*Applicant/PHRC:* ***Hetero Drugs South Africa (Pty) Ltd***

*Product proprietary name****: UROTENA 5 & 10***

*Dosage form and strength:* ***Film coated tablet, contains solifenacin succinate 5 mg & 10 mg***

**APPROVED PROFESSIONAL INFORMATION FOR UROTENA 5 & 10**

**SCHEDULING STATUS**

**S3**

**1 NAME OF THE MEDICINE**

**UROTENA 5 (film coated tablet)**

**UROTENA 10 (film coated tablet)**

**2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

**UROTENA 5:** Each film coated tablet contains 5 mg solifenacin succinate.

**UROTENA 10:** Each film coated tablet contains 10 mg solifenacin succinate.

**Contains sugar (lactose monohydrate):**

**UROTENA 5:** Contains 55,625 mg lactose monohydrate.

**UROTENA 10:** Contains 111,25 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

**3 PHARMACEUTICAL FORM**

**UROTENA 5:** White to off white colour, round, biconvex tablets debossed with “V” on one side and “18” on the other side.

**UROTENA 10:** White to off white colour, round, biconvex tablets debossed with “V” on one side and “19” on the other side.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**UROTENA** 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.

**Children**

Safety and effectiveness of **UROTENA** in children have not yet been established. Therefore, **UROTENA** 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 **UROTENA** 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**

**UROTENA** 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**

- Known hypersensitivity to solifenacin or to any of the excipients of **UROTENA** (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 (see **section 4.6**).

**4.4 Special warnings and precautions for use**

Organic reasons for urge and frequent micturition should be excluded before treatment.

**UROTENA** 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, 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 **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 **UROTENA**.

If angioedema occurs, **UROTENA** should be discontinued and appropriate therapy and/or measures should be taken.

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

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

**Lactose warning**

**UROTENA** contains lactose. 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 medicine and other forms of interaction**

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

**UROTENA** 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, **UROTENA** 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 **UROTENA** 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 **UROTENA** and strong 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 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 **UROTENA** showed no pharmacokinetic interaction between solifenacin and combined oral contraceptives (ethinyl oestradiol / levonorgestrel), both CYP3A4 substrates.

***Warfarin:***

Intake of **UROTENA** 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 **UROTENA** showed no effects on the pharmacokinetics of digoxin.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

**UROTENA** is contraindicated during pregnancy (see **section 4.3**).

Foetal toxicity has been shown in rodents.

**Lactation**

Solifenacin is excreted into breast milk. Women taking **UROTENA** should not breastfeed their infants.

**4.7 Effects on ability to drive and use machines**

Since **UROTENA** 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**

**a) Summary of the safety profile**

Due to the pharmacological effect of solifenacin, **UROTENA** may cause anticholinergic undesirable effects of (in general) mild or moderate severity. The frequency of anticholinergic side effects is dose related.

The most commonly reported adverse reaction with solifenacin, was dry mouth. It occurred in 11 % of patients treated with 5 mg once daily, in 22 % of patients treated with 10 mg once daily and in 4 % of placebo-treated patients. The severity of dry mouth was generally mild.

**b) Tabulated summary of adverse reactions**

| |
|---|
| **Infections and infestations** |
| *Less frequent:* Urinary tract infection, cystitis |
| **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:* Somnolence, dysgeusia, dizziness, headache |
| *Frequency unknown:* Glaucoma |
| **Eye disorders** |
| *Frequent:* Blurred vision |
| *Less frequent:* Dry eyes |
| **Cardiac disorders** |
| *Frequency unknown:* Torsade de Pointes, electrocardiogram, QT prolonged |
| **Respiratory, thoracic and mediastinal disorders** |
| *Less frequent:* Nasal dryness |
| *Frequency unknown:* Dysphonia |
| **Gastrointestinal disorders** |
| *Frequent:* Dry mouth, constipation, nausea, dyspepsia, abdominal pain |
| *Less frequent:* Gastro-oesophageal reflux diseases, dry throat, colonic obstruction, faecal impaction |
| *Frequency unknown:* Illeus, abdominal discomfort |
| **Hepato-biliary disorders** |
| *Frequency unknown:* Liver disorder, liver function test abnormal |
| **Skin and subcutaneous tissue disorders** |

| |
|---|
| *Less frequent:* Dry skin, pruritus, rash, erythema multiforme, urticaria, angioedema |
| *Frequency unknown:* Exfoliative dermatitis |
| **Musculoskeletal and connective tissue disorders** |
| *Frequency unknown:* Muscular weakness |
| **Renal and urinary disorders** |
| *Less frequent:* Difficulty in micturition, urinary retention |
| *Frequency unknown:* Renal impairment |
| **General disorders and administration site conditions** |
| *Less frequent:* Fatigue, peripheral oedema |

***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 to report any suspected adverse reactions via the **Med Safety APP (Medsafety X SAHPRA)** and **eReporting platform (who-umc.org)** found on SAHPRA website, and to the Holder of certificate of registration through the **mail: pvg.cdma@heterogroups.com.**

**4.9 Overdose**

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

**Treatment**

In the event of overdose with **UROTENA** 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).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

**Category and Class:** A 5.4 Cholinolytics (anticholinergics)

**Pharmacotherapeutic group:** Urinary antispasmodics**, ATC code:** G04B D08.

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) 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 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 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 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).

**Linearity/non-linearity**

Pharmacokinetics is linear in the therapeutic dose range.

**Characteristics in specific groups of subjects or 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.

***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 ≤ 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.

**Paediatric population**

The pharmacokinetics of solifenacin has not been established in children.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

- Corn starch
- Hypromellose 2910
- Lactose monohydrate
- Magnesium stearate
- Purified water
- Opadry white 03F580030 (consists of HPMC 2910/hypromellose, titanium dioxide, macrogol/PEG, talc)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 months.

### 6.4 Special precautions for storage

- Store at or below 25 °C.
- Keep the tablets in the original container until required for use.
- This medicine does not require any special storage conditions.

### 6.5 Nature and contents of container

**HDPE bottle:**

Tablets are pack in a white opaque high density polyethylene container (HDPE) container with white opaque polypropylene child resistant plastic cap with pulp liner.

Pack size: 30's and 90's

(Or)

Tablets are pack in a white opaque high density polyethylene container (HDPE) container with white opaque polypropylene, ribbed, child resistant plastic cap with pulp liner.

Pack size: 500's

**Blister strips:**

Blister strips of clear, transparent, thermoformable, rigid PVC forming film and plain soft aluminium peel-push lidding foil, containing 10 tablets per blister.

Pack sizes: 10 tablets per blister. 10's x 10 blisters packed in a box.

**Stimulated bulk pack:**

Tablets are pack in a clear translucent low density polyethylene (poly bag), plain triple laminated bag containing 5 grams of silica gel sachet.

Pack size: 1000's

HDPE bottle and blister strips are enclosed in an outer carton box.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Waterfall Corporate Campus

Building No. 2, First floor

74 Waterfall Drive

Midrand, 2066

Telephone number: 012 644 1220.

e-mail address: nokuthula.n@hetero.com

## 8 REGISTRATION NUMBER(S)

**UROTENA 5:** 56/5.4/1027.025

**UROTENA 10:** 56/5.4/1028.026

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

22 July 2025

## 10 DATE OF REVISION OF THE TEXT