

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1241/008/001

Case No: 2054810

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Astellas Pharma Co. Ltd

25 The Courtyard, Kilcarbery Business Park, Clondalkin, Dublin 22, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Vesikur® 5 mg film coated-tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **22/05/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vesikur® 5 mg, film-coated tablet.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Vesikur 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.

Vesikur 5 mg film-coated tablet: Each 5 mg tablet is a round, light-yellow tablet marked with the Yamanouchi 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, Vesikur 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 Vesikur 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

Vesikur 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 gastrointestinal 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 Vesikur. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Vesikur 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 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/gastroesophageal 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 Vesikur 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 Vesikur 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 Vesikur 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 Vesikur showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel).

Warfarin

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

Digoxin

Intake of Vesikur showed no effect on the pharmacokinetics of digoxin.

4.6 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 Vesikur 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, Vesikur 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 Vesikur 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 Vesikur completed the full study period of 12 weeks treatment.

MedDRA system organ class	Very common $\geq 1/10$	Common $>1/100, <1/10$	Uncommon $>1/1000, <1/100$	Rare $> 1/10000, <1/1000$	Very rare $<1/10,000, \text{ not known (cannot be estimated from the available data)}$
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 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:

Treatment with Vesikur 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 Vesikur 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	Vesikur 5 mg o.d.	Vesikur 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, Vesikur 10 mg and placebo were used. In 2 out of the 4 studies also Vesikur 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 Vesikur 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 the 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 - 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 $t_{1/2}$ 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 by 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

3 years.
After first opening of bottles, the tablets can be stored for 6 months. Keep the bottle tightly closed.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Container:

The tablets are packed in PVC/Aluminium blisters or in HDPE bottles with PP cap.

Pack sizes in blisters:

3, 5, 10, 20, 30, 50, 60, 90 or 100 tablets (not all pack sizes may be marketed).

Pack sizes in bottles:

100 tablets (not all pack sizes may be marketed).

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 MARKETING AUTHORISATION HOLDER

Astellas Pharma Co.Ltd
25 The Courtyard
Kilcarbery Business Park
Clondalkin
Dublin 22
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1241/008/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 August 2004

Date of last renewal: 22 May 2009

10 DATE OF REVISION OF THE TEXT

July 2009