SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Solifenacin Orion 5 mg film-coated tablets
Solifenacin Orion 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Solifenacin Orion 5 mg film-coated tablets:
Each film-coated tablet contains 5 mg solifenacin succinate, equivalent to 3.8 mg solifenacin.
Excipient with known effect: lactose monohydrate 132.9 mg.

Solifenacin Orion 10 mg film-coated tablets:
Each film-coated tablet contains 10 mg solifenacin succinate, equivalent to 7.5 mg solifenacin.
Excipient with known effect: lactose monohydrate 127.9 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

5 mg: Light yellow coloured, round shaped, biconvex, film-coated tablet, debossed with 'CC' on one side and '31' on the other side. Diameter of the tablet is 7.6 mm.

10 mg: Light pink coloured, round shaped, biconvex, film-coated tablet, debossed with 'CC' on one side and '32' on the other side. Diameter of the tablet is 7.6 mm.

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

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 (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 once daily (see section 5.2).

Patients treated with potent inhibitors of cytochrome P450 3A4
The maximum dose of Solifenacin Orion 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).

Paediatric population
The safety and efficacy of Solifenacin Orion in children and adolescents below 18 years have not yet been established. Therefore, Solifenacin Orion should not be used in children and adolescents.

Method of administration

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

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Solifenacin is contraindicated in patients with urinary retention, severe gastrointestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions.
- 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 Orion. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Solifenacin Orion 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 sections 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 sections 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 sections 4.2 and 4.5)
- hiatus hernia/gastro-esophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate esophagitis
- 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.

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

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 Orion can be determined after 4 weeks at the earliest.

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic 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 Orion, 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 gastrointestinal 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 Orion 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 contraindicated 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, carbamazepine).

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.

Breastfeeding
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 Orion should therefore be avoided during breastfeeding.

Fertility
No fertility data are available.

4.7 Effects on ability to drive and use machines

Since solifenacin, like other anticholinergics may cause blurred vision, dizziness, 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, Solifenacin Orion 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 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 solifenacin completed the full study period of 12 weeks treatment.

Tabulated list of adverse reactions

MedDRA system organ class	**Very common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥ 1/10,000 to <1/1,000**	**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*

MedDRA system organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥ 1/10,000 to <1/1,000	Very rare <1/10,000	Not known (cannot be estimated from the available data)
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-esophageal 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 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 national reporting system listed in Appendix V.

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: G04BD08.

Mechanism of action
Solifenacin is a competitive, specific cholinergic-receptor antagonist.

Pharmacodynamic effects
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.

Clinical efficacy and safety
Treatment with solifenacin 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 solifenacin produced statistically significant improvements in the primary and secondary endpoints compared with placebo. Efficacy was observed within one week of starting treatment and stabilised 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	**Solifenacin**	**Solifenacin**	**Tolterodine**

		succinate 5 mg o.d.	**succinate 10 mg o.d.**	**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, solifenacin succinate 10 mg and placebo were used. In 2 out of the 4 studies also solifenacin succinate 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.

5.2 Pharmacokinetic properties

Absorption

After intake of solifenacin, 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 45-68 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.

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.
The pharmacokinetics of solifenacin have not been established 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 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 Preclinical safety data

Non-clinical 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:
Lactose monohydrate
Maize starch
Hypromellose
Magnesium stearate
Silica, colloidal anhydrous

Film-coating:
Hypromellose
Macrogol 4000
Titanium dioxide
Talc
5 mg: Ferric oxide yellow
10 mg: Ferric oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC-Aluminium foil blister: 3, 5, 10, 20, 30, 50, 60, 90, 100 or 200 tablets.

HDPE container, polypropylene closure with wad having induction sealing liner: 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo

Finland

8. MARKETING AUTHORISATION NUMBER(S)

To be completed nationally.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be completed nationally.

10. DATE OF REVISION OF THE TEXT

2018-03-22