NEW ZEALAND DATA SHEET

SOLIFENACIN MYLAN

1. Product Name

Solifenacin Mylan, 5 mg and 10 mg, film coated tablet.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 5 mg or 10 mg of solifenacin succinate.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

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

Solifenacin Mylan 10 mg tablets: 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

Solifenacin Mylan is indicated for the treatment of unstable bladder with symptoms of increased urinary urgency, frequent micturition, and/or urge incontinence.

4.2 Dose and method of administration

Dose

Adults

The recommended dose is 5 mg once daily. If needed, this can be increase to 10 mg once daily.

Special populations

Children

Safety and effectiveness in children has not yet been established. Solifenacin Mylan is not recommended for use in children.

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 not more than 5 mg once daily. Pharmacokinetics in patients undergoing haemodialysis has not been studied.

Patients with hepatic impairment

No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate hepatic impairment should be treated with caution and receive not more than 5 mg once daily. Pharmacokinetics in patients with severe hepatic impairment has not been studied.

Strong inhibitors of cytochrome P450 3A4

The maximum dose of Solifenacin Mylan should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other strong CYP3A4-inhibitors (see section 4.5).

Method of administration

Solifenacin Mylan should be taken orally and should be swallowed whole with liquids. It can be taken with or without food, as is convenient.

4.3 Contraindications

- Hypersensitivity to solifenacin or to any of the excipients
- Urinary retention
- Uncontrolled narrow angle glaucoma
- Myasthenia gravis
- Severe gastro-intestinal condition (including toxic megacolon)
- Patients undergoing haemodialysis (see section 4.2)
- Patients with severe hepatic impairment (see sections 4.2)
- Patients with severe renal impairment or moderate hepatic impairment and on treatment with a strong CYP3A4 inhibitor e.g. ketoconazole (see section 4.5)

4.4 Special warnings and precautions for use

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

Solifenacin Mylan 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). Doses should not exceed 5 mg for these patients.
- Moderate hepatic impairment (Child-Pugh score of 7 to 9; see sections 4.2). Doses should not exceed 5 mg for these patients.
- Concomitant use of a strong CYP3A4 inhibitor, e.g. ketoconazole (see sections 4.2 and 4.5)
- 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.
- QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia.
- Anaphylactic reactions 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.
- Solifenacin succinate is not indicated for treatment of overactive bladder in the paediatric population.

4.5 Interaction with other medicines and other forms of interaction

Pharmacological interactions

Concomitant medication with other drugs with anticholinergic properties may result in more pronounced therapeutic effects and side effects. An interval of approximately one week should be allowed after stopping treatment with solifenacin, before commencing other anticholinergic therapy. The therapeutic effect of solifenacin may be reduced by concomitant administration of cholinergic receptor agonists. Solifenacin can reduce the effect of drugs that stimulate the motility of the gastro-intestinal tract, such as metoclopramide and cisapride.

Effects of other drugs on the pharmacokinetics of solifenacin

Since solifenacin is metabolised by CYP3A4, pharmacokinetic interactions are possible with other CYP3A4 substrates, inhibitors and inducers.

Ketoconazole and other CYP3A4 inhibitors:
Simultaneous administration of ketoconazole (200 mg/day) 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 strong CYP3A4 inhibitors.

Simultaneous treatment of solifenacin and a strong CYP3A4 inhibitor is contraindicated in patients with severe renal impairment or moderate hepatic impairment (see section 4.3)

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).

Effects of solifenacin on the pharmacokinetics of other medications

Pharmacokinetics 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.

Oral Contraceptives:
Intake of solifenacin showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinyl oestradiol/levonorgestrel, both CYP3A4 substrates).

Warfarin:
Intake of solifenacin did not alter the pharmacokinetics of *R*-warfarin (substrate for CYP3A4) or *S*-warfarin (substrate for CYP2C9) or their effect on prothrombin time.

Digoxin:
Intake of solifenacin showed no effects on the pharmacokinetics of digoxin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of solifenacin in pregnant women. Solifenacin Mylan is not recommended for use during pregnancy.

Lactation

No data concerning the excretion of solifenacin into human milk is available. The use of Solifenacin Mylan should be avoided during lactation.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The pharmacological effect of solifenacin may cause anticholinergic side effects of generally mild or moderate severity.

The most commonly reported adverse effects 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 did only occasionally lead to discontinuation of treatment. In general, drug compliance was very high (approximately 99%) and approximately 90% of patients treated with solifenacin completed the full study period of 12 weeks treatment.

Table 1: Tabulated list of adverse effects

MedDRA system organ class	**Very common ≥10%**	**Common ≥1%, < 10%**	**Uncommon ≥0.1%, <1%**	**Rare >0.01%, <0.1%**	**Very rare <0.01%, not known (cannot be estimated from the available data)**
Cardiac disorders					Torsade de Pointes # Atrial fibrillation # Palpitations # Tachycardia #
Gastrointestinal disorders	Dry mouth	Constipation Nausea Dyspepsia Abdominal pain	Gastro-oesophageal reflux diseases Dry throat Dysgeusia	Faecal impaction** Colonic obstruction** Vomiting #	Abdominal discomfort # Ileus #
Infections and infestations			Urinary tract Infection NOS* Cystitis NOS		
Investigations					Electrocardiogram QT prolonged#
Immune system disorder					Anaphylactic reaction #
Metabolism and nutrition disorders					Decreased appetite # Hyperkalaemia #
Musculoskeletal and connective tissue disorders					Muscular weakness #
Nervous			Somnolence #	Dizziness #	

system disorders				Headache #	
Eye disorders		Blurred vision	Dry eyes NOS		Glaucoma #
General disorders and administration site conditions			Fatigue, Peripheral oedema		
Respiratory, thoracic and mediastinal disorders			Nasal dryness		Dysphonia #
Skin and subcutaneous tissue disorders			Dry skin	Pruritus # Rash #	Urticaria # Angioedema # Erythema multiforme # Exfoliative dermatitis #
Hepatobiliary disorders					Liver disorders, mostly characterised by abnormal liver function tests (AST, ALT, GGT)#
Renal and urinary disorders			Difficulty in micturition	Urinary retention**	Renal impairment#
Psychiatric disorders					Confusional state # Hallucinations # Delirium #

* NOS = Not otherwise specified
** By nature these anticholinergic side effects can be serious.
# Observed post-marketing

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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

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), to patients who are concurrently using medicinal products known to prolong QT-interval as no data is available on potential interaction between solifenacin and drugs prone to cause QT-prolongation and to patients with relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure).

In the event of overdosage with solifenacin the patient should be treated with activated charcoal. Gastric lavage may be performed, 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.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics, ATC code: G04BD08

Mechanism of action

Solifenacin is a competitive, specific cholinergic-receptor antagonist with selectivity for the urinary bladder over salivary glands *in vivo.*

Pharmacodynamic effects

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 Table 2 (European studies) and 3 (US studies) 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. 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 with solifenacin also showed benefit on a number of Quality of Life measures, such as general limitations, emotions, symptom severity, severity measures and sleep/energy.

Table 2: Results (pooled data) of two controlled Phase 3 European studies with a treatment duration of 12 weeks

	Placebo	**Solifenacin succinate 5 mg o.d.**	**Solifenacin Succinate 10 mg o.d.**
No. of micturitions/24 hr			
Mean reduction from baseline	1.4	2.3	2.8
% change from baseline	(11%)	(19%)	(23%)
n	534	552	554
p-value*		<0.001	<0.001
No. of urgency episodes/24 hr			
Mean reduction from baseline	1.7	2.9	3.0
% change from baseline	(31%)	(49%)	(53%)
n	526	548	550
p-value*		<0.001	<0.001
No. of incontinence episodes/24 hr			
Mean reduction from baseline	1.0	1.5	1.5
% change from baseline	(33%)	(58%)	(56%)
n	306	314	323
p-value*		<0.001	<0.001
No. of nocturia episodes/24 hr			
Mean reduction from baseline	0.5	0.6	0.6
% change from baseline	(25%)	(30%)	(30%)
n	459	494	494
p-value*		0.033	0.006
Volume voided/micturition			
Mean increase from baseline	10 mL	32 mL	38 mL
% change from baseline	(7%)	(21%)	(26%)

n	534	552	554
p-value*		<0.001	<0.001
No. of pads/24 hr			
Mean reduction from baseline	0.8	1.3	1.3
% change from baseline	(27%)	(46%)	(48%)
n	238	236	242
p-value*		<0.001	<0.001

Note: Not all parameters and treatment groups were evaluated in each individual study. Therefore, the number of patients listed may deviate per parameter and treatment group.
*P-value for the pairwise comparison to placebo.

Table 3: Results (pooled data) of two controlled Phase 3 US studies with a treatment duration of 12 weeks.

	Placebo	**Solifenacin succinate 10 mg o.d.**
No. of micturitions/24 hr		
Mean reduction from baseline	1.4	2.7
% change from baseline	(12%)	(23%)
n	604	604
p-value*		<0.001
No. of urgency episodes/24 hr		
Mean reduction from baseline	2.2	3.7
% change from baseline	(31%)	(56%)
n	598	601
p-value*		<0.001
No. of incontinence episodes/24 hr		
Mean reduction from baseline	1.2	2.0
% change from baseline	(41%)	(67%)
n	475	455
p-value*		<0.001
No. of nocturia episodes/24 hr		
Mean reduction from baseline	0.4	0.5
% change from baseline	(24%)	(29%)
n	546	541
p-value*		0.012
Volume voided/micturition		
Mean increase from baseline	8 mL	47 mL
% change from baseline	(4%)	(26%)
n	601	602
p-value*		<0.001

Note: Not all parameters and treatment groups were evaluated in each individual study. Therefore, the number of patients listed may deviate per parameter and treatment group.
*P-value for the pairwise comparison to placebo.

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 62.9 ng/mL for the 5 and 10 mg solifenacin tablets, respectively. The t_{max} is independent of the dose. The C_{max} and AUC increase in proportion to the dose between 5 to 40 mg. Absolute bioavailability is approximately 90%.

Food intake does not directly affect C_{max} and AUC of solifenacin.

Distribution

The apparent volume of distribution of solifenacin following intravenous administration is about 600 litres. Solifenacin is highly bound to plasma proteins (approximately 98%), primarily to 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/hour and the terminal half-life of solifenacin is 45 - 68 hours. After oral dosing, one pharmacologically active (4*R*-hydroxy solifenacin) and three inactive metabolites (*N*-glucuronide, *N*-oxide and 4*R*-hydroxy-*N*-oxide of solifenacin) have been identified in plasma in addition to solifenacin.

Excretion

After a single administration of 10mg [^{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 drug; 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).

Characteristics in specific groups of subjects or patients

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 tmax was slightly slower in the elderly and the terminal half-life was approximately 20% longer in elderly subjects. These modest differences were considered not clinically significant.

Children and Adolescents

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 t½ 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 t½ 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, genotoxicity, carcinogenic potential and toxicity to reproduction.

6. Pharmaceutical Particulars

6.1 List of excipients

Solifenacin Mylan also contains:

Core tablet:

- lactose
- maize starch
- Hypromellose
- purified talc
- magnesium stearate.

Film Coating:

- Hypromellose
- titanium dioxide
- propylene glycol
- iron oxide yellow
- iron oxide red (10 mg).

Solifenacin Mylan is gluten free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C, protect from light.

6.5 Nature and contents of container

Solifenacin Mylan film coated tablets are available in blister packs of 30 tablets and bottles of 500 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

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9. Date of First Approval

23 October 2017

10. Date of Revision of the Text

03 September 2020

Section	Summary of new information
4.4	Clarity added that solifenacin succinate is not indicated for treatment of overactive bladder in the paediatric population.
4.6	Inserted statement re: fertility
4.8	Update adverse events: frequency; add muscular weakness, confusional state; undesirable effects marked as being observed post-marketing; Dysguesia moved to GI Disorders.
5.2	Characteristics in specific groups of subjects or patients
6.1	Minor reformatting
8	Updated phone number