Approved Professional Information for: FENENCE 5 mg/ 10 mg

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

FENENCE 5 mg Film-coated tablets

FENENCE 10 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **FENENCE** 5 mg film-coated tablet contains 5 mg solifenacin succinate.

Each **FENENCE** 10 mg film-coated tablet contains 10 mg solifenacin succinate.

Contains sugar (lactose monohydrate).

Each 5 mg film-coated tablet contains 54,25 mg of lactose monohydrate (see section 4.4).

Each 10 mg film-coated tablet contains 108,5 mg of lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

FENENCE 5 mg:

Light yellow, round, biconvex film-coated tablets.

FENENCE 10 mg:

Light pink, round, biconvex film-coated tablets with score line on one side and

plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Method of administration

FENENCE 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 FENENCE (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 FENENCE. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

FENENCE 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, FENENCE 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, FENENCE 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.

Excipients: lactose intolerance

This medicine 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 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 FENENCE, before commencing other anticholinergic therapy. The therapeutic effect of FENENCE may be reduced by concomitant administration of cholinergic receptor agonists.
FENENCE 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, FENENCE is unlikely to alter the clearance of medicines

metabolised by these CYP enzymes.

Effect of other medicine 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 FENENCE 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 FENENCE 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

FENENCE is contraindicated during pregnancy (see section 4.3).

Foetal toxicity has been shown in rodents.

Breastfeeding

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

Line

Reference

4.8 Undesirable effects

Due to the pharmacological effect of solifenacin, FENENCE 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 with FENENCE was dry mouth. The severity of dry mouth was generally mild.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Frequency unknown**
Infections and infestations		Urinary tract infection, cystitis	
Nervous system disorders		Somnolence, dysgeusia	
Eye disorders	Blurred vision	Dry eyes	
Respiratory, thoracic and mediastinal		Nasal dryness	

disorders			
Gastrointestinal disorders	Dry mouth, constipation, nausea, dyspepsia, abdominal pain.	Gastro-oesophageal reflux diseases, dry throat, colonic obstruction, faecal impaction.	
Skin and subcutaneous tissue disorders		Dry skin	
Renal and urinary disorders		Difficulty in micturition, urinary retention	
General disorders and administration site conditions		Fatigue, peripheral oedema	

Post-marketing data

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Frequency unknown**
Immune system disorders			Anaphylactic reaction

Metabolism and nutrition disorders			Decreased appetite, hyperkalaemia
Psychiatric disorders		Hallucinations, confusional state	Delirium
Nervous system disorders		Dizziness, headache	
Eye disorders			Glaucoma
Cardiac disorders			Torsade de Pointes, electrocardiogram QT prolonged, atrial fibrillation, palpitations, tachycardia
Respiratory, thoracic and mediastinal disorders			Dysphonia
Gastrointestinal disorders		Vomiting	Ileus, abdominal discomfort
Hepatobiliary			Liver disorder, liver

disorders			function test abnormal
Skin and subcutaneous tissue disorders		Pruritus, rash, erythema multiforme, urticaria, angioedema	Exfoliative dermatitis
Musculoskeletal and connective tissue and bone disorders			Muscular weakness
Renal and urinary disorders			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 FENENCE, 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: G04B D08

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 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 - 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 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

Tablet core:

Lactose monohydrate

Magnesium stearate

Maize starch

(Maize) starch, (partially) pregelatinised

Film-coating:

Ready-to-use mixture consisting of:

Hypromellose 2910 (5 mPa*s)

Iron oxide red (E172) – FENENCE 10 mg

Iron oxide yellow (E172)

Macrogol 8000

Talc

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 ºC.

6.5 Nature and contents of container

FENENCE 5 mg and 10 mg film-coated tablets are packed in Transparent PVC /PE /PVDC / Aluminium blisters or packed in Aluminium/ Aluminium blisters. The blisters are subsequently packed into cardboard boxes in pack sizes of 3, 5, 10, 20, 30, 50, 60, 90, 100 or 200 film-coated tablets.

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

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBERS

FENENCE 5 mg: 49/5.4/0329

FENENCE 10 mg: 49/5.4/0330

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 October 2021

10. DATE OF REVISION OF THE TEXT

25 December 2021