## SCHEDULING STATUS

**S3**

## 1. NAME OF THE MEDICINE

**FENSIGLEN 5 mg** (Film-coated tablet)

**FENSIGLEN 10 mg** (Film-coated tablet)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**FENSIGLEN 5 mg** (Film-coated tablet): Each film-coated tablet contains 5,00 mg solifenacin succinate. Contains sugar: lactose monohydrate: 51,25 mg.

**FENSIGLEN 10 mg** (Film-coated tablet): Each film-coated tablet contains 10,00 mg solifenacin succinate. Contains sugar: lactose monohydrate: 68,33 mg.

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (Tablet).

**FENSIGLEN 5 mg** (Film-coated tablet): Yellow coloured, round, biconvex, film coated tablets with "G" debossed on one side and "71" debossed on other side.

**FENSIGLEN 10 mg** (Film-coated tablet): Pink coloured, round, biconvex, film coated Tablets with “G” debossed on one side and “52” debossed on other side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**FENSIGLEN** 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 **FENSIGLEN** 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 **FENSIGLEN** in children have not yet been established. Therefore, **FENSIGLEN** is not recommended for children.

Method of administration

**FENSIGLEN** 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

**FENSIGLEN** is contra-indicated:

- In individuals with known hypersensitivity to solifenacin succinate or any of the excipients 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 breastfeeding (see *section 4.6*)

## 4.4 Special warnings and precautions for use

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

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

**FENSIGLEN** 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 preexisting 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 **FENSIGLEN**.

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

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

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

**FENSIGLEN** 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 medicines and other forms of interaction

**Pharmacological interactions**

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

**FENSIGLEN** 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, **FENSIGLEN** 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 **FENSIGLEN** 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 **FENSIGLEN** 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 medicines**

*Oral contraceptives*

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

*Warfarin*

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

## 4.6 Fertility, pregnancy and lactation

Pregnancy

**FENSIGLEN** is contraindicated during pregnancy (see *section 4.3*). Foetal toxicity has been shown in rodents.

Breastfeeding

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

Fertility

No data available.

## 4.7 Effects on ability to drive and use machines

Since **FENSIGLEN** 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, **FENSIGLEN** 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 solifenacin as contained in **FENSIGLEN** was dry mouth.

Tabulated summary of adverse reactions

The adverse reactions are listed by system organ class and absolute frequency.

| System Organ Class | Adverse Reactions | Frequency Category |
|---|---|---|
| ***Infections and infestations*** | Urinary tract infection, cystitis | Less frequent |
| ***Immune system disorders*** | Anaphylactic reaction | Frequency unknown |
| ***Metabolism and nutrition disorders*** | Decreased appetite, hyperkalaemia | Frequency unknown |
| ***Psychiatric disorders*** | Hallucinations, confusional state | Less frequent |
| | Delirium | Frequency unknown |
| ***Nervous system disorders*** | Somnolence, dysgeusia, dizziness, headache | Less frequent |
| ***Eye disorders*** | Blurred vision | Frequent |
| | Dry eyes | Less frequent |
| | Glaucoma | Frequency unknown |
| ***Cardiac disorders*** | Torsade de Pointes, electrocardiogram QT prolonged | Frequency unknown |
| | Nasal dryness | Less frequent |

| | | |
|---|---|---|
| ***Respiratory, thoracic and mediastinal disorders*** | Dysphonia | Frequency unknown |
| ***Gastrointestinal disorders*** | Dry mouth, constipation, nausea, dyspepsia, abdominal pain | Frequent |
| | Gastrooesophageal reflux diseases, dry throat, colonic obstruction, faecal impaction | Less frequent |
| | Ileus, abdominal discomfort | Frequency unknown |
| ***Hepato-biliary disorders*** | Liver disorder, liver function test abnormal | Frequency unknown |
| ***Skin and subcutaneous tissue disorders*** | Dry skin, pruritus, rash, erythema Multiforme, urticaria, angioedema | Less frequent |
| | Exfoliative dermatitis | Frequency unknown |
| **Musculoskeletal and Connective tissue disorders** | Muscular weakness | Frequency unknown |
| **Renal and urinary disorders** | Difficulty in micturition, urinary retention | Less frequent |
| | Renal impairment | Frequency unknown |
| ***General disorders and administration site conditions*** | Fatigue, peripheral oedema | Less frequent |

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.

*Treatment*

In the event of overdose with **FENSIGLEN** 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, arrhythmia, congestive heart failure).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

A 5.4 Cholinolytics (anticholinergics)

Pharmacotherapeutic group: Urinary antispasmodics, ATC code: G04B D08Solifenacin is a competitive, specific cholinergic-receptor antagonist. *In vitro* studies demonstrated that solifenacin binds to muscarinic receptors, with high affinity.

The urinary bladder is innervated by parasympathetic cholinergic nerves. Acetylcholine contracts the detrusor smooth muscle through muscarinic receptors of which the M3 subtype is predominantly involved. *In vitro* and *in vivo* pharmacological studies indicate that solifenacin is a competitive inhibitor of the muscarinic M3 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*

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 (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 drug; about 18 % as the N-oxide metabolite, 9 % as the 4R-hydroxy-N-oxide metabolite and 8 % as the 4R-hydroxy metabolite (active metabolite).

*Dose Proportionality*

Pharmacokinetics is linear in the therapeutic dose range.

<u>Characteristics in specific patients</u>

*Elderly*

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 ≤ 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Corn starch, hypromellose, isopropyl alcohol, lactose monohydrate, magnesium stearate, methylene chloride.

Coating:

Instacoat Universal A05G32262, Instacoat Universal A05G32262, purified water.

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister strips in outer carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN.

### 6.5 Nature and contents of container

Multilayer aluminium foil with a blue to greenish inner layer / aluminium layer blister strip, containing 10 tablets each, packed in an outer carton.

Pack sizes: 30 tablets (10 tablets per blister strip and 3 blister strips in each pack) OR

100 tablets (10 tablets per blister strip and 10 blister strips in each pack).

### 6.6 Special precautions for disposal and other handling

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

**Glenmark Pharmaceuticals South Africa (Pty) Ltd**

34 Monte Carlo Crescent,

Block A, First floor,

Kyalami Park,

Midrand,

1684

## 8. REGISTRATION NUMBER(S)

**FENSIGLEN 5 mg:** 54/5.4/0064

**FENSIGLEN 10 mg:** 54/5.4/0065

## 9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

17 September 2024

## 10. DATE OF REVISION OF TEXT