

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vesitirim 5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vesitirim 5 mg film-coated tablet:

Each tablet contains 5 mg solifenacin succinate, corresponding to 3.8 mg solifenacin.

Excipients: lactose monohydrate (107.5 mg)

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

Product imported from the UK:

Round, light-yellow tablet marked with the company logo and “150” on the same side.

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.

Children and adolescents

Safety and effectiveness in children have not yet been established. Therefore, Vesitirim should not be used in children.

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 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).

Potent inhibitors of cytochrome P450 3A4

The maximum dose of Vesitirim 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

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

4.3 Contraindications

Solifenacin 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 precautions for use

Other causes of frequent urination (heart failure or renal disease) should be assessed before treatment with Vesiitim. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Vesiitim 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 \leq 30 ml/min; see Section 4.2 and 5.2), and doses should not exceed 5 mg for these patients.
- moderate hepatic impairment (Child-Pugh score of 7 to 9; see Section 4.2 and 5.2), and doses should not exceed 5 mg for these patients.
- concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole (see 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.

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.

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

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 Vesiitim, 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 Vesiitim should be restricted to 5 mg, when used simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole) (see Section 4.2).

Simultaneous treatment of solifenacin and a potent CYP3A4 inhibitor is contra-indicated in patients with severe renal impairment or moderate hepatic impairment.

The effects of enzyme induction on the pharmacokinetics of solifenacin and its metabolites have not been 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 Vesiirim showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel).

Warfarin

Intake of Vesiirim did not alter the pharmacokinetics of *R*-warfarin or *S*-warfarin or their effect on prothrombin time.

Digoxin

Intake of Vesiirim 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.

Lactation

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 Vesiirim should therefore be avoided during breast-feeding.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Due to the pharmacological effect of solifenacin, Vesiirim 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 Vesiirim 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 Vesiirim 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* |

| | | | | | |
|---|-----------|---|--|---|--|
| Nervous system disorders | | | Somnolence Dysgeusia | | Dizziness*, headache* |
| Eye disorders | | Blurred vision | Dry eyes | | |
| Respiratory, thoracic and mediastinal disorders | | | Nasal dryness | | |
| Gastrointestinal disorders | Dry mouth | Constipation Nausea Dyspepsia Abdominal pain | Gastro-oesophageal reflux diseases Dry throat | Colonic obstruction Faecal impaction | Vomiting* |
| Skin and subcutaneous tissue disorders | | | Dry skin | | Erythema multiforme* Pruritus*, rash*, urticaria* |
| Renal and urinary disorders | | | Difficulty in micturition | Urinary retention | |
| General disorders and administration site conditions | | | Fatigue Peripheral oedema | | |

* observed post-marketing

QT prolongation and Torsade de Pointes have been reported in association with solifenacin use in worldwide post marketing experience. Because these spontaneously reported events are from the worldwide post marketing experience, the frequency of events and the role of solifenacin in their causation cannot be reliably determined.

4.9 Overdose

Symptoms

Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects. 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

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

As for other anticholinergics, symptoms can be treated as follows:

- Severe central anticholinergic effects such as hallucinations or pronounced excitation: treat with physostigmine or carbachol.
- Convulsions or pronounced excitation: treat with benzodiazepines.
- Respiratory insufficiency: treat with artificial respiration.
- Tachycardia: treat with beta-blockers.
- Urinary retention: treat with catheterisation.
- Mydriasis: treat with pilocarpine eye drops and/or place patient in dark room.

As with other antimuscarinics, in case of overdosing, specific attention should be paid to patients with known risk for QT-prolongation (i.e. hypokalaemia, bradycardia and concurrent administration of medicinal products known to prolong QT-interval) and relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics, ATC code: G04B D08.

Mechanism of action:

Solifenacin is a competitive, specific cholinergic-receptor antagonist.

The urinary bladder is innervated by parasympathetic cholinergic nerves. Acetylcholine contracts the detrusor smooth muscle through muscarinic receptors of which the M_3 subtype is predominantly involved. In vitro and in vivo pharmacological studies indicate that solifenacin is a competitive inhibitor of the muscarinic M_3 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:

Treatment with Vesitirim 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 Vesitirim 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 | Vesitirim 5 mg o.d. | Vesitirim 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, Vesihirim 10 mg and placebo were used. In 2 out of the 4 studies also Vesihirim 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

General characteristics

Absorption

After intake of Vesihirim tablets, 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.

Metabolism

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.

Excretion

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).

Dose Proportionality

Pharmacokinetics are linear in the therapeutic dose range.

Characteristics in patients

Age

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 ≤ 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 $t_{1/2}$ 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 $t_{1/2}$ 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet:

Maize starch
Lactose monohydrate
Hypromellose
Magnesium stearate

Film Coating:

Macrogol 8000
Talc
Hypromellose
Titanium dioxide (E171)
Yellow ferric oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the container and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Over-labelled cardboard carton containing three blister strips (10 tablets per blister).

Pack size : 30 tablets

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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Ballycoolin
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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 1500/82/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd September 2011

10 DATE OF REVISION OF THE TEXT