4.4 Special warnings and precautions for use

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

SOLIFENACIN UNICHEM should be used with caution in patients with:

- clinically significant decompensated 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 sections 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 torsades 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 UNICHEM. If angioedema occurs, SOLIFENACIN UNICHEM should be discontinued and appropriate therapy and/or measures should be taken.

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

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

Lactose

SOLIFENACIN UNICHEM contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take SOLIFENACIN UNICHEM.

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

SOLIFENACIN UNICHEM 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 UNICHEM is unlikely to alter the clearance of medicines metabolised by these CYP enzymes.

Effect of other medicines on the pharmacokinetics of SOLIFENACIN UNICHEM

Since solifenacin is metabolised by CYP3A4, pharmacokinetic interactions are possible with other CYP3A4 substrates, inhibitors and inducers. 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 SOLIFENACIN UNICHEM 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 UNICHEM and a potent CYP3A4 inhibitor 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 UNICHEM 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 UNICHEM on the pharmacokinetics of other medicines

Oral contraceptives

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

Warfarin

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

Digoxin

Intake of SOLIFENACIN UNICHEM showed no effect on the pharmacokinetics of digoxin.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of SOLIFENACIN UNICHEM is contraindicated during pregnancy (see section 4.3).

No clinical data are available from women who became pregnant while taking SOLIFENACIN UNICHEM. Foetal toxicity has been shown in rodents.

Breastfeeding

Solifenacin is excreted into breastmilk. Women taking SOLIFENACIN UNICHEM should not breastfeed their infants.

Fertility

No data are available on the effect of SOLIFENACIN UNICHEM on fertility.

4.7 Effects on ability to drive and use machines

SOLIFENACIN UNICHEM may cause blurred vision, somnolence, fatigue and possibly hallucinations and dizziness (see section 4.8), which may affect the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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

The most commonly reported adverse reaction with SOLIFENACIN UNICHEM is dry mouth. The severity of dry mouth is generally mild.

Tabulated summary of adverse reactions

Infections 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 experience

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: torsades 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 disorders

Less frequent: pruritis, rash, erythema multiforme, urticaria, angioedema

Frequency unknown: exfoliative dermatitis

Musculoskeletal and connective tissue 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 SOLIFENACIN UNICHEM is important. It allows continued monitoring of the benefit/risk balance of SOLIFENACIN UNICHEM. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

Overdosage with SOLIFENACIN UNICHEM 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 hospitalisation.

Treatment

In the event of overdose with SOLIFENACIN UNICHEM, 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 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

Category and class: A 5.4 Cholinolytics (anticholinergics)

Pharmacotherapeutic group: Urologicals, drugs for urinary frequency and incontinence

ATC code: G04BD08

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 M_3 subtype is predominantly involved. *In vitro* studies demonstrated that solifenacin binds to muscarinic receptors, with high affinity. *In vitro* and *in vivo* pharmacological studies indicate that solifenacin is a competitive inhibitor of the muscarinic M_3 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 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 (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

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 (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 has not been studied.

5.3. Preclinical safety data

No further information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Hypromellose (E464)

Lactose monohydrate

Maize starch

Pregelatinised starch

Magnesium stearate (E572)

Film-coating:

SOLIFENACIN 5 mg UNICHEM 5:

Hypromellose (E464)

Iron oxide yellow (E172)

Polyethylene glycol (E1521)

Talc (E553b)

Titanium dioxide (E171)

SOLIFENACIN 10 mg UNICHEM:

Hypromellose (E464)

Iron oxide red (E172)

Polyethylene glycol (E1521)

Talc (E553b)

Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

Clear PVC/PVDC and silver aluminium blister strips, placed in an outer carton.

Pack size: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Unichem SA (Pty) Ltd

San Domenico

Ground Floor, Unit G4

10 Church Street

Durbanville

7551 Cape Town

8. REGISTRATION NUMBERS

SOLIFENACIN 5 mg UNICHEM: 55/5.4/0554

SOLIFENACIN 10 mg UNICHEM: 55/5.4/0555

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 May 2023

10. DATE OF REVISION OF THE TEXT

Not yet revised.