Vesicare® 5 mg
Vesicare® 10 mg

1. TRADE NAME OF THE MEDICINAL PRODUCT

Vesicare

2. QUALITATIVE AND QUANTITATIVE COMPOSITION OF ACTIVE SUBSTANCE

Active ingredient : solifenacin succinate

Each tablet contains 5 or 10 mg of solifenacin succinate formulated for oral administration.

3. PHARMACEUTICAL FORM

Film-coated tablets:

5 mg (color: light yellow, debossed: company logo, 150) and 10 mg (color: light pink, debossed:company logo, 151)

4. CLINICAL PARTICULARS

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

Posology

Adults, including the elderly

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

Children and adolescents

Safety and effectiveness in children have not yet been established.

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 (see Section 5.2).

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 (see Section 5.2) .

Potent inhibitors of cytochrome P450 3A4

The maximum dose of Vesicare 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

Vesicare should be taken orally and should be swallowed whole with liquids. It can be taken with or without food.

4.3 Contra-indications

Solifenacin succinate 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.
- 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 special precautions for use

Vesicare should be used with caution in patients with:

- ***Risk of Urinary Retention:***
  Solifenacin succinate should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention
- ***Gastrointestinal obstructive disorders and decreased gastrointestinal motility (including risk of gastric retention):***
  Solifenacin succinate should be administered with caution to patients with gastrointestinal obstructive disorders and decreased gastrointestinal motility
- ***QT prolongation and Torsade de Pointes:***
  QT prolongation and Torsade de Pointes have been observed in patients with risk factors,
  such as pre-existing long QT syndrome and hypokalaemia.
- ***Anaphylactic Reaction:***
  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.
- ***Renal Impairment:***
  Solifenacin succinate should be used with caution in patients with reduced renal function. Doses of solifenacin succinate greater than 5 mg are not recommended in patients with severe renal impairment. (see section 4.2)
- ***Hepatic Impairment:***
  Solifenacin succinate should be used with caution in patients with reduced hepatic function. Doses of solifenacin succinate greater than 5 mg are not recommended in patients with moderate hepatic impairment. (see section 4.2)
- ***Pediatric Use:***
  The safety and effectiveness of solifenacin succinate in pediatric patients have not been established.
- Concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole (see 4.2 and 4.5).
- Hiatus hernia/gastro-oesophagal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.
- Autonomic neuropathy.

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacological interactions

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 Vesicare, 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.

Pharmacokinetic interactions

Drugs Metabolized by Cytochrome P450:

In vitro studies have demonstrated that at clinically-relevant concentrations, solifenacin and its metabolites (*N*-glucuronide, *N*-oxide and 4*R*-hydroxy-*N*-oxide of solifenacin, 4*R*-hydroxy solifenacin) do not inhibit human CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 activity. Therefore, solifenacin succinate may be co-administered with drugs that undergo CYP mediated metabolism.

Effect of other medicinal products on the pharmacokinetics of solifenacin

CYP3A4 Inhibitors:

In vitro drug metabolism studies have shown that solifenacin is a substrate of CYP3A4. Inducers or inhibitors of CYP3A4 could potentially alter solifenacin pharmacokinetics.

Following the administration of 10 mg of solifenacin succinate in the presence of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, the mean Cmax and AUC of solifenacin increased by 1.5 and 2.7 fold, respectively. Therefore, the recommended dose of solifenacin succinate can be given, when administrated with the therapeutic doses of CYP 3A4 inhibitors such as ketoconazole up to 400 mg daily or other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole).

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 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, carbamazepin).

Effect of solifenacin on the pharmacokinetics of other medicinal products

Oral Contraceptives:

In the presence of solifenacin succinate, there were no changes in the plasma concentrations of combined oral contraceptives (ethinyl estradiol/levonorgestrel, both CYP3A4 substrates).

Warfarin:

Solifenacin succinate had no effect on the pharmacokinetics of *R*-warfarin (substrate for CYP3A4) or *S*-warfarin (substrate for CYP2C9) or their effect on prothrombin time.

Digoxin:
Solifenacin succinate had no effect on the pharmacokinetics of digoxin (0.125 mg /day) in healthy subjects.

4.6 Use during pregnancy and lactation

PREGNANCY
There are no adequate data from the use of solifenacin succinate in pregnant women.

LACTATION
Solifenacin succinate should not be administered during nursing.

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. undesirable effects), the ability to drive and use machines may be negatively affected.

4.8 Undesirable effects

Due to the pharmacological effect of solifenacin, Vesicare 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 Vesicare 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 and did only occasionally lead to discontinuation of treatment. In general, medicinal product compliance was very high (approximately 99%) and approximately 90% of the patients treated with Vesicare completed the full study period of 12 weeks treatment

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			
Psychiatric disorders					Hallucinations* Confusional state*	Delirium*
Nervous system disorders			Somnolence Dysgeusia	Dizziness* Headache*		
Cardiac disorders						Atrial fibrillation* Palpitations* Tachycardia* Torsade de Pointes*
Eye disorders		Blurred vision	Dry eyes			Glaucoma*
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*
Skin and subcutaneous tissue disorders			Dry skin	Pruritus* Rash*	Erythema multiforme* , Urticaria* Angioedema*	Exfoliative dermatitis*
Renal and urinary disorders			Difficulty in micturition	Urinary retention		Renal impairment*
General disorders and administration site conditions			Fatigue Peripheral oedema			
Hepatobiliary disorders						Liver disorders, mostly characterized by abnormal liver function tests (AST, ALT, GGT)*
Immune system disorders						Anaphylactic reaction*
Investigations						Electrocardiogram QT prolonged*
Metabolism and nutrition disorders						Decreased appetite* Hyperkalaemia*
Musculoskeletal and connective tissue disorders						Muscular weakness*

*observed post-marketing

4.9 Overdose

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

Treatment of Overdosage:

In the event of an overdose with solifenacin succinate, treat with gastric lavage and activated charcoal. Anticholinergic effects should be treated accordingly.

- 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 catheterization.
- Mydriasis : treat with pilocarpine eye drops and/or place patient in dark room.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action:

Solifenacin is a competitive muscarinic M_3 receptor antagonist with selectivity for the urinary bladder over salivary glands *in vivo*. Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of urinary bladder smooth muscle and stimulation of salivary secretion

Pharmacodynamic effects:

Treatment with solifenacin succinate in doses of 5 mg and 10 mg daily was studied in several double blind, randomized, controlled clinical trials in men and women with overactive bladder.

Results (pooled data) of four controlled Phase 3 studies with a treatment duration of 12 weeks

	Placebo	**SOLIFENACIN SUCCINATE 5 mg o.d.**	**SOLIFENACIN SUCCINATE 10 mg o.d.**
No. of micturitions/24 h			
Mean reduction from baseline	1.4	2.3	2.7
% change from baseline	(12%)	(19%)	(23%)
n	1138	552	1158
p-value*		<0.001	<0.001
No. of urgency episodes/24 h			
Mean reduction from baseline	2.0	2.9	3.4
% change from baseline	(325%)	(49%)	(55%)
n	1124	548	1151
p-value*		<0.001	<0.001
No. of incontinence episodes/24 h			
Mean reduction from baseline	1.1	1.5	1.8
% change baseline	(38%)	(58%)	(62%)
n	781	314	778
p-value*		<0.001	<0.001
No. of nocturia episodes/24 h			
Mean reduction from baseline	0.4	0.6	0.6
% change from baseline	(22%)	(30%)	(33%)
n	1005	494	1035
p-value*		0.025	<0.001
Volume voided/micturition			
Mean increase from baseline	9 ml	32 ml	43 ml
% change from baseline	(5%)	(21%)	(26%)
n	1135	552	1156
p-value*		<0.001	<0.001
No. of pads/24 h			
Mean reduction from baseline	0.8	1.3	1.3
% change from baseline	(27%)	(46%)	(48%)
n	238	236	242
p-value*		<0.001	<0.001

Note: Not all parameters and treatment groups were evaluated in each individual study. Therefore, the numbers of patients listed may deviate per parameter and treatment group.

* P-value for the pairwise comparison to placebo

Both the 5 mg and 10 mg doses of solifenacin succinate produced statistically significant improvements in the primary and secondary endpoints compared with placebo. After 12 weeks of treatment approximately 50% of patients suffering from incontinence before treatment were free of incontinence episodes, and in addition 35% of patients achieved a micturition frequency of less than 8 micturitions per day.

Effect on QT interval

A placebo-controlled, double-blind study was conducted in 86 healthy adult women to evaluate the effect on QT interval after repeated administration of solifenacin

succinate. In the steady state following administration of solifenacin succinate at a dose of 10 mg, the change in QT interval was similar to that in the placebo group. At a dose of 30 mg, the change in QT interval compared to placebo was 6 msec.

Change in QT interval from Baseline in the Steady State (difference from placebo group)

Compound	QTc (msec)	90% confidence	
		Lower limit	Upper limit
Solifenacin succinate 10 mg/day	0	-5	5
Solifenacin succinate 30 mg/day [1)]	6	1	11
Moxifloxacin [2)] 400 mg/day	10	6	13

[1)] Three times the maximum recommended therapeutic dose corresponding to the plasma concentration following administration of solifenacin succinate at a dose of 10 mg with potent CYP3A4 inhibitors

[2)] Positive control to verify the sensitivity of the study

Postmarketing pharmacovigilance data confirmed QT prolongation associated with therapeutic doses of solifenacin succinate in cases with known risk factors (see also sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption:

After oral administration of solifenacin succinate to healthy volunteers, peak plasma Levels (C_{max}) of solifenacin were reached within 3 to 8 hours after administration and

at steady state ranged from 32.3 to 62.9 ng/mL for the 5 and 10 mg solifenacin succinate tablets, respectively. The absolute bioavailability of solifenacin is approximately 90%, and plasma concentrations of solifenacin are proportional to the dose administered.

Distribution:

Solifenacin is approximately 98% *(in vivo*) bound to human plasma proteins, principally to α_1- acid glycoproteins. Solifenacin is highly distributed to tissues having a mean steady-state volume of distribution of 600 L.

Metabolism:

Solifenacin is extensively metabolized in the liver. The primarily pathway for Elimination is by way of CYP3A4, however, alternate metabolic pathways exist.

The systemic clearance of solifenacin is 9.39 L/h and the terminal half-life of solifenacin is 45-68 hours.

After oral dosing, one pharmacologically active (4*R*-hydroxy solifenacin) and three inactive metabolite (*N*-glucuronide, *N*-oxide and 4*R*-hydroxy-*N*-oxide of solifenacin) have been identified in plasma in addition to solifenacin.

Excretion:

Following the administration of 10 mg of ^{14}C-solifenacin succinate to healthy volunteers, 69.2 % of the radioactivity was recovered in the urine and 22.5 % in the feces over 26 days. Less than 15% (as mean value) of the dose was recovered in the urine as intact solifenacin. The major metabolites identified in urine were *N*-oxide of solifenacin, 4*R*-hydroxy solifenacin and 4*R*-hydroxy-*N*-oxide of solifenacin and in feces 4*R*-hydroxy solifenacin.

Age:

No dosage adjustment based on patient age is required. Multiple dose studies of

solifenacin succinate in elderly volunteers (65 to 80 years) and population pharmacokinetics in patients enrolled in randomized, placebo-controlled double blind studies of solifenacin succinate indicate that there is no clinically significant change in the pharmacokinetics of solifenacin with age. In placebo- controlled clinical studies, no overall differences were observed in the safety of solifenacin between older and younger patients treated for 4 to 12 weeks with 5 to 10 mg of solifenacin succinate.

Gender:

The pharmacokinetics of solifenacin is not influenced by gender.

Effect of food:

There is no clinically significant effect of food on the pharmacokinetics of solifenacin succinate

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 $\leq$ 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 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 $t_{½}$ doubled. Pharmacokinetics of solifenacin in patients with severe hepatic impairment have not been studied.

5.3 Pre-clinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

Juvenile mice treated from 10 days after birth revealed higher exposures and more severe toxicity than adult mice.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate, Corn starch (Maize starch), Hypromellose, Magnesium stearate, Talc, polyethylene glycol (Macrogol) 8000, Titanium dioxide, Yellow ferric oxide (Vesicare® 5 mg), Red ferric oxide (Vesicare® 10 mg)

6.2 Incompatibility

Not applicable

6.3 Shelf life

The expiry date is indicated on the packaging.

6.4 Special precautions for storage

Store below 30ºC

6.5 Nature and contents of container

Container : The tablets are packed in PVC / Aluminium blisters
Pack sizes : 30 tablets

6.6 Instructions for use and handling

No special requirements

Manufactured by:
Delpharm Meppel B.V.
Meppel, The Netherlands

Imported by :
Astellas Pharma (Thailand) Co.,Ltd
Bangkok, Thailand

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