AUSTRALIAN PRODUCT INFORMATION

SOLIFENACIN VIATRIS

solifenacin succinate film-coated tablets

1 NAME OF THE MEDICINE

Solifenacin succinate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each SOLIFENACIN VIATRIS tablet contains 5 mg or 10 mg of solifenacin succinate as the active ingredient.

Excipients with known effect: sugars as lactose and trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

SOLIFENACIN VIATRIS 5 mg tablets: A yellow film-coated, round, biconvex tablet debossed with M on one side of the tablet and SF over 5 on the other side.

SOLIFENACIN VIATRIS 10 mg tablets: A pink film-coated, round, biconvex tablet debossed with M on one side of the tablet and SF over 10 on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency or increased urinary frequency.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Adults, including the elderly

The recommended dose is 5 mg solifenacin succinate once daily. If needed, the dose may be increased to a maximum of 10 mg solifenacin succinate once daily.

Children and adolescents

Safety and effectiveness in children have not yet been established. Therefore, SOLIFENACIN VIATRIS 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.

Patients with hepatic impairment

No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate hepatic impairment (Child-Pugh B) should be treated with caution and receive no more than 5 mg once daily. SOLIFENACIN VIATRIS is contraindicated in patients with severe hepatic impairment (Child-Pugh C).

Co-medication

The maximum dose of SOLIFENACIN VIATRIS should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4- inhibitors e.g. ritonavir, nelfinavir, itraconazole, ciclosporin, macrolide antibiotics. (see also Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Method of administration

SOLIFENACIN VIATRIS 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
- patients with uncontrolled narrow-angle glaucoma
- patients who have demonstrated hypersensitivity to the drug substance or other components of the product
- severe gastro-intestinal condition (including toxic megacolon and gastric retention)
- myasthenia gravis
- patients undergoing haemodialysis
- patients with severe hepatic impairment
- patients with severe renal impairment or moderate hepatic impairment and who are on treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Solifenacin succinate 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.
- in patients being treated for narrow-angle glaucoma.
- hiatus hernia/gastro-oesophagal reflux and/or who are concurrently taking medicinal products that can cause or exacerbate oesophagitis.
- autonomic neuropathy.
- known risk factors for QT prolongation, such as pre-existing long QT syndrome and hypokalaemia

Angioedema

Angioedema with airway obstruction has been reported in some patients on solifenacin succinate. If angioedema occurs, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken.

Anaphylactic Reaction

Anaphylactic reaction has been reported in some patients treated with solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued and appropriate therapy and/or measures taken.

QT Prolongation and Torsade de Pointes

QT Prolongation and Torsade de Pointes have been observed in patients with known risk factors for these conditions.

As with other drugs in this class, caution is advised in patients with known risk factors for QT-prolongation (i.e. history of QT prolongation, long QT syndrome, hypokalaemia, bradycardia, coadministration of drugs known to prolong the QT interval) and relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure) (see Section 5.1 PHARMACODYNAMIC PROPERTIES – Clinical

Trials, Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Appropriate investigations (e.g. ECG) should be considered in patients with risk factors for QTc prolongation.

Use in Hepatic Impairment

Doses of solifenacin succinate greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). Solifeancin succinate is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (see Section 4.3 – CONTRAINDICATIONS).

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.

Use in Renal Impairment

Solifenacin succinate should be used with caution in patients with reduced renal function. Solifenacin succinate should be used with caution in patients with severe renal impairment (creatinine clearance < 30 mL/min), and doses should not exceed 5 mg for these patients.

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 hemodialysis have not been studied.

Use in the Elderly

No dosage adjustment based on patient age is required. Studies in the elderly have shown that C_{max}, AUC and $t_{1/2}$ values were 20-25% higher as compared to the younger volunteers (18-55 years). No overall differences were observed in the safety of solifenacin between older and younger patients treated for 4 to 12 weeks with 5 to 10 mg solifenacin succinate.

Paediatric Use

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

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 succinate is not likely to interact with the CYP mediated metabolism of co-administered drugs.

Effect of other medicinal products on the pharmacokinetics of solifenacin

In vitro drug metabolism studies have shown that solifenacin is a substrate of CYP3A4. Inducers or inhibitors of CYP3A4 may alter solifenacin pharmacokinetics. Simultaneous administration of ketoconazole (200 mg/day), a potent CYP3A4 inhibitor, resulted in a two-fold increase of the AUC of solifenacin, while ketoconazole at a dose of 400 mg/day resulted in a three-fold increase of the AUC of solifenacin. Therefore, the maximum dose of solifenacin should be restricted to 5 mg, when used simultaneously with ketoconazole

or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole, ciclosporin, macrolide antibiotics).

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.

Drugs which prolong the QT/QTc interval:

There is no satisfactory information on the concurrent use of solifenacin succinate with drugs known to prolong the QT/QTc interval. In the absence of such information on these combinations the potential risk of pathological QT/QTc prolongation resulting in arrhythmias cannot be ruled out. Drugs known to prolong the QT/QTc interval include: erythromycin, quinidine, procainamide, disopyramide, sotalol, amiodarone, cisapride, fluconazole, amitriptyline, haloperidol, chlorpromazine, thioridazine, pimozide and droperidol.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Solifenacin had no effect on reproductive function, fertility or early embryonic development after oral treatment of male and female mice, which resulted in 13 times exposure at the maximum recommended human dose (MRHD).

Use in Pregnancy (Category B3)

Solifenacin (and/or its metabolites) has been shown to cross the placenta in pregnant mice. No embryotoxicity or teratogenicity was observed in mice treated with 1.2 times exposure at the maximum recommended human dose (MRHD). In one of two studies, higher doses (3.6 times exposure at the MRHD) resulted in maternal toxicity and reduced fetal body weight. No embryotoxic effects were observed in rabbits at up to 1.8 times exposure at the MRHD.

In utero and lactational exposures to maternal doses of solifenacin 3.6 times exposures at the MRHD resulted in reduced peripartum and postnatal survival, reductions in body weight gain, and delayed physical development (e.g. eye opening).

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, solifenacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

Solifenacin is excreted into the breast milk of mice. There were no significant adverse effects at 1.2 times exposure at the maximum recommended human dose (MRHD) in a pre- and postnatal study in mice. Pups of female mice treated at 3.6 times exposure at the MRHD showed reduced body weights, postpartum pup

mortality or delays in the onset of reflex and physical development during the lactation period. It is expected that solifenacin is excreted in human milk and solifenacin should not be administered 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, the ability to drive and use machines may be negatively affected (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

In the four 12-week double-blind clinical trials 3027 patients were involved (1811 on Solifenacin and 1216 on placebo), and approximately 90% of these patients completed the 12-week studies. The most frequent reason for discontinuation due to an adverse event was dry mouth, 1.5%. There were three intestinal serious adverse events in patients all treated with solifenacin succinate 10 mg (one faecal impaction, one colonic obstruction, and one intestinal obstruction).

The table below lists the adverse events reported in ≥ 1.0% of the patients in the 12 week studies. The relationship to study medication for most of these events is uncertain; many are thought to represent spontaneous events reported by patients with bladder dysfunction (and other concomitant diseases) and are not necessarily causally related to solifenacin succinate.

Numbers (%) of patients with treatment-emergent adverse events reported by 1% or more patients: controlled phase 3 studies (all combined)			
SYSTEM ORGAN CLASS **MedDRA Preferred Term**	**Placebo (%)**	**Solifenacin 5 mg (%)**	**Solifenacin 10 mg (%)**
Number of patients	1216	578	1233
Number of patients with treatment-emergent AE	634	265	773
GASTROINTESTINAL DISORDERS			
Dry mouth	4.2	10.9	27.6
Constipation	2.9	5.4	13.4
Nausea	2.0	1.7	3.3
Dyspepsia	1.0	1.4	3.9
Diarrhoea NOS	2.1	0.7	1.9
Vomiting NOS	0.9	0.2	1.1
Abdominal pain upper	1.0	1.9	1.2
Abdominal pain NOS	1.2	0.2	0.6
INFECTIONS AND INFESTATIONS			
Urinary tract infection NOS	2.8	2.8	4.8
Upper respiratory tract infection NOS	2.0	0.9	1.5
Influenza	1.3	2.2	0.9
Sinusitis NOS	1.2	0.9	1.0
Nasopharyngitis	2.7	0.9	1.0
Pharyngitis NOS	1.0	0.3	1.1
Bronchitis	1.1	0.7	0.7
NERVOUS SYSTEM DISORDERS			
Headache	4.5	1.9	1.8
Dizziness	1.8	1.9	1.8
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia	2.2	0.7	1.2
Back pain	1.8	0.5	1.5
Neck pain	0.5	0.3	0.1
GENERAL DISORDERS AND ADMINISTRATION SITE DISORDERS			
Fatigue	1.1	1.0	2.1
Oedema lower limb	0.7	0.3	1.1
Influenza like illness	0.5	0.3	0.3
EYE DISORDERS			

Vision blurred	1.8	3.8	4.8
Dry Eye NOS	0.6	0.3	1.6
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough	0.2	0.2	1.1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Rash	1.0	0	0.6
RENAL AND URINARY DISORDERS			
Urinary retention	0.6	0	1.4
Dysuria	0.4	0.3	0.7
PSYCHIATRIC DISORDERS			
Insomnia	1.2	0.3	1.1
Depression NOS	0.8	1.2	0.8
VASCULAR DISORDERS			
Hypertension NOS	0.6	1.4	0.5

Adverse reactions reported in the clinical trials with a frequency of occurrence less than 1% are:

Gastrointestinal disorders: flatulence, gastro-oesophageal reflux diseases, throat irritation, eructation, dry throat

Infections and infestations: cystitis

Nervous system disorders: somnolence, dysgeusia, syncope

General disorders and administration site disorders: thirst, suprapubic pain, chest tightness

Renal and urinary disorders: difficulty in micturition, bladder pain, micturition urgency

Respiratory, thoracic and mediastinal disorders: nasal dryness

Investigations: abnormal liver function tests (AST, ALT, GGT), electrocardiogram QT prolonged

Musculoskeletal and connective tissue disorders: peripheral swelling

Skin and subcutaneous tissue disorders: dry skin

Vascular disorders: hot flushes

Post Marketing Experience:

The following adverse reactions have been spontaneously reported during worldwide post-approval use of solifenacin succinate. The adverse reactions reported are presented below according to System Organ Class and frequency.

Adverse event frequencies are defined as follows: Very common (≥10%), common (≥1%, < 10%), uncommon (≥0.1%, <1%), rare (>0.01%, <0.1%) and very rare (<0.01%), not known (cannot be estimated from the available data).

Cardiac disorders

Very Rare: Torsade de Pointes, atrial fibrillation, palpitations, tachycardia

Eye disorders

Very rare: glaucoma

Gastrointestinal disorders

Very rare: Gastro-oesophageal reflux disease, vomiting, ileus

General disorders and administration site conditions

Very rare: Peripheral oedema

Hepatobiliary disorders

Very rare: Liver disorders mostly characterised by abnormal liver function tests (AST, ALT, GGT)

Immune System Disorders

Very rare: Anaphylactic reaction

Investigations

Very rare: Electrocardiogram QT prolonged

Metabolism and nutrition disorders

Very rare: Decreased appetite, hyperkalaemia

Musculoskeletal and connective tissue disorders

Very rare: Muscular weakness

Nervous system disorders

Very rare: Dizziness, headache, somnolence

Psychiatric disorders

Very rare: Hallucinations, delirium, confusion state

Renal and urinary disorders

Very rare: Renal impairment, urinary retention

Respiratory, thoracic and mediastinal disorders

Very rare: dysphonia, nasal dryness

Skin and subcutaneous tissue disorders

Very rare: Pruritus, rash, urticaria, angioedema, erythema multiforme, exfoliative dermatitis

Postmarketing pharmacovigilance data confirmed QT prolongation associated with therapeutic doses of solifenacin succinate in cases with known risk factors (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects (headache, dry mouth, dizziness, drowsiness and blurred vision) and should be treated accordingly. The highest dose of solifenacin succinate accidentally given to a single patient was 280 mg in a 5 hour period, resulting in mental status changes not requiring hospitalisation.

Overdosage with solifenacin succinate may prolong the QTc interval, therefore, in the event of overdosage, ECG monitoring is recommended and standard supportive measures for managing QT prolongation should be adopted.

Treatment

No cases of acute overdosage have been reported. In the event of an overdose with solifenacin succinate, treat with activated charcoal.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of Action

Solifenacin is a competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergic mediated functions, including contractions of urinary bladder smooth muscle and stimulation of the salivary secretion.

Clinical Trials

Four randomised, double blind, placebo controlled pivotal studies were performed of 12 weeks duration to assess solifenacin for the treatment of overactive bladder in patients having symptoms of urinary frequency, urgency and/or urge or mixed incontinence (with the predominance of urge). Entry criteria required that patients have symptoms of overactive bladder for ≥ 3 months duration. These studies involved 3027 patients (1811 on solifenacin and 1216 on placebo), and approximately 90% of these patients completed the 12-week studies. Two of the four studies evaluated the 5 and 10 mg solifenacin doses and the other two evaluated only the 10 mg dose. The studies assessed the standard primary efficacy endpoint of number of micturitions per 24 hours, along with a number of usual secondary endpoints, including incontinence episodes, urgency episodes, urge incontinence episodes, nocturia episodes, all per 24 hours, and volume voided per micturition, using patient diaries.

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 stabilises over a period of 12 weeks. 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. All patients completing the 12-week studies were eligible to enter an open label, long term extension study and 81% of patients enrolling completed the additional 40-week treatment period demonstrating maintenance of effect. 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 5 mg o.d.	Solifenacin 10 mg o.d.
No. of micturitions/24 h			
Mean baseline	11.9	12.1	11.9
Mean reduction from baseline	1.4	2.3	2.7
% change from baseline	(12%)	(19%)	(23%)
n	1138	552	1158
Diff. vs placebo (95% CI)[1]		0.9 (0.6;1.3)	1.3 (1.0;1.6)
p-value*		<0.001	<0.001
No. of urgency episodes/24 h			
Mean baseline	6.3	5.9	6.2
Mean reduction from baseline	2.0	2.9	3.4
% change from baseline	(32%)	(49%)	(55%)
n	1124	548	1151
Diff. vs placebo (95% CI)[1]		1.1 (0.7;1.5)	1.5 (1.2;1.8)
p-value*		<0.001	<0.001
No. of incontinence episodes/24 h			
Mean baseline	2.9	2.6	2.9
Mean reduction from baseline	1.1	1.5	1.8
% change from baseline	(38%)	(58%)	(62%)
n	781	314	778
Diff. vs placebo (95% CI)[1]		0.7 (0.4;1.1)	0.7 (0.5;1.0)
p-value*		<0.001	<0.001
No. of nocturia episodes/24 h			
Mean baseline	1.8	2.0	1.8
Mean reduction from baseline	0.4	0.6	0.6
% change from baseline	(22%)	(30%)	(33%)
n	1005	494	1035
Diff. vs placebo (95% CI)[1]		0.1 (0.0;0.3)	0.2 (0.0;0.3)
p-value*		0.025	<0.001
Volume voided/micturition			
Mean baseline	166 mL	146 mL	163 mL
Mean increase from baseline	9 mL	32 mL	43 mL
% change from baseline	(5%)	(21%)	(26%)
n	1135	552	1156
Diff. vs placebo (95% CI)[1]		25 (19;32)	34 (29;39)
p-value*		<0.001	<0.001
No. of pads/24 h			
Mean baseline	3.0	2.8	2.7
Mean reduction from baseline	0.8	1.3	1.3
% change from baseline	(27%)	(46%)	(48%)
n	238	236	242
Diff. vs placebo (95% CI)[1]		0.6 (0.2;0.9)	0.7 (0.3;1.0)
p-value*		<0.001	<0.001

Note: In 4 of the pivotal studies, Solifenacin 10 mg and placebo were used. In 2 out of the 4 studies also Solifenacin 5 mg was used.

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

[1] As estimated from the statistical model

Clinical QT Interval Data

Two dedicated QT studies have been performed with solifenacin.

The first study was an open label, multiple dose escalating study in 60 healthy subjects. In this study solifenacin was administered starting at a dose of 10 mg once daily for 2 weeks and proceeded in 10 mg increments for 2 weeks at each dose level. The highest tolerated dose was 40 mg. The results are presented in the table below. There was no significant change in QTc interval using the Bazett as well as the Friderica method for the 10 mg solifenacin compared to baseline. Depending on the method applied, some prolongation was seen for the 20 mg and 30 mg doses, which are higher than the recommended therapeutic dose. However, both methods suggest no prolongation for the 40 mg dose, which is four times the highest recommended therapeutic dose.

Treatment Least Squares Means of Change from Baseline QTc (Bazett and Friderica) ANCOVA Model

Dose (mg)	Bazett Method		Friderica Method	
	Estimate	95% Confidence Interval	Estimate	95% Confidence Interval
10	0.8	(-2.1, 3.6)	-0.6	(-3.3, 2.0)
20	5.4	(2.6, 8.3)	2.5	(-0.2, 5.2)
30	5.5	(2.5, 8.5)	1.3	(-1.5, 4.2)
40	-0.1	(-3.4, 3.1)	-4.7	(-7.8, -2.0)

There were no QTc intervals > 500 msec; increases of >60 msec occurred in 1 subject (on 30 mg), while change <60 msec but >30 msec occurred in 34 subjects (11 changes on 10 mg, 20 changes on 20 mg, 27 changes on 30 mg, 9 changes on 40 mg).

The second study was a double blind, multiple dose, placebo and positive controlled (moxifloxacin 400 mg) study in 76 female volunteers aged 19 to 79 years. This second QT study was a dedicated thorough QT study with the subjects randomised to one of two treatment groups after receiving placebo and moxifloxacin sequentially. One group (n=51) went on to complete 3 additional sequential periods of dosing with solifenacin 10, 20, and 30 mg, while the second group (n=25) in parallel completed a sequence of placebo and moxifloxacin. The 30 mg dose of solifenacin succinate (three times the highest recommended dose) was chosen for use in this study because this dose results in a solifenacin exposure that covers the exposure observed upon co- administration of 10 mg solifenacin with potent CYP3A4 inhibitors (e.g. ketoconazole, 400 mg). Due to the sequential dose escalating nature of the study, baseline ECG measurements were separated from the final QT assessment (of the 30 mg dose level) by 33 days.

The median difference from baseline in heart rate associated with the 10 and 30 mg doses of solifenacin succinate compared to placebo was –2 and 0 beats/minute, respectively. Because a significant period effect on QTc was observed, the QTc effects were analysed utilising the parallel placebo control arm rather than the pre- specified intra-patient analysis (Fridericia method). Representative results for solifenacin are shown in the table below.

QTc changes in msec (90% Confidence Interval) from baseline at T_{max} (relative to placebo)

Dose (mg)	Treatment	Result of Friderica method (using mean difference)
10 mg	Solifenacin 10 mg once daily for 14 days	2 (-3, 6)
30 mg	Solifenacin 30 mg once daily for 14 days	8 (4, 13)

Moxifloxacin was included as a positive control in this study and, given the length of the study, its effect on the QT interval was evaluated in 3 different sessions. The placebo subtracted mean changes (90% Confidence Interval) in QTcF for moxifloxacin in the three sessions were 11 msec (7, 14), 12 msec (8,17) and 16 msec (12, 21), respectively.

There were no subjects with a mean QTc > 500 msec. Four subjects experienced increases in mean QTcF that were greater than 60 msec from the time-matched baseline. Three subjects received 30 mg solifenacin and the fourth received 400 mg moxifloxacin.

A change in QTc of < 60 msec but > 30 msec occurred in 29 subjects on 10 mg and in 31 subjects during 30 mg solifenacin treatment.

The QT interval prolonging effect appeared to be greater for the 30 mg compared to the 10 mg dose of solifenacin. Although the effect of the highest solifenacin dose (three times the maximum therapeutic dose) studied did not appear as large as that of the positive control moxifloxacin at its therapeutic dose, the confidence intervals overlapped. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels.

Across the four controlled phase 3 studies, QTc interval prolongation was seen of approximately up to 5 msec, along with PR interval prolongation. There were 12 patients with a change in QTc from baseline of > 60 msec and 6 patients with QTc > 500 msec at any time point on solifenacin. There were no reports of VT or VF or association between these QT changes and death, syncope, dizziness or ventricular arrhythmias.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After intake of Solifenacin tablets, maximum solifenacin plasma concentrations (C_{max}) are reached after 3 to 8 hours and at steady state ranged from 32.3 to 69.9 ng/mL for the 5 and 10 mg Solifenacin tablets, respectively. 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 in the liver. The primary pathway for elimination is by way of CYP3A4; however, alternate metabolic pathways exist. The primary metabolic routes of solifenacin are through *N*-oxidation of the quinuclidin ring and 4*R*-hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (4*R*-hydroxy solifenacin), occurring at low concentrations and unlikely to contribute significantly to clinical activity, and three pharmacologically inactive metabolites (*N*-glucuronide and the *N*-oxide and 4*R*-hydroxy-*N*-oxide of solifenacin) have been found in human plasma after oral dosing.

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 4*R*-hydroxy-*N*-oxide metabolite and 8% as the 4*R*-hydroxy metabolite (active metabolite). The systemic clearance of solifenacin is about 9.5 L/h. The elimination half-life of solifenacin following chronic dosing is approximately 45 – 68 hours.

Dose Proportionality

Pharmacokinetics are linear in the therapeutic dose range.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Solifenacin was not mutagenic in the *in vitro* Salmonella typhimurium or Escherichia coli microbial mutagenicity test or chromosomal aberration test in human peripheral blood lymphocytes, with or without metabolic activation, or in the in vivo micronucleus test in rats.

Carcinogenicity

No significant increase in tumors was found following the administration of solifenacin to male and female mice for 104 weeks up to 5 and 9 times exposure at the maximum recommended human dose (MRHD), respectively, and male and female rats for 104 weeks at doses that resulted in <1 times exposure at the MRHD.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate, maize starch, hypromellose, purified talc and magnesium stearate. The film coating contains proprietary ingredients, OPADRY complete film coating system 03H520077 YELLOW (ARTG PI No: 109790) (5 mg tablets only) and OPADRY complete film coating system 03H540078 PINK (ARTG PI No: 109766) (10 mg tablets only).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

SOLIFENACIN VIATRIS 5 mg and 10 mg tablets: PVC/Aluminium blister packs of 10 (sample) and 30 tablets and HDPE bottles with PP closures of 30 (child resistant closure), 90 and 500 tablets.

Some pack sizes and strengths may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 268512 – SOLIFENACIN VIATRIS solifenacin succinate 5 mg tablet bottle

AUST R 268515 – SOLIFENACIN VIATRIS solifenacin succinate 10 mg tablet bottle

AUST R 268516 – SOLIFENACIN VIATRIS solifenacin succinate 10 mg tablet blister pack

AUST R 268517 – SOLIFENACIN VIATRIS solifenacin succinate 5 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

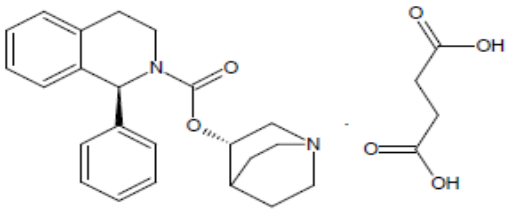
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name : (1S)-(3R)-1-azabicyclo [2.2.2] oct-3-yl 3, 4-dihydro-1-phenyl-2(1H)-isoquinoline carboxylate Succinate.

Structural formula :



Molecular formula : $C_{23}H_{26}N_2O_2.C_4H_6O_4$

Molecular weight : 480.55

Solifenacin succinate appears as white or almost white crystalline powder. Freely soluble in methanol, chloroform and water, freely soluble in dimethyl sulphoxide, acetic acid, dimethyl formamide & soluble in ethanol. Very soluble in pH- 1.2 buffer, Freely soluble in pH- 4.5 buffer & sparingly soluble in pH- 6.8 buffer.

CAS Number

242478-38-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

19/03/2020

10 DATE OF REVISION

06/12/2022

Summary Table of Changes

Section Changed	Summary of New Information
All	Change trade name from SOLIFENACIN MYLAN to SOLIFENACIN VIATRIS.

2, 5.1, 6.1, 6.5	Minor editorial changes
6.5	Insert AUST R numbers Add container closure material
8	Update sponsor's details

SOLIFENACIN VIATRIS_pi\Dec22/01