NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Solifenacin succinate (Max Health)
Solifenacin succinate 5 mg and 10 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each 10 mg tablet contains 10 mg solifenacin succinate, equivalent to 7.5 mg solifenacin.

Excipient(s) with known effect: lactose monohydrate 105.5 mg (5 mg tablet) and 100.5 mg (10 mg tablet)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solifenacin succinate 5 mg tablet: The film-coated tablet is light yellow colored, round, biconvex, film coated tablets, debossed with “EG” on one side and “1” on other side.

Solifenacin succinate 10 mg tablet: The film-coated tablet is light pink colored, round, biconvex, film coated tablets, debossed with “EG” on one side and “2” on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Solifenacin succinate 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

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

Adults:
In adults, the recommended dose is 5mg once daily. If needed, this can be increased to 10mg once daily.

Children:
Safety and effectiveness in children has not yet been established. Therefore, solifenacin succinate 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 succinate should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other strong CYP3A4-inhibitors (see **Section 4.5** below).

4.3 Contraindications

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

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

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.
- hiatus hernia/gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis
- autonomic neuropathy
- 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 **Section 4.2**). Doses should not exceed 5 mg for these patients.
- Concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole (see **Sections 4.2 and 4.5**).

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.

QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia.

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

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

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 should be taken.

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

4.5 Interaction with other medicines and other forms of interaction

Pharmacological interactions:
Concomitant medication with other medicines 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 succinate 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 medicines 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 medicines metabolised by these CYP enzymes.

Effects of other medicines on the pharmacokinetics of solifenacin

Solifenacin is metabolised by CYP3A4.

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

Simultaneous treatment of solifenacin and a potent 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

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

Warfarin:
Intake of solifenacin succinate did not alter the pharmacokinetics of *R*-warfarin or *S*-warfarin or their effect on prothrombin time.

Digoxin:
Intake of solifenacin succinate 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 succinate in pregnant women. Consequently, solifenacin succinate is not recommended for use during pregnancy.

Breast-feeding
No data concerning the excretion of solifenacin into human milk are available. Consequently, the use of solifenacin succinate should be avoided during lactation.

Fertility
No fertility data are available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Due to the pharmacological effect of solifenacin, solifenacin succinate may cause anticholinergic side effects of generally mild or moderate severity. The frequency of anticholinergic undesirable effects is dose related.

The most commonly reported adverse reaction with solifenacin succinate 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, medicine compliance was very high (approximately 99%) and approximately 90% of the patients treated with solifenacin succinate completed the full study period of 12 weeks treatment.

Table 1 Tabulated list of adverse reactions

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***
Cardiac disorders					Torsade de Pointes*# Atrial fibrillation*# Palpitations*# Tachycardia*# Electrocardiogram QT prolonged*#
Gastrointestinal disorders	Dry mouth	Constipation, nausea, dyspepsia,	Gastro-oesophageal reflux diseases,	Faecal impaction,	Abdominal discomfort*#, Ileus*#

		abdominal pain	dry throat	Colonic obstruction, Vomiting#	
Infections and infestations			Urinary tract infection*, Cystitis*		
Investigations					Electrocardiogram QT prolonged#
Immune system disorder					Anaphylactic reaction*#
Metabolism and nutrition disorders					Decreased appetite*# Hyperkalaemia*#
Nervous system disorders			Somnolence, Dysgeusia	Dizziness #, Headache #	
Eye disorders		Blurred vision	Dry eyes		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)*#
Musculoskeletal and connective tissue disorders					Muscular weakness*#
Renal and urinary disorders			Difficulty in micturition	Urinary retention	Renal impairment*#
Psychiatric disorders					Confusional state#, Hallucinations # Delirium #*

Observed post-marketing

* Cannot be estimated from the available data.

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://pophealth.my.site.com/carmreportnz/s/

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 succinate and medicines 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 succinate 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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 with selectivity for the urinary bladder over salivary glands in vivo.

Pharmacodynamic effects:
Treatment with solifenacin succinate 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 **Table 3** (US studies) below, both the 5 mg and 10 mg doses of solifenacin succinate 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 succinate 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 % change from baseline n p-value*	1.4 (11%) 534	2.3 (19%) 552 <0.001	2.8 (23%) 554 <0.001
No. of urgency episodes/24 hr			
Mean reduction from baseline % change from baseline n p-value*	1.7 (31%) 526	2.9 (49%) 548 <0.001	3.0 (53%) 550 <0.001
No. of incontinence episodes/24 hr			
Mean reduction from baseline % change from baseline n p-value*	1.0 (33%) 306	1.5 (58%) 314 <0.001	1.5 (56%) 323 <0.001
No. of nocturia episodes/24 hr			
Mean reduction from baseline % change from baseline n p-value*	0.5 (25%) 459	0.6 (30%) 494 0.033	0.6 (30%) 494 0.006
Volume voided/micturition			
Mean increase from baseline % change from baseline n p-value*	10 mL (7%) 534	32 mL (21%) 552 <0.001	38 mL (26%) 554 <0.001
No. of pads/24 hr			
Mean reduction from baseline % change from baseline n p-value*	0.8 (27%) 238	1.3 (46%) 236 <0.001	1.3 (48%) 242 <0.001

Note: 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 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 % change from baseline n p-value*	1.4 (12%) 604	2.7 (23%) 604 <0.001
No. of urgency episodes/24 hr		

Mean reduction from baseline % change from baseline n p-value*	2.2 (31%) 598	3.7 (56%) 601 <0.001
No. of incontinence episodes/24 hr		
Mean reduction from baseline % change from baseline n p-value*	1.2 (41%) 475	2.0 (67%) 455 <0.001
No. of nocturia episodes/24 hr		
Mean reduction from baseline % change from baseline n p-value*	0.4 (24%) 546	0.5 (29%) 541 0.012
Volume voided/micturition		
Mean increase from baseline % change from baseline n p-value*	8 mL (4%) 601	47 mL (26%) 602 <0.001

Note: 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 pairwise comparison to placebo.

5.2 Pharmacokinetic properties

Absorption:

After intake of solifenacin succinate 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 10mg 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 40mg. 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 (approx: 98%), primarily to α1-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 medicine; 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).

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

Core tablet:
Maize starch
Lactose monohydrate
Hypromellose
Magnesium stearate

Film coating:
Opadry yellow 02F520011 (5 mg tablet)
Opadry pink 02F540006 (10 mg tablet)

6.2 Incompatibilities

Nil

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Solifenacin succinate 5 mg tablets are packed in PVC/Aluminium blisters in 30 tablet packs.
Solifenacin succinate 10 mg tablets are packed in PVC/Aluminium blisters in 30 tablet packs.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

23 August 2018

10 DATE OF REVISION OF THE TEXT

15 August 2024

SUMMARY TABLE OF CHANGES

Section Changed	**Summary of new information**
All	Editorial
4.3	Minor wording updates
4.4	Additional precautions regarding: Hiatus hernia/gastro-oesophageal reflux; autonomic neuropathy; safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity; rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption. The maximum effect of solifenacin can be determined after 4 weeks at the earliest.
4.5	Minor wording updates. Addition of examples of potent CYP3A4 inhibitors: ritonavir, nelfinavir, itraconazole.
4.8	Additional wording regarding the frequency of anticholinergic undesirable effects is dose related. Updated adverse events (table 1) Updated hyperlink for AE reporting
8	Updated sponsor address