SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vesicare 1 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vesicare oral suspension contains 1 mg/ml solifenacin succinate, equivalent to 0.75 mg/ml solifenacin.

Excipients with known effect:
Benzoic acid (E210) 0.015 mg/ml.
Methyl parahydroxybenzoate (E218) 1.6 mg/ml.
Propylene glycol (E1520) 20mg/ml.
Propyl parahydroxybenzoate (E216) 0.2 mg/ml.
This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per maximum daily dose (10 ml Vesicare oral suspension). Ethanol originates from the natural orange flavour.

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Oral suspension

A white to off-white coloured aqueous, homogeneous suspension with an orange flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Overactive bladder in adults
Vesicare oral suspension is indicated for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder (OAB) syndrome.

Neurogenic detrusor overactivity
Vesicare oral suspension is indicated for treatment of neurogenic detrusor overactivity (NDO) in paediatric patients aged 2 to 18 years.

4.2 Posology and method of administration

Posology

Overactive bladder

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

Paediatric population:
The efficacy of Vesicare in children and adolescents with overactive bladder has not been established. Therefore, Vesicare should not be used for treatment of overactive bladder in children and adolescents under 18 years of age. Currently available data are described in Section 5.1 and 5.2.

Neurogenic detrusor overactivity

Paediatric population (age 2 to 18 years):
The recommended dose of Vesicare oral suspension is determined based on patient weight. Treatment should be initiated at the recommended starting dose. Thereafter, the dose may be increased to the lowest effective dose. The maximum dose should not be exceeded. During long-term therapy, patients should be periodically evaluated for treatment continuation and for potential dose adjustment, at least annually or more frequently if indicated. The doses according to the patient's body weight are found in the table below.

Weight range (kg)	Starting dose (ml) §[1]	Maximum dose (ml) §[2]
9 to 15	2	4
>15 to 30	3	5
>30 to 45	3	6
>45 to 60	4	8
>60	5	10

§ The oral suspension formulation of Vesicare has a concentration of 1 mg/ml.
[1] Equivalent to steady-state exposure after a 5 mg daily dose in adults
[2] Equivalent to steady-state exposure after a 10 mg daily dose in adults

Vesicare oral suspension should be taken once daily by mouth.

Vesicare oral suspension should not be used in children below age of 2 years.

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 (5 ml) once daily (adults) and no more than the starting dose (children and adolescents) (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 no more than 5 mg (5 ml) once daily (adults) and no more than the starting dose (children and adolescents) (see Section 5.2).

Potent inhibitors of cytochrome P450 3A4
The maximum dose of Vesicare oral suspension should be limited to 5 mg (5 ml) (adults) and no more than the starting dose (children and adolescents) 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 oral suspension should be taken orally followed by a glass of water. It should not be ingested together with food and/or other drinks. This ingestion with food and/or drinks may cause a release of solifenacin in the mouth resulting in a bitter taste and a feeling of numbness in the mouth.
An appropriate oral syringe and adaptor should be selected to measure the correct dose (see Section 6.6).

4.3 Contraindications

When used for treatment of overactive bladder solifenacin is contraindicated in patients with urinary retention.

When used for treatment of overactive bladder or neurogenic detrusor overactivity solifenacin is contraindicated in

- Patients with 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 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 in the absence of clean intermittent catheterization because of the risk of urinary retention.
- gastrointestinal obstructive disorders.
- risk of decreased gastrointestinal motility.
- severe renal impairment (creatinine clearance $\leq$ 30 ml/min), and doses should not exceed 5 mg (5 ml) in adults or the starting dose in children and adolescents for these patients (see Section 4.2 and 5.2).
- moderate hepatic impairment (Child-Pugh score of 7 to 9), and doses should not exceed 5 mg (5 ml) in adults or the starting dose in children and adolescents for these patients (see Section 4.2 and 5.2).
- concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole, and doses should not exceed 5 mg (5 ml) in adults or the starting dose in children and adolescents for these patients (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 observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia.

Angioedema with airway obstruction has been reported in some patients on solifenacin. If angioedema occurs, solifenacin 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, solifenacin 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.

Vesicare oral suspension contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. This may cause allergic reactions (possibly delayed).

Vesicare oral suspension contains small amounts of ethanol (alcohol), less than 100 mg per maximum daily dose (10 ml Vesicare oral suspension).

Vesicare Oral Suspension contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

Vesicare Oral Suspension contains 0.015 mg benzoic acid in each ml which is equivalent to 0.15 mg/10 ml.

Vesicare Oral Suspension contains 20 mg propylene glycol in each ml which is equivalent to 200 mg/10 ml.

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 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.

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, 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, 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 (5 ml) for adults or the starting dose for children and adolescents, 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 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
Intake of solifenacin showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel).
Warfarin
Intake of solifenacin did not alter the pharmacokinetics of *R*-warfarin or *S*-warfarin or their effect on prothrombin time.
Digoxin
Intake of solifenacin showed no effect on the pharmacokinetics of digoxin.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical data are available from women who became pregnant while taking solifenacin. 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 unknown. Caution should be exercised when prescribing to pregnant women.

Breast-feeding
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 (see Section 5.3). The use of solifenacin should therefore be avoided during breast-feeding.

Fertility
There are no clinical data available on effects of solifenacin on fertility. No effects on fertility were observed in animals.

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

Summary of the safety profile
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.

Tabulated list of adverse reactions in adults

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* Confusional state*	Delirium*
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*

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)
General disorders and administration site conditions			Fatigue Peripheral oedema			

*observed post-marketing

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

Treatment
In the event of overdose with solifenacin 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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urologicals, Drugs for urinary frequency and incontinence, 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 M3 subtype receptor. In addition, solifenacin showed to be a specific antagonist for muscarinic receptors by displaying low or no affinity for various other receptors and ion channels tested.

Pharmacodynamic effects

Adults:
Treatment with Vesicare in doses of 5 mg and 10 mg daily was studied in several double blind, randomised, controlled clinical trials in men and women with overactive bladder.
As shown in the table below, both the 5 mg and 10 mg doses of Vesicare produced statistically significant improvements in the primary and secondary endpoints compared with placebo. Efficacy was observed within one week of starting treatment and stabilises over a period of 12 weeks. A long-term open label study demonstrated that efficacy was maintained for at least 12 months. 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. Treatment of the symptoms of overactive bladder also results in a benefit on a number of Quality of Life measures, such as general health perception, incontinence impact, role limitations, physical limitations, social limitations, emotions, symptom severity, severity measures and sleep/energy.

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

	Placebo	Vesicare 5 mg o.d.	Vesicare 10 mg o.d.	Tolterodine 2 mg b.i.d.
No. of micturitions/24 h				
Mean baseline	11.9	12.1	11.9	12.1
Mean reduction from baseline	1.4	2.3	2.7	1.9
% change from baseline	(12%)	(19%)	(23%)	(16%)
n	1138	552	1158	250
p-value*		<0.001	<0.001	0.004
No. of urgency episodes/24 h				
Mean baseline	6.3	5.9	6.2	5.4
Mean reduction from baseline	2.0	2.9	3.4	2.1
% change from baseline	(32%)	(49%)	(55%)	(39%)
n	1124	548	1151	250
p-value*		<0.001	<0.001	0.031
No. of incontinence episodes/24 h				
Mean baseline	2.9	2.6	2.9	2.3
Mean reduction from baseline	1.1	1.5	1.8	1.1
% change from baseline	(38%)	(58%)	(62%)	(48%)
n	781	314	778	157
p-value*		<0.001	<0.001	0.009
No. of nocturia episodes/24 h				
Mean baseline	1.8	2.0	1.8	1.9
Mean reduction from baseline	0.4	0.6	0.6	0.5
% change from baseline	(22%)	(30%)	(33%)	(26%)
n	1005	494	1035	232
p-value*		0.025	<0.001	0.199
Volume voided/micturition				
Mean baseline	166 ml	146 ml	163 ml	147 ml
Mean increase from baseline	9 ml	32 ml	43 ml	24 ml
% change from baseline	(5%)	(21%)	(26%)	(16%)
n	1135	552	1156	250
p-value*		<0.001	<0.001	<0.001
No. of pads/24 h				
Mean baseline	3.0	2.8	2.7	2.7
Mean reduction from baseline	0.8	1.3	1.3	1.0
% change from baseline	(27%)	(46%)	(48%)	(37%)
n	238	236	242	250
p-value*		<0.001	<0.001	0.010

Note: In 4 of the pivotal studies, Vesicare 10 mg and placebo were used. In 2 out of the 4 studies also Vesicare 5 mg was used and one of the studies included tolterodine 2 mg bid.

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 pair wise comparison to placebo

Paediatrics:

Overactive bladder

Children and adolescents (age 5 years and older):

Treatment with Vesicare oral suspension was studied in two clinical studies. A 12-week double-blind, randomised, placebo-controlled, clinical trial (905-CL-076) was performed in 189 paediatric patients with OAB (73 children aged 5 to 11 years and 22 adolescents aged 12 to 17 years were treated with solifenacin). This was followed by a 40-week long-term open-label extension study (905-CL-077) in 148 paediatric patients (119 children and 29 adolescents were treated with solifenacin). In both studies, the majority of patients were up-titrated to the weight-based equivalent of 10 mg in adults.
In study 905-CL-076 Vesicare oral suspension did not show a statistically significant improvement in the primary endpoint of mean volume voided per micturition compared with placebo in the overall population.
In children (aged 5 to 11 years) a statistically significant difference was observed for this primary endpoint. No statistically significant improvement was observed in the secondary endpoints of micturition frequency, number of incontinence episodes per day and number of dry days per week. No unexpected or unlisted adverse events were reported for the entire dose range tested.
In the open-label extension study, no unexpected or unlisted adverse events were reported. The safety profile for solifenacin in paediatric patients during long-term exposure was comparable to that observed in adults.

Neurogenic detrusor overactivity

Children and adolescents (age 6 months to less than 18 years):
Vesicare oral suspension was evaluated in two 52-week, open-label, baseline-controlled, sequential dose titration studies for the treatment of neurogenic detrusor overactivity (NDO) in paediatric patients aged 6 months to less than 18 years (studies 905-CL-074 and 905-CL-047).

In study 905-CL-074, a total of 4 subjects aged 6 months to less than 2 years and 19 subjects aged 2 to less than 5 years of age received treatment with Vesicare oral suspension, while in study 905-CL-047, a total of 76 subjects aged 5 to less than 18 years of age received treatment with Vesicare oral suspension.

In both studies the primary endpoint was the change from baseline in maximum cystometric capacity (MCC) after 24 weeks of Vesicare oral suspension treatment. Children treated with Vesicare oral suspension had a statistically significant increase in MCC compared with baseline after 24 weeks of treatment.The magnitude of the observed changes in both the primary and secondary endpoints in children (5 to less than 12 years of age) and in adolescents (12 to less than 18 years of age) was comparable.

The results for the primary endpoint in the clinical studies of Vesicare oral suspension in pediatric patients with NDO are reported in the table below. Treatment effects were maintained over 52-weeks.

Change from Baseline to 24 Weeks for Vesicare oral suspension

Parameter	**Aged 6 months to Less than 5 Years Mean (SD, n)**	**Aged 5 to Less than 18 Years Mean (SD, n)**
Primary Endpoint		
Maximum Cystometric Capacity (ml)		
Baseline Week 24 Change from baseline	92.3 (38.2, 21) 129.4 (40.2, 21) 37.0 (35.9, 21) P = < 0.001 95% CI: 20.7, 53.4	223.7 (132.9, 55) 279.1 (126.8, 49) 57.2 (107.7, 49) P = < 0.001 95% CI: 26.3, 88.1

Secondary urodynamic measurements also demonstrated an improvement from baseline to 24 weeks in both age groups. In subjects aged 6 months to less than 5 years of age, bladder compliance increased (mean change: 5.1 ml/cmH_2O; SD: 6.82; 95% CI: 2.0, 8.2), number of overactive contractions > 15 cmH_2O decreased (mean change: -7.0; SD: 8.6; 95% CI: -11.0, -3.1) and bladder volume until first detrusor contraction > 15 cmH_2O, expressed as % of expected bladder capacity, improved (baseline median: 38.00%; week 24 median 99.89%). In subjects aged 5 to less than 18 years of age, bladder compliance increased (mean change: 9.1 ml/cmH_2O; SD: 28.6; 95% CI: 1.0, 17.2), number of overactive contractions > 15 cmH_2O decreased (mean change: -2.3; SD: 5.1; 95% CI: -3.7, -0.8) and bladder volume until first detrusor contraction > 15 cmH_2O, expressed as % of expected bladder capacity, improved (baseline median: 28.25%; week 24 median 58.28%).

Additional diary-based measurements demonstrated improvement from baseline to 24 weeks in both age groups. In subjects aged 6 months to less than 5 years of age, the average maximum catheterized volume per day increased (mean change: 40.3 ml; SD: 50.0; 95% CI: 16.2, 64.4), and average number of periods between clean intermittent catheterisations with incontinence episodes per 24 hours decreased (mean change: -1.31; SD: 1.35; 95% CI: -1.99, -0.64). In subjects aged 5 to less than 18 years, the average maximum catheterized volume per day increased (mean change: 67.45 ml; SD: 88.07; 95% CI: 42.68, 92.22) and the average number of incontinence episodes per 24 hours decreased (mean change: -1.60; SD: 2.04; 95% CI: -2.18, -1.03).

The treatment with Vesicare oral suspension in children and adolescents was well-tolerated at all dose levels. No new safety concerns were identified compared with the known safety profile of solifenacin in adults.

There is no clinical study data available beyond one year in treatment of NDO in children and adolescents.

There is insufficient clinical experience in paediatric patients with NDO less than 2 years of age. Clinical studies have not been conducted in paediatric patients with NDO less than 6 months of age.

5.2 Pharmacokinetic properties

Absorption
After oral intake of solifenacin by adults, maximum solifenacin plasma concentrations (C_{max}) are reached after 4 to 12 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 - 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 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. 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.

Children and adolescents (age 2 to 18 years):
The pharmacokinetics of solifenacin following weight-adjusted dosing in children and adolescents with OAB (aged 5 years and older) and NDO (aged 2 to 18 years) were similar to those observed in adults after body weight adjustment, with a slightly shorter t_{max} and $t_{1/2}$; these differences were not considered clinically significant.

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 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 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 Preclinical safety data

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 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 occurred 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 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. Vesicare oral suspension showed no potential for irritation to the eyes when tested in rabbits.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polacrilin potassium
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Propylene glycol (E1520)
Simethicone emulsion 30%; consisting of simethicone, polyethylene glycol sorbitan tristearate (E436), methylcellulose (E461), polyethylene glycol stearate, glycerides, xanthan gum (E415), benzoic acid (E210), sorbic acid (E200), sulphuric acid (E513) and water.
Carbomer
Xylitol (E967)
Acesulfame potassium (E950)

Natural orange flavour; consisting of orange essential oils, natural flavouring substances, ethanol, propylene glycol (E1520), butylated hydroxyanisol (E320) and water
Sodium hydroxide
Purified water

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products or food.

6.3 Shelf life

3 years.

After first opening of the bottle, the oral suspension can be stored for 28 days.

6.4 Special precautions for storage

Store in the original bottle in order to protect from light.

This product does not require any special temperature storage conditions.

6.5 Nature and contents of container

150 ml Vesicare oral suspension in amber polyethylene terephthalate (PET) bottle with a child resistant and high density polyethylene- polypropylene cap with a pulp and vinyl seal liner, packed in a carton. Devices for dosing and administration are packed in the carton: 5 ml oral syringe and press-in bottle neck adaptor.

6.6 Special precautions for disposal and other handling

No special requirements.
Discard any medicine remaining after 28 days after opening the bottle. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

An appropriate commercially available oral syringe and adaptor suitable for dispensing of liquid medicines should be selected by the health care professional to measure the correct dose. Recommended syringe capacity for measuring the dose of Vesicare oral suspension is presented in the table below.

Suggested Syringe capacity for accurate dispensing

Prescribed Dosing Volume	Recommended Syringe Capacity
2 ml	2 ml syringe
2 ml – 5 ml	5 ml syringe
5 ml – 10 ml	10 ml syringe

As for the adaptor; a commercially available adaptor should be selected that is suitable for use in combination with the selected oral syringe and fits the bottle neck size for example a press in bottles adaptor, 24 mm or universal bottle adapter.

7 MARKETING AUTHORISATION HOLDER

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300 Dashwood Lang Road
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United Kingdom
KT15 2NX

8 MARKETING AUTHORISATION NUMBER(S)

PL 00166/0406

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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