NAME OF THE MEDICINAL PRODUCT

Vesicare® 5 mg Tablet
Vesicare® 10 mg Tablet

QUALITATIVE AND QUANTITATIVE COMPOSITION OF ACTIVE SUBSTANCE
Active ingredients : solifenacin succinate
Vesicare® 5 mg Tablet : each tablet contains 5 mg of solifenacin succinate formulated for oral administration.
Vesicare® 10 mg Tablet : each tablet contains 10 mg of solifenacin succinate formulated for oral administration.

PHARMACEUTICAL FORM
Film coated tablets:
Each 5 mg tablet is light-yellow tablet marked with company logo, and "150"
Each 10 mg tablet is light-pink tablet marked with company logo, and "151"

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

CONTRA-INDICATIONS
Solifenacin succinate is contraindicated in

- patients with urinary retention, severe gastrointestinal condition (including toxic magecolon), 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
- patients with severe hepatic impairment
- patients with severe renal impairment or moderate hepatic impairment nad who are on treatment with a potent CYP3A4 inhibitor,e.g.ketoconazole

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

- **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.

- **Renal impairment:**
  Solifenacin succinate should be used with caution in patients with reduced renal function. Doses of solifenacine succinate greater than 5 mg are not recommended in patients with severe renal impairment.
- **Hepatic Impairment:**
  Solifenacin succinate should be used with caution in patients with reduced hepatic function. Doses of solifenacine succinate greater than 5 mg are not recommended in patients with moderate hepatic impairment.
- **Pediatric Use:**
  The safety and effectiveness of solifenacin succinate in pediatric patients have not been established.
- Solifenacin succinate should be administered with caution to patients with concomitant use of a potent CYP3A4 inhibitor,e.g.ketoconazole.
- Solifenacin succinate should be administered with caution to patients hiatus hernia/gastrooesophageal reflux and/or who are concurrently taking medicinal products such as bisphosphonates) that can cause or exacerbate oesophagitis.
- Solifenacin succinate should be administered with caution to patients autonomic neuropathy.

Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor over activity.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
The maximum effect of Vesicare can be determined after 4 weeks at the earliest.

POSOLOGY AND METHOD OF ADMINISTRATION

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. Therefore, Vesicare 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 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 no more than 5 mg once daily.

Potent inhibitors of Cytochrome P450 3A4 (CYP3A4)
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.

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 Vesicare before commencing other anticholinergic therapy. The therapeutic effect of solifenacin may be reduced by concomitant administration of cholinergic receptor antagonists. Solifenacin can reduce the effect of medicinal products that stimulate the motility of the gastrointestinal tract, such as metoclopramide and cisapride.
Drugs Metabolized by Cytochrome P450:
In vitro studies have demosntrated that at clinically-relevant concentrations, solifenacin did not inhibit human CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 activity. Therefore, solifenacin succinate is unlikely to alter the clearance of drugs metabolized by these CYP enzymes.

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.
Simultaneous administration of ketoconazole (200 mg/day), a potent CYP3A4 inhibitor, 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 Vesicare should be restricted to 5 mg when used simultaneous with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole).
Simultaneous treatment of solifenacin and a potent CYP3A4 inhibitor is contraindicated in patients with severe renal impairment or moderate hepatic impairment.
The effect 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 metabolized 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).

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 did not alter 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.

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.
No data on the excretion of solifenacin in human milk are available. In mice, solifenacin and/or its metabolites was excreted in milk, and caused a dose dependent failure to thrive in neonatal mice.
EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Patients should be informed that antimuscarinic agents such as solifenacin succinate might produce blurred vision. Since solifenacin, like other anticholinergics may cause blurred vision, and, uncommonly, somnolence and fatigue, the ability to drive and use machines may be negatively affected.

UNDESIRABLE EFFECTS
Due to the pharmacological effect of solifenacin, Vesicare may cause anticholinergic undesirable effect of (in general) mild or moderate severity. The frequency of anticholinergic undesirable effect 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 only occasionally led 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.
These data obtained with Vesicare in clinical trials:
Gastrointestinal disorders:
Very common: Dry mouth
Common: Constipation, Nausea, Dyspepsia, Abdominal pain
Uncommon : Gastrooesophageal reflux diseases, Dry throat
Rare : Colonic abstruction, Faecal impaction
Infections and infestations:
Uncommon: Urinary tract infection, Cystitis
Nervous system disorders:
Uncommon: Somnolence, Dysgeusia
Eye disorders:
Common: Blurred vision
Uncommon: Dry eyes
General disorders and administration site conditions:
Uncommon: Fatigue, **Oedema peripheral**
Respiratory, thoracic and mediastinal disordes:
Uncommon: Nasal dryness
Skin and subcutaneous tissue disorders:
Uncommon: Dry skin
Renal and urinary disorders:
Uncommon: Difficulty in micturition
Rare: Urinary retention
Allergic reactions were not observed during the clinical development. However, the occurrence of allergic reactions can never be excluded.
Post Approval Report
Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events cannot be estimated from the available data.
Gastrointestinal disorders: Vomiting
Nervous system disorders: Dizziness, Headache
Psychiatric disorders: Hallucination
Skin and subcutaneous tissue disorders: Pruritus, Rash, Urticaria

OVERDOSE

Over dosage 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.

As for other anticholinergic, symptom can be treated as follows:

- Severe central antocholinergic effects such as hallucination 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 a 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.hypokalemia, bradycardia and concurrent administration of medicinal products known to prolong QT-interval) and relevant pre-existing cardiac diseases (i.e.myocardial ischemia, arrhytmia, congestive heart failure).

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of action:

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

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.

Result (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 % change from baseline n p-value*	1.4 (12%) 1138	2.3 (19%) 552 <0.001	2.7 (23%) 1158 <0.001
No. of urgency episodes/24 h			
Mean reduction from baseline % change from baseline n p-value*	2.0 (32%) 1124	2.9 (49%) 548 <0.001	3.4 (55%) 151 <0.001
No. of incontinence episodes/24 h			
Mean reduction from baseline % change from baseline n p-value*	1.1 (38%) 781	1.5 (58%) 314 <0.001	1.8 (62%) 778 <0.001
No. of nocturia episodes/24 h			
Mean reduction from baseline % change from baseline n p-value*	0.4 (22%) 1005	0.6 (30%) 494 0.025	0.6 (33%) 1035 <0.001
Volume voided/micturition			
Mean increase from baseline % change from baseline n p-value*	9 ml (5%) 1135	32 ml (21%) 552 <0.001	43 ml (26%) 1156 <0.001
No. of pads/24 h			

Mean reduction from baseline % change from baseline n p-value*	0.8 (27%) 238	1.3 (46%) 236 <0.001	1.3 (48%) 242 <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 gtreatment approximately 50% of patients suffering from incontinence before treatment were free of incontinence episodes, and in addition 35% of patients achived 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 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	OTc (msec)	90% confidence interval	
		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

Pharmacokinetic properties

Absorption:
After oral administration of solifenacin succinate to healthy volunteers, peak plasma levels (Cmax) of solifenacin were reached within 3 to 8 hours after administration and at steady state range 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 glycoprotein. Solifenacin is highly distributed to trissues having a mean steady-state volume of distribution of 600 L.

Metabolism:
Solifenacin is extensively metabolized in the liver. The primary pathway for elimination is by way of CYP3A4, however, alternate metabolic pathways exist. The systemic clearance of solifenacin is 9.39 L/h and terminal half-life of solifenacin is 45-68 hours.
After oral dosing, one pharmacologically active (4*R*-hydroxy solifenacin) and three inactive metabolites (*N*-glucoronide, *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 4R-hydroxy solifenacin and 4R-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 were not significantly different from that found in healthy volunteers. In patients with severe renall impairment (creatinine clearance ≤30ml/min), exposure to solifenacin was significantly greater than in 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 clearance. Pharmacokinetics in patients undergoing haemodialysis has not been

studied.

Hepatic impairment
In patient with moderate hepatic impairment (Child-Pugh score of 7 to 9) the C_{max} is not affected, AUC increased by 60% and $t_{1/2}$ doubled. Pharmacokinetics of solifenacin in patients with severe hepatic impairment has not been studied.

Pre-clinical safety data
Preclinical data reveal no special hazard for human based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.
In the 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.

Packaging

Vesicare® 5 mg Tablet:
Box of 3 x 10 Tablets

Vesicare ® 10 mg Tablet:
Box of 3 x 10 Tablets

Store below 30°C

"Harus dengan resep dokter"

Reg.No
Vesicare® 5mg Tablet
Vesicare® 10 mg Tablet

Manufactured by:
Astellas Pharma Europe B.V.,The Netherlands

Imported by:
P.T.Astellas Pharma Indonesia, Jakarta