SUMMARY OF PRODUCT CHARACTERISTICS

VESIZEN TABLETS 5MG
(Solifenacin Succinate Tablets 5mg)

1. NAME OF THE MEDICINAL PRODUCT

Vesizen Tablets 5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Solifenacin succinate……5 mg

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

3. PHARMACEUTICAL FORM

Film-coated Tablets

4 CLINICAL PARTICULARS[1]

4.1 Therapeutic indications

Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

4.2 Posology and method of administration

Adults, including the elderly
The recommended dose is 5 mg solifenacin succinate once daily. If needed, the dose may be increased to 10 mg solifenacin once daily.

Paediatric population
The safety and efficacy of solifenacin in children have not yet been reportedly established. Therefore, solifenacin should not be used in children.

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 no 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 no more than 5 mg once daily.

Potent inhibitors of cytochrome P450 3A4
The maximum dose of solifenacin should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4-inhibitors e.g. ritonavir, nelfinavir, itraconazole (see **section 4.5**).

Method of administration
VESIZEN tablets should be taken orally and should be swallowed whole with liquids. It can be taken with or without food.

4.3 Contraindications

VESIZEN tablets is contraindicated in patients with urinary retention, severe gastro-intestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions.

- Patients hypersensitive to the active substance or to any of the excipients (listed in **section 6.1**)
- Patients undergoing haemodialysis (see **section 5.2)**
- Patients with severe hepatic impairment (see **section 5.2**)
- Patients with severe renal impairment or moderate hepatic impairment and who are on treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole (see **section 4.5**)

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

Solifenacin should be used with caution in patients with:

- Clinically significant 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 **section 4.2** and **4.5).**
- Hiatus hernia/gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.
- Autonomic neuropathy.

QT prolongation and Torsade de Pointes have been reported in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia.

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

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

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

The maximum effect of solifenacin succinate can be determined after 4 weeks at the earliest.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant medication with other medicinal products 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, before commencing other anticholinergic therapy. The therapeutic effect of solifenacin may be reduced by concomitant administration of cholinergic receptor agonists.

Solifenacin can reduce the effect of medicinal products that stimulate the motility of the gastro-intestinal tract, such as metoclopramide and cisapride.

Reported *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 is unlikely to alter the clearance of drugs metabolised by these CYP enzymes.

Effect of other medicinal products on the pharmacokinetics of solifenacin

Solifenacin is metabolised by CYP3A4. Simultaneous administration of ketoconazole (200 mg/day), a potent CYP3A4 inhibitor, reportedly 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 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 and a potent CYP3A4 inhibitor is contra-indicated in patients with severe renal impairment or moderate hepatic impairment.

The effects of enzyme induction on the pharmacokinetics of solifenacin and its metabolites have not been reported 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 medicinal products

Oral Contraceptives
Intake of solifenacin reported no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel).

Warfarin
Intake of solifenacin reportedly did not alter the pharmacokinetics of R-warfarin or S-warfarin or their effect on prothrombin time.

Digoxin
Intake of solifenacin reported no effect on the pharmacokinetics of digoxin.

4.6 Fertility, Pregnancy and lactation

Pregnancy
No clinical data are reported from women who became pregnant while taking solifenacin. Reported animal studies do not indicate direct harmful effects on fertility, embryonal/foetal development or parturition (see **section 5.3**). The potential risk for humans is reportedly unknown. Caution should be exercised when prescribing to pregnant women.

Lactation

No data are reported on the excretion of solifenacin in human milk. In a reported animal study in mice, solifenacin and/or its metabolites was excreted in milk, and caused a dose dependent failure to thrive in neonatal mice (see **section 5.3**). The use of solifenacin should therefore be avoided during breast-feeding.

4.7 Effects on ability to drive and use machines

Since solifenacin, like other anticholinergics may cause blurred vision, and, uncommonly, somnolence and fatigue (see **section 4.8**), the ability to drive and use machines may be negatively affected.

4.8 Undesirable effects

Summary of the safety profile

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

The most commonly reported adverse reaction with solifenacin was dry mouth. It was reported 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 reported to be generally mild and did only occasionally lead to discontinuation of treatment. In general, medicinal product compliance was reported to be very high (approximately 99%) and approximately 90% of the patients treated with solifenacin have been reported to complete full study period of 12 weeks treatment.

Tabulated list of adverse reactions

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100, <1/10**	**Uncommon ≥1/1000, <1/100**	**Rare ≥ 1/10000, <1/1000**	**Very rare <1/10,000**	**Not known (cannot be estimated from the available data)**
Infections and infestations			Urinary tract infection Cystitis			
Immune system disorders						Anaphylactic reaction*
Metabolism and nutrition disorders						Decreased appetite* Hyperkalaemia*
Psychiatric disorders					Hallucinations*	Delirium*

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100, <1/10**	**Uncommon ≥1/1000, <1/100**	**Rare ≥ 1/10000, <1/1000**	**Very rare <1/10,000**	**Not known (cannot be estimated from the available data)**
					Confusional state*	
Nervous system disorders			Somnolence Dysgeusia	Dizziness*, Headache*		
Eye disorders		Blurred vision	Dry eyes			Glaucoma*
Cardiac disorders						Torsade de Pointes* Electrocardiogram QT prolonged* Atrial fibrillation* Palpitations* Tachycardia*
Respiratory, thoracic and mediastinal disorders			Nasal dryness			Dysphonia*
Gastrointestinal disorders	Dry mouth	Constipation Nausea Dyspepsia Abdominal pain	Gastro-oesophageal reflux diseases Dry throat	Colonic obstruction Faecal impaction, Vomiting*		Ileus* Abdominal discomfort*
Hepatobiliary disorders						Liver disorder* Liver function test abnormal*
Skin and subcutaneous tissue disorders			Dry skin	Pruritus*, Rash*	Erythema multiforme*, Urticaria*, Angioedema*	Exfoliative dermatitis*
Musculoskeletal and connective tissue disorders						Muscular weakness*
Renal and urinary disorders			Difficulty in micturition	Urinary retention		Renal impairment*
General disorders			Fatigue Peripheral			

MedDRA system organ class	Very common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1000, <1/100	Rare ≥ 1/10000, <1/1000	Very rare <1/10,000	Not known (cannot be estimated from the available data)
and administration site conditions			oedema			

*observed post-marketing

4.9 Overdose

Symptoms

Overdosage with solifenacin can potentially result in severe anticholinergic effects. The highest dose of solifenacin succinate accidentally given to a single patient has been reported to be 280 mg in a 5 hour period, resulting in mental status changes not requiring hospitalization.

Treatment

In the event of overdose with solifenacin succinate the patient should be treated with activated charcoal. Gastric lavage is useful if performed within 1 hour, but vomiting should not be induced.

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.

As with other antimuscarinics, in case of overdosing, 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[1]

5.1 Pharmacodynamic properties

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. Reported *in vitro* and *in vivo* pharmacological studies indicate that solifenacin is a competitive inhibitor of the muscarinic M3 subtype receptor. In addition, solifenacin is reported to be a specific antagonist for muscarinic receptors by displaying low or no affinity for various other receptors and ion channels tested.

5.2 Pharmacokinetics properties

Absorption
After intake of solifenacin tablets, maximum solifenacin plasma concentrations (C_{max}) is reported to reach after 3 to 8 hours. The t_{max} is independent of the dose. The C_{max} and area under the curve (AUC) has been reported to increase in proportion to the dose between 5 to 40 mg. Absolute bioavailability is reported to be 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 - 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 reportedly 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.

Other special populations

Elderly
No dosage adjustment based on patient age is required. Reported 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 reported in children and adolescents.

Gender
The pharmacokinetics of solifenacin are not influenced by gender.

Race
The pharmacokinetics of solifenacin are 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 reported in healthy volunteers. In patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) exposure to solifenacin was reported to be 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 reported between creatinine clearance and solifenacin clearance.

Pharmacokinetics in patients undergoing haemodialysis have not been reported.

Hepatic impairment
In patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) the C_{max} is not affected, AUC reportedly increased with 60% and $t_{½}$ doubled. Pharmacokinetics of solifenacin in patients with severe hepatic impairment have not been reported.

5.3 Preclinical safety data

Reported preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility, embryofetal development, genotoxicity, and carcinogenic potential. In the reported pre- and postnatal development study in mice, solifenacin treatment of the mother during lactation caused dose-dependent lower postpartum survival rate, decreased pup weight and slower physical development at clinically relevant levels. Dose related increased mortality without preceding clinical signs reported in juvenile mice treated from day 10 or 21 after birth with doses that achieved a pharmacological effect and both groups had higher mortality compared to adult mice. In another reported study, juvenile mice treated from postnatal day 10, plasma exposure was higher than in adult mice; from postnatal day 21 onwards, the systemic exposure was comparable to adult mice. The clinical implications of the increased mortality in juvenile mice are not known.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous lactose, Hypromellose, Corn starch, Magnesium stearate, Ferric oxide (Yellow), and Opadry white YS-1-7040.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C.
Keep all medicines out of the reach of children.

6.5 Nature and contents of container

PVC/PVdC blister pack of 3x10's tablets

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Sun Pharmaceuticals Industries Limited

8. MARKETING AUTHORISATION NUMBER(S)

B4-8259

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

March 2022

REFERENCES

1. Summary of Product Characteristics of Vesicare 5 mg and 10 mg film coated tablets, Astellas Pharma Ltd., UK, November 2019.

Information compiled in March 2022