PROFESSIONAL INFORMATION

FLOLOC CHEWS

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINAL PRODUCT

FLOLOC CHEWS 5 mg and 10 mg chewable tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each **FLOLOC CHEWS** 5 mg chewable tablet contains 5 mg Solifenacin succinate equivalent to 3,8 mg Solifenacin.

Each **FLOLOC CHEWS** 10 mg chewable tablet contains 10 mg Solifenacin succinate equivalent to 7,5 mg Solifenacin.

Contains sugar:

FLOLOC CHEWS 5 mg: Lactose monohydrate 43 mg and mannitol 125 mg per tablet

FLOLOC CHEWS 10 mg: Lactose monohydrate 86 mg and mannitol 250 mg per tablet

Contains sweetener:

FLOLOC CHEWS 5 mg: sucralose 5 mg per tablet

FLOLOC CHEWS 10 mg: sucralose 10 mg per tablet

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

3. PHARMACEUTICAL FORM

FLOLOC CHEWS 5 and 10 are chewable tablets.

FLOLOC CHEWS 5: White to off white, round, flat tablet with “5” engraved on one side.

FLOLOC CHEWS 10: White to off white, round, flat tablet with “10” engraved on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

FLOLOC CHEWS 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 (Child-Pugh score of 7 to 9) should be treated with caution and receive not more than 5 mg once daily.

Potent inhibitors of cytochrome P450 3A4

The maximum dose of **FLOLOC CHEWS** should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other CYP3A4-inhibitors e.g. ritonavir, nelfinavir, itraconazole.

Paediatric population

Safety and effectiveness in children have not yet been established. Therefore, **FLOLOC CHEWS** is not recommended for children.

Method of administration:

FLOLOC CHEWS should be taken orally and chewed. It can be taken with or without food, as is convenient.

4.3 Contraindications:

FLOLOC CHEWS is contra-indicated in the following situations:

- Hypersensitivity to the solifenacin or to any of the excipients of **FLOLOC CHEWS** (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 (Creatine clearance < 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. Other causes of frequent urination (heart failure or renal disease) should be assessed before treatment with **FLOLOC CHEWS**. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

FLOLOC CHEWS 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 pateints.
- Concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole

- Hiatus hernia/gastro-oesophageal reflux and/or who are currently taking medicinal products (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.

Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity.

Angiodema with airway obstruction has been reported in some patients on solifenacin. If angioedema occurs, **FLOLOC CHEWS** 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, **FLOLOC CHEWS** should be discontinued and appropriate therapy and/or measures should be taken.

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

FLOLOC CHEWS contains lactose. Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose should not take **FLOLOC CHEWS**.

FLOLOC CHEWS contains mannitol and may have laxative effect.

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 side effects. An interval of approximately one week should be allowed after stopping treatment with **FLOLOC CHEWS,** before commencing other

anticholinergic therapy. The therapeutic effect of **FLOLOC CHEWS** may be reduced by concomitant administration of cholinergic receptor agonists.

FLOLOC CHEWS 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, **FLOLOC CHEWS** is unlikely to alter the clearance of medicines metabolised by these CYP enzymes.

Effects 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.

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 **FLOLOC CHEWS** should be restricted to 5 mg, when used with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors. Simultaneous treatment of **FLOLOC CHEWS** and strong CYP3A4 inhibitors is contra-indicated in patients with severe renal impairment or moderate hepatic impairment (see section 4.3).

Effects 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), both CYP3A4 substrates.

Warfarin:

Intake of solifenacin did not alter the pharmacokinetics of *R*-warfarin (substrate for CYP3A4) or *S*-warfarin (substrate for CYP2C9) on their effect on the INR.

Digoxin:

Intake of solifenacin showed no effects on the pharmacokinetics of digoxin.

4.6 Fertility, pregnancy and lactation

Pregnancy:

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

Breastfeeding:

Solifenacin is excreted into breastmilk. Women taking **FLOLOC CHEWS** should not breastfeed their infants.

4.7 Effects on ability to drive and use machines:

Since **FLOLOC CHEWS**, may cause blurred vision, somnolence and fatigue (see section 4.8), the ability to drive and use machinery may be negatively affected.

4.8 Undesirable effects:

Summary of safety profile

Due to the pharmacological effect of solifenacin. FLOLOC CHEWS may cause anticholinergic side effects of mild to moderate severity in general. The frequency of anticholinergic side effects is dose related. The most frequently reported adverse reaction was dry mouth. The severity of dry mouth was generally mild

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.

Eye disorders:

Frequent: Blurred vision.

Less frequent: Dry eyes.

Frequency unknown: Glaucoma.

Cardiac disorders:

Frequency unknown: Torsades de Pointes, electrocardiogram QT prolonged, atrial fibrillation, palpitations, tachycardia,

Respiratory, thoracic and mediastinal disorders:

Less frequent: Nasal dryness.

Frequency unknown: Dysphonia.

Gastro-intestinal disorders:

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

Less frequent: Gastro-oesophageal reflux diseases, dry throat, colonic obstruction, faecal impaction, vomiting.

Frequency unknown: Ileus, abdominal discomfort.

Hepatobiliary disorders:

Frequency unknown: Liver disorder, liver function test abnormal.

Skin and subcutaneous tissue disorders:

Less frequent: Dry skin, pruritis, rash, erythema multiforme, urticaria, angiodema.

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. Healthcare professionals 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 and signs:

Overdose with **FLOLOC CHEWS** can potentially result in severe anticholinergic effects. After receiving a single dose of 100 mg Solifenacin succinate, the most frequent adverse events were headache, dry mouth, dizziness, drowsiness and blurred vision.

Treatment:

In the event of overdosage with **FLOLOC CHEWS** 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 disease (i.e. myocardial ischemia, dysrhythmia, congestive heart failure).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 5.4 Cholinolytics (anticholinergics)

Pharmacotherapeutic group: Urinary antispasmodics ATC code: G04B D08

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 M3 subtype

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

5.2 Pharmacokinetics properties:

Absorption:

Following 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 to a great extent (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 (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 single administration of 10 mg [^{14}C-labelled] solifenacin, about 70 %of the radioactivity was detected in the urine and 23 % in the 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.

Other special populations:

Elderly:

No dose 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 and adolescents.

Gender:

The pharmacokinetics of solifenacin is not influenced by gender.

Race:

The pharmacokinetics of solifenacin is not influenced by race.

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 $t_{1/2}$ of more than 60 %. A statistically significant relationship was observed between creatinine clearance and solifenacin succinate 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 $t_{1/2}$ doubled. Pharmacokinetics of solifenacin in patients with severe hepatic impairment have not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Croscarmellose sodium
- Lactose monohydrate
- Magnesium stearate
- Maize starch (partially pregelatinised)
- Mannitol
- Microcrystalline cellulose
- Purified water
- Strawberry vanilla flavour

- Sucralose

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

The shelf life of **FLOLOC CHEWS** is 36 months.

6.4 Special precautions for storage:

This medicine does not require any special storage conditions.

Do not store above 30 °C.

6.5 Nature and contents of container:

FLOLOC CHEWS 5 mg and 10 mg chewable tablets are packed in Aluminium / Aluminium blisters. The blisters are subsequently packed into cardboard boxes.

6.6 Special precautions for disposal:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du cap

Mispel street

Belville

7350

RSA

8. REGISTRATION NUMBER:

FLOLOC CHEWS 5: 53/5.4/0052

FLOLOC CHEWS 10: 53/5.4/0053

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

28 June 2022