PRODUCT MONOGRAPH

[Pr]TARO-SOLIFENACIN

Solifenacin Succinate Tablets

5 mg and 10 mg

Urinary antispasmodic

ATC: G04BD08

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Nonmedicinal Ingredients
Oral	tablet, film coated 5 mg, 10 mg	anhydrous lactose, corn starch, hypromellose, magnesium stearate, polyethylene glycol, red ferric oxide (10 mg), talc, titanium dioxide and yellow ferric oxide (5 mg)

INDICATIONS AND CLINICAL USE

TARO-SOLIFENACIN (solifenacin succinate) is indicated for:

- Treatment of overactive bladder in adults with symptoms of urge urinary incontinence, urinary urgency and urinary frequency.

Geriatrics:

In placebo controlled clinical studies, similar safety and effectiveness were observed between older (623 patients ≥ 65 years and 189 patients ≥ 75 years) and younger patients (1188 patients < 65 years) treated with solifenacin succinate (see ACTION AND CLINICAL PHARMACOLOGY).

Pediatrics:

Safety and effectiveness in children have not yet been established.

CONTRAINDICATIONS

- Patients with urinary retention, dependent on dialysis, gastroparesis or narrow angle glaucoma

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

General

TARO-SOLIFENACIN, like other anticholinergic drugs, should be administered with caution in patients with impaired ability to sweat, to reduce the risk of heat prostration, and in patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

TARO-SOLIFENACIN may cause blurred vision and somnolence. Patients should be advised to exercise caution in driving or operating machinery until the drug's effect on vision and somnolence has been determined.

Angioedema of the face, lips, tongue, and/or larynx have been reported with solifenacin. In some cases angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, solifenacin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Anaphylactic reaction has been reported in some patients treated with solifenacin succinate. In patients who develop anaphylactic reactions, TARO-SOLIFENACIN should be discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Monitoring and Laboratory Tests

Monitoring of the QT/QTc interval and/or serum electrolyte levels may be appropriate in high risk patients who are being treated with solifenacin succinate, such as:

Patients with known congenital or acquired QT/QTc interval prolongation or electrolyte disturbances;

Patients who are taking drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes such as Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or those taking potent CYP3A4 inhibitors.

Carcinogenesis and Mutagenesis

Solifenacin succinate 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.

No increase in tumors was found following the administration of solifenacin succinate to male and female mice for 104 weeks at doses up to 200 mg/kg/day (5 and 9 times human exposure at the maximum recommended human dose [MRHD], respectively), and male and female rats for 104 weeks at doses up to 20 and 15 mg/kg/day, respectively (< 1 times exposure at the MRHD).

Cardiovascular

A study of the effect of solifenacin on the QT interval was conducted in 76 healthy women. The QTc interval prolongation effect appeared 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 interval overlapped. This study was not designed to draw direct statistical comparison between the drugs or the dose levels (see ACTION AND CLINICAL

PHARMACOLOGY). This observation should be considered in clinical decisions to prescribe solifenacin succinate for patients with a known history of QT prolongation or patients who are taking medications known to prolong the QT interval.

The effect of solifenacin on QTc interval change in males has not been investigated, and caution should be taken in extrapolating the findings of this study to male subjects.

The effect of solifenacin on QTc interval change in elderly subjects with occult renal insufficiency, (in whom plasma concentration of solifenacin might be higher than those observed in younger subjects), has not been investigated.

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

Caution should be used when prescribing antimuscarinics/anticholinergics to patients with pre-existing cardiac diseases.

Gastrointestinal

TARO-SOLIFENACIN, like other anticholinergics, should be used with caution in patients with decreased gastrointestinal motility.

Hepatic

TARO-SOLIFENACIN should be used with caution in patients with reduced hepatic function. Doses of TARO-SOLIFENACIN greater than 5 mg are not recommended in patients with moderate hepatic impairment. (Child-Pugh B). TARO-SOLIFENACIN is not recommended for patients with severe hepatic impairment (Child-Pugh C) (see ACTION AND CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Renal

Use with caution in patients with reduced renal function. Doses of TARO-SOLIFENACIN greater than 5 mg are not recommended in patients with severe renal impairment (CL_{cr} < 30 mL/min) (see ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

TARO-SOLIFENACIN is contraindicated in dialysis dependent patients (see CONTRAINDICATIONS).

Sexual Function / Reproduction

No clinical data are available from reproductively competent women who have received long-term treatment with solifenacin succinate. The potential risk to such women is presently unknown. Therefore, TARO-SOLIFENACIN should be used during pregnancy only if the potential benefit for the mother justifies the potential risk for the fetus. Women of childbearing potential should be considered for treatment only if using adequate contraception.

In a 13-week toxicity study in mice treated with 400 mg/kg/day (15 times exposure at the maximum recommended human dose [MRHD]) of solifenacin succinate and in a 26-week toxicity study in rats treated with 30 mg/kg/day (< 1 times exposure at the MRHD) or greater of solifenacin succinate, follicular degeneration/reduced corpora lutea in the ovaries and/or uterine atrophy were observed in female animals that died or were sacrificed in extremis. Low uterine

weight and uterine immaturity were observed in female dogs treated with 3 mg/kg/day (< 1 times exposure at the MRHD) or greater of solifenacin succinate in the 13-week toxicity study.

Solifenacin succinate had no effect on reproductive function, fertility or early embryonic development of the fetus in male and female mice treated with 250 mg/kg/day (13 times exposure at the MRHD) of solifenacin succinate for 4 weeks and 2 weeks, respectively, and in male rats treated with 50 mg/kg/day (< 1 times exposure at the MRHD) for 4 weeks and female rats treated with 100 mg/kg/day (1.7 times exposure at the MRHD) for 2 weeks.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies investigating the effects of solifenacin succinate in pregnant women. Animal reproduction studies are not always predictive of human response; therefore, TARO-SOLIFENACIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Women of childbearing potential should be considered for treatment only if using adequate contraception.

Reproduction studies have been performed in mice, rats and rabbits. After oral administration of ^{14}C-solifenacin succinate to pregnant mice, drug-related material has been shown to cross the placental barrier. No embryotoxicity or teratogenicity was observed in mice treated with 30 mg/kg/day (1.2 times exposure at the maximum recommended human dose [MRHD]). Administration of solifenacin succinate to pregnant mice, at doses of 100 mg/kg and greater (3.6 times exposure at the MRHD), during the major period of organ development resulted in reduced fetal body weights. Administration of 250 mg/kg/kg (7.9 times exposure at the MRHD) to pregnant mice resulted in an increased incidence of cleft palate. *In utero* and lactational exposures to maternal doses of solifenacin succinate of 100 mg/kg/day and greater (3.6 times exposure at the MRHD) resulted in reduced peripartum and postnatal survival, reductions in body weight gain, and delayed physical development (eye opening and vaginal patency). An increase in the percentage of male offspring was also observed in litters from offspring exposed to maternal doses of 250 mg/kg/day. No embryotoxic effects were observed in rats at up to 50 mg/kg/day (< 1 times exposure at the MRHD) or in rabbits at up to 50 mg/kg/day (1.8 times exposure at the MRHD).

The effect of solifenacin succinate on labor and delivery in humans has not been studied. There were no effects on natural delivery in mice treated with 30 mg/kg/day (1.2 times exposure at the MRHD). Administration of solifenacin succinate at 100 mg/kg/day (3.6 times exposure at the MRHD) or greater increased peripartum pup mortality.

Nursing Women: It is not known whether solifenacin is excreted in human milk. Because many drugs are excreted in human milk, TARO-SOLIFENACIN should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue TARO-SOLIFENACIN in nursing mothers.

After oral administration of ^{14}C-solifenacin succinate to lactating mice, radioactivity was detected in maternal milk. There were no adverse observations in mice treated with 30 mg/kg/day (1.2 times exposure at the maximum recommended human dose [MRHD]). Pups of female mice treated with 100 mg/kg/day (3.6 times exposure at the MRHD) or greater revealed

reduced body weights, postpartum pup mortality or delays in the onset of reflex and physical development during the lactation period.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Expected side effects of antimuscarinic agents are dry mouth, constipation, blurred vision (accommodation abnormalities), urinary retention, and dry eyes. The most common adverse events reported in patients treated with solifenacin succinate were dry mouth and constipation and the incidence of these side effects was higher in the 10 mg compared to the 5 mg dose group. Compared to twelve weeks of treatment with solifenacin succinate, the incidence and severity of adverse events were similar in patients who remained on the drug for up to 12 months. The most frequent reason for discontinuation due to an adverse event was dry mouth, 1.5%.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Solifenacin succinate has been evaluated for safety in 1811 patients in randomized, placebo-controlled trials. In the four 12-week double-blind clinical trials, there were three intestinal serious adverse events in patients, all treated with solifenacin succinate 10 mg (one fecal impaction, one colonic obstruction, and one intestinal obstruction). The overall rate of serious adverse events in the double-blind trials was 2%.

Table 1 lists adverse events, regardless of causality, that were reported in randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with solifenacin succinate 5 or 10 mg once daily for up to 12 weeks.

Table 1: Percentages of Patients with Treatment-Emergent Adverse Events Exceeding Placebo Rate and Reported by 1% or More Patients for Combined Pivotal Studies

SYSTEM ORGAN CLASS MedDRA Preferred Term	Placebo (%)	Solifenacin Succinate 5 mg (%)	Solifenacin Succinate 10 mg (%)
Number of Patients	1216	578	1233
Number of Patients with Treatment-emergent AE	634	265	773
Eye Disorders			
Vision Blurred	1.8	3.8	4.8
Dry Eyes NOS	0.6	0.3	1.6
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
Abdominal Pain Upper	1.0	1.9	1.2
Vomiting NOS	0.9	0.2	1.1
General Disorders And Administration Site Conditions			
Fatigue	1.1	1.0	2.1
Edema Lower Limb	0.7	0.3	1.1
Infections And Infestations			
Urinary Tract Infection NOS	2.8	2.8	4.8
Influenza	1.3	2.2	0.9
Pharyngitis NOS	1.0	0.3	1.1
Nervous System Disorders			
Dizziness	1.8	1.9	1.8
Psychiatric Disorders			
Depression NOS	0.8	1.2	0.8
Renal And Urinary Disorders			
Urinary Retention	0.6	0	1.4
Respiratory, Thoracic And Mediastinal Disorders			
Cough	0.2	0.2	1.1
Vascular Disorders			
Hypertension NOS	0.6	1.4	0.5

One young male subject developed a reversible increase in hepatic enzymes following a single dose of solifenacin during a Phase I study. Although causality has not been established, special attention should be paid to subjects who develop abnormal liver function tests after starting solifenacin and consideration given to discontinuing treatment.

Post-Market Adverse Drug Reactions

In addition to the adverse events observed in clinical trials, the following events have been reported in association with solifenacin succinate use in worldwide post-marketing experience, although the frequency of events or a causal relationship with solifenacin succinate could not always be confirmed.

General: peripheral edema

Cardiovascular: atrial fibrillation, tachycardia, palpitations, and Torsades de Pointes

Eye Disorder: glaucoma

Gastrointestinal: abdominal pain, dysgeusia, gastroesophageal reflux disease, ileus, stomach discomfort, and vomiting

Hepatobiliary: liver disorders mostly characterized by abnormal liver function tests: AST (aspartate aminotransferase), ALT (alanine aminotransferase), and GGT (gamma-glutamyl transferase)

Immune System: anaphylactic reaction and hypersensitivity reactions including rash, pruritus, and urticaria

Investigations: electrocardiogram QT prolonged

Metabolism and Nutrition: decreased appetite and hyperkalemia

Musculoskeletal and Connective Tissue Disorders: muscular weakness

Nervous System: dizziness, headache, and somnolence

Psychiatric: confusional state, delirium, disorientation, and hallucination

Renal and Urinary: renal impairment and urinary retention

Respiratory, Thoracic and Mediastinal Disorders: dysphonia and nasal dryness

Skin and Subcutaneous Tissue: angioedema with airway obstruction, dry skin, exfoliative dermatitis, and erythema multiforme

DRUG INTERACTIONS

Overview

Concomitant medication with other medicinal products with anticholinergic properties may result in more pronounced therapeutic effects and undesirable effects. An interval of approximately 1-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 may reduce the effect of medicinal products that stimulate the motility of the gastrointestinal tract, such as metoclopramide.

Drugs Metabolized by Cytochrome P450: At therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes.

CYP3A4 Inhibitors*: In vitro* drug metabolism studies have shown that solifenacin is a substrate of CYP3A4. Inducers or inhibitors of CYP3A4 may alter solifenacin pharmacokinetics. Therefore, the dose of solifenacin should be maintained at, or dropped to, 5 mg daily while patients are taking a potent CYP3A4 inhibitor such as ketoconazole, clarithromycin, erythromycin, diclofenac, nefazodone, verapamil and others.

Drug-Drug Interactions

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 solifenacin succinate should be restricted to 5 mg, when used simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors. Table 2 shows the investigated potential drug-drug interactions.

Table 2: Investigated Potential Drug-Drug Interactions

Drug Name	Ref	Effect	Clinical Comment
Digoxin	CT	No significant effect on pharmacokinetics of digoxin in healthy subjects.	
Ketoconazole	CT	↑ solifenacin The mean C_{max} and AUC of solifenacin increased by 1.5 and 2.7-fold, respectively.	It is recommended not to exceed a 5 mg daily dose of solifenacin succinate when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors.
Oral Contraceptives (OCP)	CT	No significant effect on plasma concentration of combined OCPs (ethinyl estradiol/levonorgestrel)	
Warfarin	CT	No significant effect on pharmacokinetics of *R*-warfarin or *S*-warfarin	

CT= Clinical Trial

Drug-Food Interactions: Co-ingestion of grapefruit juice with TARO-SOLIFENACIN may increase the serum level of solifenacin.

Drug-Herb Interactions: Interactions with herbal products have not been established and caution should be taken if such agents are used by patients.

Drug-Laboratory Test Interactions: Interactions with laboratory tests have not been investigated.

DOSAGE AND ADMINISTRATION

Dosing Considerations:

Dose Adjustment in Renal Impairment:

For patients with severe renal impairment (CL_{cr} < 30 mL/min), a daily dose of TARO-SOLIFENACIN greater than 5 mg is not recommended. TARO-SOLIFENACIN is contraindicated in dialysis-dependent patients (see CONTRAINDICATIONS).

Dose Adjustment in Hepatic Impairment:

For patients with moderate hepatic impairment (Child-Pugh B), a daily dose of TARO-SOLIFENACIN greater than 5 mg is not recommended. Use of TARO-SOLIFENACIN in patients with severe hepatic impairment (Child Pugh C) is not recommended.

Dose Adjustment with CYP3A4 Inhibitors:
When administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors, a daily dose of TARO-SOLIFENACIN should be maintained at, or dropped to, 5 mg daily.

Recommended Dose and Dosage Adjustment
The recommended dose of TARO-SOLIFENACIN is 5 mg once daily. If the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily.

TARO-SOLIFENACIN should be taken with liquids and swallowed whole. TARO-SOLIFENACIN can be administered with or without food, without regard to meals.

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

Missed Dose
If a dose is missed, the next tablet should be taken as planned. Doses should not be doubled to make up for a missed dose.

OVERDOSAGE

Acute: 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. The patient was given charcoal treatment and recovered without sequelae.

Chronic: Intolerable anticholinergic side effects (fixed and dilated pupils, blurred vision, failure of heel-to-toe exam, tremors and dry skin) occurred on day 3 in normal volunteers taking 50 mg daily (5 times the maximum recommended therapeutic dose) and resolved within 7 days following discontinuation of drug.

Treatment of Overdosage: In the event of overdose with solifenacin succinate, treat with gastric lavage and appropriate supportive measures. ECG monitoring is also recommended.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of urinary bladder smooth muscle and stimulation of salivary secretion. Solifenacin is a competitive muscarinic receptor antagonist with selectivity for the urinary bladder over salivary glands *in vitro* and *in vivo* (mice, rats and monkeys). In cells isolated from rats and monkeys, solifenacin inhibited carbachol-induced intracellar calcium mobilization more potently in bladder smooth muscle cells than in salivary gland cells. The bladder selectivity of solifenacin in monkeys is significantly greater than those of other antimuscarinics as illustrated by selectivity ratios (bladder/salivary gland) of 2.1, 0.51, 0.65, 0.46 and 0.61 for solifenacin, oxybutynin, tolterodine, darifenacin and atropine, respectively. In anesthetized rats, solifenacin is also more potent in inhibiting carbachol-induced increases in intravesical pressure than in

inhibiting salivary secretion. Although other antimuscarinics also showed some tissue selectivity, the selectivity ratio of solifenacin (6.5) estimated from its potency to inhibit urinary bladder and salivary gland was the greatest among all antimuscarinics tested (1.0 to 2.4).

Pharmacokinetics

Table 3: Summary of Pharmacokinetic Parameters in the Normal Population

Solifenacin Dose	C_{max} ng/mL	$t_{½}$ (h)	AUC $_{0\text{-}24h}$ ng•h/mL
5 mg o. d.	32.3 (11.2)	64.4 (18.6)	637 (239)
10 mg o. d.	62.9 (23.1)	60.9 (17.1)	1236 (459)

Data are expressed as mean (SD)

Absorption: After oral administration of solifenacin succinate to healthy volunteers, peak plasma levels (C_{max}) of solifenacin are reached within 3 to 8 hours after administration and at steady state, ranged from 32.3 to 62.9 ng/mL for the 5 and 10 mg solifenacin succinate tablets, respectively. The absolute bioavailability of solifenacin is approximately 90%, and plasma concentrations of solifenacin are proportional to the dose administered.

Effect of Food*:* There is no significant effect of food on the pharmacokinetics of solifenacin.

Distribution: Solifenacin is approximately 98% (*in vivo*) bound to human plasma proteins, principally to α_1-acid glycoprotein. Solifenacin is highly distributed to non-CNS tissues, having a mean steady-state volume of distribution of 600 L.

Metabolism: Solifenacin is extensively metabolized 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: Following the administration of 10 mg of ^{14}C-solifenacin succinate to healthy volunteers, 69.2% of the radioactivity was recovered in the urine and 22.5% in the feces over 26 days. Less than 15% (as mean value) of the dose was recovered in the urine as intact solifenacin. The major metabolites identified in urine were *N*-oxide of solifenacin, 4*R*-hydroxy solifenacin and 4*R*-hydroxy-*N*-oxide of solifenacin and in feces, 4*R*-hydroxy solifenacin. The elimination half-life of solifenacin following chronic dosing is approximately 45 - 68 hours.

Special Populations and Conditions

Geriatrics: Multiple dose studies of solifenacin succinate in elderly volunteers (65 to 80 years) showed that C_{max}, AUC and $t_{1/2}$ values were 20 – 25% higher as compared to the younger volunteers (18 to 55 years) (see INDICATIONS AND CLINICAL USE).

Pediatrics: The pharmacokinetics of solifenacin have not been established in pediatric patients.

Gender: The pharmacokinetics of solifenacin are not significantly influenced by gender.

Renal Insufficiency: Solifenacin succinate should be used with caution in patients with renal impairment. There is a 2.1-fold increase in AUC and 1.6-fold increase in $t_{1/2}$ of solifenacin in patients with severe renal impairment. Doses of solifenacin succinate greater than 5 mg are not recommended in patients with severe renal impairment (CL_{cr} < 30 mL/min) (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION). Solifenacin succinate is contraindicated in dialysis-dependent patients (see CONTRAINDICATIONS).

Hepatic Insufficiency: Solifenacin succinate should be used with caution in patients with reduced hepatic function. There is a 2-fold increase in the $t_{1/2}$ and 35% increase in AUC of solifenacin in patients with moderate hepatic impairment. Doses of solifenacin succinate greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). Solifenacin succinate is not recommended for patients with severe hepatic impairment (Child-Pugh C) (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Cardiac Electrophysiology

The effect of 10 mg and 30 mg solifenacin succinate on the QT interval was evaluated at the time of peak plasma concentration of solifenacin in a multi-dose, randomized, double-blind, placebo and positive-controlled (moxifloxacin 400 mg) trial. Patients were randomized 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. Study subjects were female volunteers aged 19 to 79 years. 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 those observed upon co-administration of 10 mg solifenacin succinate with potent CYP3A4 inhibitors (e.g., ketoconazole, 400 mg). Due to the sequential dose escalating nature of the study, baseline EKG 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, QTc effects were analyzed utilizing the parallel placebo control arm rather than the pre-specified intra-patient analysis. Representative results are shown in Table 4.

Table 4: QTc Changes in msec (90% CI) from Baseline at T_{max} (Relative to placebo)

Drug/Dose	Fridericia Method (Using Median Difference)
Solifenacin 10 mg	0 (-5,5)
Solifenacin 30 mg	7 (2,12)

Results displayed are those derived from the parallel design portion of the study and represent the comparison of Group 1 to time-matched placebo effects in Group 2.

The effect of moxifloxacin on the QT interval was evaluated in 3 different sessions of the trial. All subjects received moxifloxacin in Session 1 while only those subjects in the placebo/moxifloxacin group received moxifloxacin in Sessions 3 and 5. The placebo-subtracted mean changes (90% CI) for moxifloxacin in the three sessions (1, 3 and 5) were 11 (7, 14), 12 (8, 17), and 16 (12, 21), respectively.

The QT interval prolonging effect appeared greater for the 30 mg compared to the 10 mg dose of solifenacin. The lower limit of the 90% confidence interval was greater than zero in the 30 mg dose of solifenacin. This study was not designed to draw direct statistical conclusions between the drugs or the dose levels.

The effect of solifenacin on QTc interval change in males has not been investigated, and caution should be taken in extrapolating the findings of this study to male subjects.

STORAGE AND STABILITY

Store between 15°C to 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TARO-SOLIFENACIN 5 mg tablets are off white to light yellow colored, film coated, round, biconvex tablets marked with code '**RK75**' on one side and plain on the other side. These are available in HDPE bottles of 30's, 100's and 500's and blister pack of 10's (1 X 10 tablets).

TARO-SOLIFENACIN 10 mg tablets are light pink colored, film coated, round, biconvex tablets marked with code '**RK76**' on one side and plain on the other side. These are available in HDPE bottles of 30's, 100's and 500's and blister pack of 10's (1 X 10 tablets).

Each TARO-SOLIFENACIN tablet, containing 5 mg or 10 mg of solifenacin succinate (equivalent to solifenacin 3.8 mg and 7.5 mg, respectively), is formulated for oral administration. In addition to the active ingredient, solifenacin succinate, each TARO-SOLIFENACIN tablet also contains the following inert ingredients: anhydrous lactose, corn starch, hypromellose, magnesium stearate, polyethylene glycol, red ferric oxide (10 mg), talc, titanium dioxide, and yellow ferric oxide (5 mg).

PART II: SCIENTIFIC INFORMATION

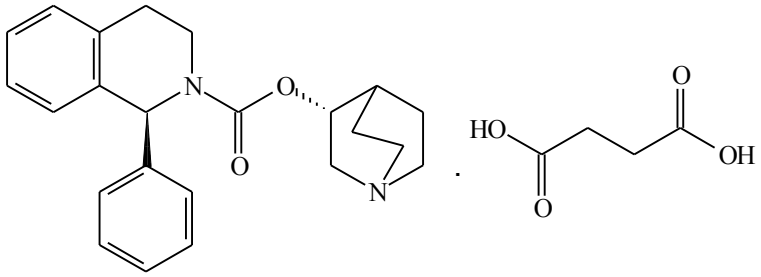
PHARMACEUTICAL INFORMATION

Proper Name: Solifenacin succinate

Molecular Formula: $C_{23}H_{26}N_2O_2 \cdot C_4H_6O_4$

Molecular Weight: 480.6 g/mol

Structural Formula:



Solifenacin Succinate

Physicochemical Properties:

Chemically, solifenacin succinate is butanedioic acid, compounded with (1*S*)-(3*R*)-1-azabicyclo[2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1*H*)-isoquinolinecarboxylate (1:1).

Solifenacin succinate is a white to off-white powder.

Solubility:

It is freely soluble in methanol and chloroform and soluble in water.

CLINICAL TRIALS

COMPARATIVE BIOAVAILABILITY STUDIES

A blinded, randomized, two-treatment, two-period, two-sequence, single-dose, crossover, bioequivalence study of TARO-SOLIFENACIN 10 mg tablets (Sun Pharma Canada Inc.) versus Vesicare® (solifenacin succinate) 10 mg tablets (Astellas Pharma Canada, Inc) was conducted in 22 healthy adult human male subjects under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Solifenacin (1 x 10 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_{0-72} (ng.hr/mL)	737.7 768.7 (30.7)	709.1 731.8 (24.7)	104.0	96.7-112.0
C_{max} (ng/mL)	18.7 19.3 (27.1)	18.1 18.5 (20.8)	103.3	96.4#-110.8#
T_{max}^ (h)	5.3 (3.0-9.0)	4.8 (3.0-7.0)	-	-

*TARO-Solifenacin (Solifenacin succinate Tablets 10 mg) (Sun Pharma Canada Inc.).
† Vesicare® (Solifenacin succinate) 10 mg tablets (Astellas Pharma Canada, Inc.) were purchased in Canada.
^ Expressed as Median (Range) only.
# For Information Purpose only.

Study Demographics and Trial Design

Table 5: Summary of Patient Demographics in Pivotal Clinical Trials

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age	Gender (%)		
905-CL-015	Randomized, double-blind, placebo-controlled, parallel-group, fixed dose	Placebo, 5 & 10 mg solifenacin and 4 mg tolterodine 12-week	Total :1077 Placebo: 267 Solifenacin 5 mg: 279, 10 mg: 268, Tolterodine: 263	Placebo: 58 Solifenacin 5 mg: 58 10 mg: 57 Tolterodine: 57		F	M
					Placebo:	76	24
					Solifenacin		
					5 mg:	73	27
					10 mg:	71	29
					Tolterodine	80	20
905-CL-018	"	Placebo, 5 & 10 mg solifenacin 12-week	Total: 907 Placebo: 301 5 mg: 299 10 mg: 307	Placebo: 56 5 mg: 55 10 mg: 56	Placebo:	81	19
					5 mg:	83	17
					10 mg:	82	18
905-CL-013	"	Placebo, 10 mg solifenacin 12-week	Total: 672 Placebo: 332 10 mg: 340	Placebo: 59 10 mg: 58	Placebo:	83	17
					10 mg:	80	20
905-CL-014	"	"	Total: 634 Placebo: 316 10 mg: 318	Placebo: 60 10 mg: 60	Placebo:	82	18
					10 mg:	83	17

Solifenacin succinate was evaluated in four twelve-week, double-blind, randomized, placebo-controlled, parallel group, multicenter clinical trials for the treatment of overactive bladder in patients having symptoms of urinary frequency, urgency and/or urge, or mixed incontinence (with a predominance of urge) [Table 5]. Study 015 also included a tolterodine group. Entry criteria required that patients have symptoms of overactive bladder for ≥ 3 months duration. These studies involved 3027 patients (1811 on solifenacin succinate 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 succinate doses and the other two evaluated only the 10 mg dose. 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. The majority of patients were Caucasian (93%) and female (80%) with a mean age of 58 years.

The primary endpoint in all four trials was the mean change from baseline to 12 weeks in number of micturitions/24 hours. Secondary endpoints included mean change from baseline to 12 weeks in number of incontinence episodes/24 hours, and mean volume voided per micturition. The efficacy of solifenacin succinate was similar across patient age and gender. The mean reduction in the number of micturitions per 24 hours was significantly greater with solifenacin succinate 5 mg (2.3; $p < 0.001$) and solifenacin succinate 10 mg (2.7; $p < 0.001$) compared to placebo (1.4).

The mean reduction in the number of incontinence episodes per 24 hours was significantly greater with solifenacin succinate 5 mg (1.5; $p < 0.001$) and solifenacin succinate 10 mg (1.8; $p < 0.001$) treatment groups compared to placebo (1.1). The mean increase in the volume voided per micturition was significantly greater with solifenacin succinate 5 mg (32.3 mL; $p < 0.001$) and solifenacin succinate 10 mg (42.5 mL; $p < 0.001$) compared with placebo (8.5 mL).

The results for the primary and secondary endpoints in the four individual 12-week clinical studies of solifenacin succinate are reported in Tables 6 through 9.

Table 6: Mean Change from Baseline to Endpoint for Solifenacin Succinate (5 mg and 10 mg Daily) and Placebo: 905-CL-015

Parameter	Placebo (N=253) Mean (SE)	Solifenacin Succinate 5 mg (N=266) Mean (SE)	Solifenacin Succinate 10 mg (N=264) Mean (SE)	Tolterodine (N=250) Mean (SE)
Urinary Frequency (Number of Micturitions / 24 Hours)*				
Baseline	12.2 (0.26)	12.1 (0.24)	12.3 (0.24)	12.1
Reduction	1.2 (0.21)	2.2 (0.18)	2.6 (0.20)	1.9
P value vs. Placebo		< 0.001	< 0.001	< 0.05
Number of Incontinence Episodes / 24 Hours**				
Baseline	2.7 (0.23)	2.6 (0.22)	2.6 (0.23)	2.3
Reduction	0.8 (0.18)	1.4 (0.15)	1.5 (0.18)	1.1
P value vs. Placebo		< 0.01	< 0.01	N.S.
Volume Voided per Micturition [mL]**				
Baseline	143.8 (3.37)	149.6 (3.35)	147.2 (3.15)	147.0
Increase	7.4 (2.28)	32.9 (2.92)	39.2 (3.11)	24.4
P value vs. Placebo		< 0.001	< 0.001	< 0.001

*Primary Endpoint
**Secondary Endpoint

Table 7: Mean Change from Baseline to Endpoint for Solifenacin Succinate (5 mg and 10 mg Daily) and Placebo: 905-CL-018

Parameter	Placebo (N=281) Mean (SE)	Solifenacin succinate 5 mg (N=286) Mean (SE)	Solifenacin succinate 10 mg (N=290) Mean (SE)
Urinary Frequency (Number of Micturitions / 24 Hours)*			
Baseline	12.3 (0.23)	12.1 (0.23)	12.1 (0.21)
Reduction	1.7 (0.19)	2.4 (0.17)	2.9 (0.18)
P value vs. Placebo		< 0.001	< 0.001
Number of Incontinence Episodes / 24 Hours**			
Baseline	3.2 (0.24)	2.6 (0.18)	2.8 (0.20)
Reduction	1.3 (0.19)	1.6 (0.16)	1.6 (0.18)
P value vs. Placebo		< 0.01	0.016
Volume Voided per Micturition [mL]**			
Baseline	147.2 (3.18)	148.5 (3.16)	145.9 (3.42)
Increase	11.3 (2.52)	31.8 (2.94)	36.6 (3.04)
P value vs. Placebo		< 0.001	< 0.001

*Primary Endpoint
**Secondary Endpoint

Table 8: Mean Change from Baseline to Endpoint for Solifenacin Succinate (10 mg Daily) and Placebo: 905-CL-013

Parameter	Placebo (N=309) Mean (SE)	Solifenacin Succinate 10 mg (N=306) Mean (SE)
Urinary Frequency (Number of Micturitions / 24 Hours)*		
Baseline	11.5 (0.18)	11.7 (0.18)
Reduction	1.5 (0.15)	3.0 (0.15)
P value vs. Placebo		< 0.001
Number of Incontinence Episodes / 24 Hours**		
Baseline	3.0 (0.20)	3.1 (0.22)
Reduction	1.1 (0.16)	2.0 (0.19)
P value vs. Placebo		< 0.001
Volume Voided per Micturition [mL]**		
Baseline	190.3 (5.48)	183.5 (4.97)
Increase	2.7 (3.15)	47.2 (3.79)
P value vs. Placebo		< 0.001

*Primary Endpoint
**Secondary Endpoint

Table 9: Mean Change from Baseline to Endpoint for Solifenacin Succinate (10 mg Daily) and Placebo: 905-CL-014

Parameter	Placebo (N=295) Mean (SE)	Solifenacin Succinate 10 mg (N=298) Mean (SE)
Urinary Frequency (Number of Micturitions / 24 Hours)*		
Baseline	11.8 (0.18)	11.5 (0.18)
Reduction	1.3 (0.16)	2.4 (0.15)
P value vs. Placebo		< 0.001
Number of Incontinence Episodes / 24 Hours**		
Baseline	2.9 (0.18)	2.9 (0.17)
Reduction	1.2 (0.15)	2.0 (0.15)
P value vs. Placebo		< 0.001
Volume Voided per Micturition [mL]**		
Baseline	175.7 (4.44)	174.1 (4.15)
Increase	13.0 (3.45)	46.4 (3.73)
P value vs. Placebo		< 0.001

*Primary Endpoint
**Secondary Endpoint

DETAILED PHARMACOLOGY

Animal Pharmacology

Solifenacin is a competitive muscarinic receptor antagonist. In radioligand binding assay, solifenacin has a high affinity for the human muscarinic M_3 receptor, with an affinity constant (Ki value) of 9.9 nM. It has marginal selectivity for the muscarinic M_3 receptor over the M_1 receptor (2.4 times) and moderate selectivity for the muscarinic M_3 receptor over the M_2 receptor (12 times). Solifenacin does not show any affinity for various other receptors and ion channels except for the sigma receptor and sodium channel site 2, but the affinity for these sites are 100-fold or more lower than that for the muscarinic M_3 receptor. In strips of rat and guinea pig urinary bladder, solifenacin competitively antagonized carbachol-induced contractile responses in a concentration-dependent manner. In anesthetized rats, solifenacin increased maximum bladder capacity and decreased maximum intravesical pressure in a dose-dependent manner.

In studies to assess the tissue selectivity of solifenacin using cells isolated from rats and monkeys, solifenacin inhibited carbachol-induced increases in cytosolic-free calcium ion levels ($[Ca^{2+}]i$) more potently in bladder smooth muscle cells than in salivary gland cells. Further, the bladder selectivity of solifenacin in monkeys was significantly greater than that of other antimuscarinics as illustrated by selectivity ratios (bladder/salivary gland) of 2.1, 0.51, 0.65 and 0.46 for solifenacin, oxybutynin, tolterodine and darifenacin, respectively. In anesthetized mice, solifenacin did not inhibit carbachol-induced salivary secretion at doses which potently inhibited carbachol-induced increases in intravesical pressure. Moreover, intravenously administered solifenacin was significantly more potent in inhibiting carbachol-induced increases in intravesical pressure (ID_{30} = 0.023 mg/kg) than in inhibiting salivary secretion (ID_{30} = 0.15 mg/kg) in anesthetized rats, with the bladder selectivity of 6.5. The bladder selectivity of tolterodine estimated from its potency to inhibit urinary bladder and salivary gland was 2.4, whereas oxybutynin (1.1) and darifenacin (1.2) did not show functional selectivity for urinary bladder.

Effects on the respiratory and cardiovascular system have been investigated. In the electrophysiological studies, solifenacin and tolterodine inhibited the potassium current in Chinese hamster ovary (CHO) cells expressing the *human ether-a-go-go*-related gene (hERG) using a whole-cell patch clamp technique, with IC_{50} values of 0.27 and 0.0089 μM, respectively. The IC_{50} value for solifenacin is 78 times higher than the maximum unbound human plasma concentration ($C_{max, u}$) at the maximum recommended human dose (MRHD). However, solifenacin at concentrations up to 0.3 μM (87 times higher than the $C_{max, u}$ at the MRHD) had no effect on action potential parameters in dog Purkinje fibers and guinea pig papillary muscles. Further, *in vivo* studies using anesthetized dogs demonstrated that intravenous administered solifenacin increased respiration rate, decreased blood pressure and left ventricular pressure and prolonged PR interval at 1 mg/kg or higher doses, however it had no effect on the QT interval at doses up to 3 mg/kg. At a dose of 10 mg/kg, complete atrioventricular block was observed in 4 of 5 animals and one of the 4 animals died.

Effects of orally administered solifenacin on the central nervous system, pupil size, gastrointestinal system and urinary excretion have been investigated. Solifenacin did not markedly affect the behavior of mice at doses up to 30 mg/kg. In mice and rabbits, solifenacin induced mydriasis, which is attributed to the primary action on muscarinic receptor, at 10 mg/kg or higher doses. Solifenacin at 3 mg/kg or higher doses induced emesis in dogs. However, solifenacin at doses up to 30 mg/kg did not affect gastrointestinal transit in mice and was not irritating to the gastric mucosa of rats. Solifenacin at doses up to 30 mg/kg had no effects on urine volume or electrolyte excretion in saline-loaded rats.

TOXICOLOGY

Table 10: Key Toxicological Findings in Experimental Animals with Solifenacin Succinate and Respective Multiples of Human Exposure at the Maximum Recommended Therapeutic Dose

Species/ Duration	Key Findings	Dose (mg/kg)	Multiples of Systemic Exposure Compared to Clinical	
			C_{max}	AUC
Repeat-Dose Toxicity				
Mouse, 13 weeks	Underactivity, ataxia, tremor, prostration, death	250 (male)	24.5	12.9
		250 (female)	23.1	13.1
Mouse, 26 weeks	Injuries in the mucosa of the small intestine	100 (male)	8.4	3.4
		100 (female)	7.0	2.4
Rat, 4 weeks	Decreased body weight gain and food consumption	25 (male)	< 1	< 1
		25 (female)	< 1	< 1
Rat, 26 weeks	Wet/yellow staining on perigenital area, high ALP and phosphorus, low ALT and cholesterol	10 (male)	< 1	< 1
		10 (female)	< 1	< 1
Dog, 4 weeks	Salivation, vomiting, tremor, decreased locomotor activity, decreased body weight and food consumption, ECG changes	30 (male)	19.1	12.1
		30 (female)	11.8	8.1
Dog, 13 weeks	Salivation, vomiting, ataxia, prostration, tremor, convulsion, abnormal gait/posture, abnormal respiration, ECG changes	18 (male)	5.3	2.5
	Low uterine weight, uterine immaturity	3 (female)	< 1	< 1
Dog, 52 weeks	Salivation, vomiting, ECG changes	20 (male)	11.8	6.0
		20 (female)	9.9	5.7
Genotoxicity				
Rat, Single	No clastogenicity	1000 (male)	8.2	4.9
Carcinogenicity				
Mouse, 2 years	No carcinogenicity	200 (male)	11.9	5.0
		200 (female)	14.4	9.0
Rats, 2 years	No carcinogenicity	20 (male)	< 1	< 1
		15 (female)	< 1	< 1
Reproductive and Developmental Toxicity				
Mouse, Pregnant	Low maternal and fetal body weights, an increase in peripartum pup mortality, delays in pup development	100 (female)	11.9	3.6
Rabbit, Pregnant	No effects on embryo-fetal development	50 (female)	4.9	1.8
Human PK Data at the Proposed Maximum Recommended Therapeutic Dose (10 mg/Day) for Comparison:				
Human (steady state)		10	1	1

Single-Dose Toxicity

Single-dose toxicity studies were conducted in rats and dogs. The approximate lethal doses were considered to be 1000 mg/kg for male rats, 500 mg/kg for female rats and 60 mg/kg for dogs. The results are shown in Table 11.

Table 11: Results of Single-Dose Toxicity Studies with Solifenacin Succinate

Species	Route	Dose (mg/kg/day)	No. of Animals	Duration	Findings
Rat (F344)	Oral (gavage)	Males: 0, 250, 500, 1000, 2000 Females: 0, 125, 250, 500, 1000	5/sex	1 Day	≥ 125 : Mydriasis. ≥ 250 : Body weight loss or decreased body weight gain in males and females. Decreased locomotor activity in females. 500 : 1 female died. ≥ 500 : Decreased locomotor activity in males. Small thymus in females. 1000 : 2 males and 4 females died. Prone position and ocular discharge in males and females. Salivation and chronic convulsion in females. 2000 : 5 males died. Prone position, lateral position, salivation, twitching, clonic convulsion, edema and necrosis in the glandular mucosa of the stomach.
Dog (Beagle)	Oral (capsule)	0, 10, 30, 60	1/sex	1 Day	≥ 10 : Vomiting and retching in the male and female. 30 : Mucous stool in the male. 60 : The female died. Twitching, mydriasis, abnormal gait, urinary incontinence and tonic convulsion in the female that died.

Repeat-Dose Toxicity

Repeat-dose toxicity studies were conducted in mice, rats and dogs. Based on the results of metabolism studies, it became clear that the mouse, dog and human have a similar metabolic profile. Thus the mouse and dog are considered to be appropriate species for the toxicological evaluation of solifenacin succinate. The results are summarized in Table 12.

Table 12: Results of Repeat-Dose Toxicity Studies with Solifenacin Succinate

Species, Strain, Number/Sex	Dose (mg/kg/day) Route Duration of Treatment	Findings (at mg/kg/day)	No-adverse-effect-level (NOAEL) (mg/kg/day)
Mouse (CD-1) 12 (main) 6 (recovery)	0, 30, 100, 250, 400 Oral (gavage) 13 weeks 0, 250, 400 Oral (gavage) 13 weeks followed by 5 weeks recovery	≥ 30 : Mydriasis in males. 250 : 1 female died. ≥ 250 : Underactivity, ataxia, tremor and prostration in males. Mydriasis, low submandibular gland and spleen weights in females. 400 : 5 males and 6 females died. Hunched posture, piloerection and abnormal respiration in males and females. Decreased body weight gain, low triglyceride and high relative liver weight in males. Underactivity, ataxia, tremor, prostration, convulsion, low glucose, high relative kidney weight, follicular degeneration, reduced corpora lutea and uterine atrophy in females. All changes reversed during the recovery period.	100
Mouse (CD-1) 15	0, 10, 30, 100, 200 Oral (gavage) 26 weeks	100 : Inflammation of the ileum in males and females. Epithelial regeneration and erosion of the duodenum in females. 200 : Pigment deposition in the Harderian gland, epithelial regeneration of the duodenum, ulcer of the ileum in males and females. Low total protein and albumin, mobilization of Kupffer cells in the liver, ulcer and inflammation of the jejunum in males. High plasma sodium, low plasma potassium and erosion of the duodenum in females.	30
Rat (F344) 12 (main) 6 (recovery)	0, 5, 10, 25, 50 Oral (gavage) 4 weeks 0, 25, 50 Oral (gavage) 4 weeks followed by 4 weeks recovery	≥ 10 : Mydriasis and abnormal respiratory sound in males and females. Salivation in males. ≥ 25 : Decreased food consumption in males and females. Decreased body weight gain in males. Salivation, soiled fur around the urethral orifice and a soiled coat around the nose and mouth in females. 50 : 1 female died. Decreased body weight gain and water consumption in females. All changes recovered or tended to recover during the recovery period.	10

Table 12: Results of Repeat-Dose Toxicity Studies with Solifenacin Succinate

Species, Strain, Number/Sex	Dose (mg/kg/day) Route Duration of Treatment	Findings (at mg/kg/day)	No-adverse-effect-level (NOAEL) (mg/kg/day)
Rat (F344) 15-18 (main)	Male: 0, 3, 10, 30, 100/75* Female:0, 3, 10, 30, 60/45* Oral (gavage) 26 weeks	≥ 3 : Mydriasis in females. ≥ 10 : Salivation and wet/yellow staining on perigenital area in males and females. Mydriasis in males. High ALP and phosphorus, low ALT and cholesterol in females. 30 : 5 females died. ≥ 30 : Decreased body weight gain and high adrenal weight in males and females. Decreased food consumption, high ALP and low ALT in males. Respiratory noises, high WBC, neutrophil, lymphocyte and urine pH, low AST, phospholipid and total protein, follicular degeneration and uterine atrophy in females. 60/45 : 15 females died. Piloerection, decreased food consumption, high platelet, low glucose and albumin. 100/75 : 1 male died. Respiratory noises, high phosphorus, low AST, cholesterol, triglyceride, phospholipid, urine volume, urine potassium and spleen weights.	3
6 (recovery)	Male: 0, 30, 100/75* Female: 0, 30, 60/45* Oral (gavage) 26 weeks followed by 10 weeks recovery *reduced from week 14	All changes recovered or tended to recover during the recovery period.	
Dog (Beagle) 3	0, 1, 3, 10, 30 Oral (capsule) 4 weeks	≥ 10 : Vomiting in males and females. 30 : Mydriasis, salivation, decreased locomotor activity, decreased body weight and food consumption, ECG changes (increased amplitude of P-wave, prolongation of P-wave, PR, QRS, QT and QTc intervals) and thymic involution in males and females. Tremor and high kidney weight, surface mucous cell swelling in the fundic region of the stomach in males.	3
Dog (Beagle) 3-4	0, 3, 6, 12, 25/18* Oral (capsule) 13 weeks *reduced from week 7	≥ 3 : Low uterine weight and uterine immaturity in females. 25/18 : Salivation, vomiting, ataxia, prostration, tremor, convulsion, abnormal gait/posture, abnormal respiration and ECG changes (prolongation of P-wave, PR and QTc intervals) in males and females. Transiently high hematocrit and hemoglobin in males and urea nitrogen in females.	Male : 12 Female : Not established
Dog (Beagle) 4	0, 3, 6, 12, 20 Oral (capsule) 52 weeks	20 : Salivation, vomiting, ECG changes (prolongation of P-wave, PR, QRS, QT and QTc intervals) in males and females. Perivascular lymphoid accumulation, edema, transitional cell hyperplasia and vacuolation in the submucosa or submucosa/muscle layer in the urinary bladder in females.	12

Genotoxicity
The genotoxic potential of solifenacin succinate was evaluated in both *in vitro* and *in vivo* studies. Solifenacin succinate was not mutagenic or clastogenic in the *in vitro* and *in vivo* studies. The results are shown in Table 13.

Table 13: Results of Genotoxicity Studies with Solifenacin Succinate

Study Type	Species or Cell Type	Dose Levels	Results
In vitro bacterial mutagenicity	*S. typhimurium* TA98, TA100, TA1535, TA1537 *E. coli* WP2*uvrA*	0, 5-1250 mcg/plate	Negative
In vitro clastogenicity	Human blood lymphocytes	0, 20.97-160 mcg/mL	Negative
In vivo clastogenicity	Bone marrow erythrocytes of F344 rats	0, 250, 500, 1000 mg/kg	Negative

Carcinogenicity
The carcinogenic potential of solifenacin succinate was evaluated in mice and rats. Administration of solifenacin succinate for up to 104 weeks in mice and rats did not produce significant increases in any tumor type in either males or females. The results are shown in Table 14.

Table 14: Results of Carcinogenicity Studies with Solifenacin Succinate

Species, Strain Number/Sex	Dose (mg/kg/day) Duration of Treatment	Results
Mouse (CD-1) 70	0, 10, 30, 100, 200 Oral (gavage) 2 years	≥ 100 : Increased mortality, low body weight and decreased food consumption in males and females. No increases in any type of tumor in males or females.
Rat (F344) 60	Males: 0, 3, 10, 20 Females: 0, 3, 7.5, 15 Oral (gavage) 2 years	≥ 10 : Low body weight in males and females. 15 : Increased mortality in females. 20 : Decreased food consumption in males. No increases in any type of tumor in males or females.

Reproductive and Developmental Toxicity
Reproductive and developmental toxicity studies were conducted in mice, rats and rabbits to assess the effects of solifenacin succinate on fertility and early embryonic development, embryo-fetal development and prenatal/postnatal development, including maternal function. The results are summarized in Table 15.

Table 15: Results of Reproductive and Developmental Toxicity Studies with Solifenacin Succinate

Study Type	Species, Strain, Number/Sex	Doses (mg/kg/day) Route Duration of Treatment	Important Findings (at mg/kg/day)	No-adverse-effect-level (NOAEL) (mg/kg/day)
Segment I Fertility and early embryonic development	Mouse (CD-1) 24 males and 24 females	0, 30, 100, 250 Oral (gavage) Males: 4 weeks prior to and during mating Females: 2 weeks prior to and during mating through Gestation day 6	≥ 100 : Decreased food consumption in males. 250 : 3 males and 2 females died. No adverse effects on fertility of males or females, or early embryonic development.	F_0 males: 30 F_0 females: 100 F_1 litters: 250
	Rat (SD) 20 males	0, 5, 15, 50 Oral (gavage) 4 weeks prior to and during mating	50 : Mydriasis. No adverse effects on fertility or early embryonic development.	F_0 males: 50 F_1 litters: 50
	Rat (SD) 20 females	0, 15, 50, 100 Oral (gavage) 2 weeks prior to and during mating through Gestation day 7	≥ 15 : Mydriasis. 100 : Decreased body weight gain and food consumption. No adverse effects on fertility or early embryonic development.	F_0 females: 50 F_1 litters: 100
Segment II Embryo-fetal development	Mouse (CD-1) 24 females	0, 30, 100, 250 Oral (gavage) Gestation day 6-15	≥ 30 : Decreased maternal food consumption. ≥ 100 : Decreased maternal body weight gain and low fetal body weight. 250 : 5 females died. An increase in the incidence of fetuses with cleft palate.	F_0 females: < 30 F_1 litters: 30
	Mouse (CD-1) 24 females (Additional study)	0, 250 Oral (gavage) Gestation day 6-9, 10-15, 6-15	250 : No increase in the incidence of fetuses with cleft palate in any dosing period.	F_0 females: < 250 F_1 litters: 250
	Rat (SD) 20 females	0, 5, 15, 50 Oral (gavage) Gestation day 7-17	≥ 15 : Mydriasis. 50 : No maternal toxicity or adverse effects on embryo-fetal development.	F_0 females: 50 F_1 litters: 50
	Rabbit (NZW) 20 females	0, 10, 25, 50 Oral (gavage) Gestation day 6-18	50 : Decreased maternal food consumption, no adverse effects on embryo-fetal development.	F_0 females: 25 F_1 litters: 50

Study Type	Species, Strain, Number/Sex	Doses (mg/kg/day) Route Duration of Treatment	Important Findings (at mg/kg/day)	No-adverse-effect-level (NOAEL) (mg/kg/day)
Segment III Prenatal and postnatal development	Mouse (CD-1) 24-30 females	0, 30, 100, 250 Oral (gavage) Gestation day 6 to Lactation day 20	100 : 3 females died. ≥ 100 : Decreased maternal food consumption, increased peripartum pup mortality, low pup body weight, delays in eye opening and vaginal patency. 250 : 9 females died. Increased postpartum pup mortality, delays in surface righting and pinna unfolding.	F_0 females: 30 F_1 males: 30 F_1 females: 30

Local Tolerance and Other Studies

Solifenacin succinate was irritating to the eyes of rabbits. The severity of ocular irritation was dose-dependent. Ocular findings were reduced if the eyes were rinsed immediately after exposure. Solifenacin succinate did not cause dermal or vascular/perivascular irritation in rabbits. Solifenacin succinate was not antigenic in the delayed type skin reaction assay in guinea pigs and did not induce hemolysis in human peripheral blood.

REFERENCES

1. Product Monograph for Vesicare® (Solifenacin Succinate Tablets 5 mg and 10 mg). Astellas Pharma Canada Inc., Submission Control No.: 220842; Date of Revision: December 31, 2018.

PART III: CONSUMER INFORMATION

PrTARO-SOLIFENACIN

Solifenacin Succinate Tablets

5 mg and 10 mg

This leaflet is part III of a three-part "Product Monograph" published when TARO-SOLIFENACIN was approved for sale in Canada. It is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TARO-SOLIFENACIN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TARO-SOLIFENACIN is used in the treatment of overactive bladder in adults with symptoms of frequent and urgent need to urinate (urinary frequency, urinary urgency) with urine leakage (urge urinary incontinence).

What it does:
TARO-SOLIFENACIN is a urinary antispasmodic medication that helps to relax the smooth muscle of the bladder which leads to reduction of the symptoms caused by overactive bladder.

When it should not be used:
You should not take TARO-SOLIFENACIN:

- If you are not able to empty your bladder (also called urinary retention).
- If you have End-Stage Kidney Disease and require dialysis.
- If you are not able to empty your stomach (also called gastroparesis).
- If you have narrow-angle glaucoma (high pressure and pain in the eyes).
- If you are allergic to solifenacin succinate or any of the other ingredients in TARO-SOLIFENACIN. See 'What the non-medicinal ingredients are'

What the medicinal ingredient is:
The medicinal ingredient in TARO-SOLIFENACIN tablet is 'solifenacin succinate'.

What the non-medicinal ingredients are:
Each TARO-SOLIFENACIN tablet contains the following inert ingredients: anhydrous lactose, corn starch, hypromellose, magnesium stearate, polyethylene glycol, red ferric oxide (10 mg), talc, titanium dioxide, and yellow ferric oxide (5 mg).

What dosage form it comes in:
TARO-SOLIFENACIN is available in 5 and 10 mg tablets

WARNINGS AND PRECAUTIONS

Before you use TARO-SOLIFENACIN, talk to your doctor or pharmacist if you:

- Have stomach problems affecting passage and digestion of food, or severe constipation.
- Have glaucoma.
- Have difficulty urinating, or weak urine stream.
- Have heart disease
- Have a rare heart problem called QT/QTc prolongation or family history of QT/QTc prolongation.
- Have kidney or liver problems.
- Have reduced ability to sweat.
- Are pregnant or planning to become pregnant. Women who might get pregnant should use an effective birth control method while taking TARO-SOLIFENACIN.
- Are breastfeeding or plan to breastfeed.

TARO-SOLIFENACIN should not be given to children or adolescents.

TARO-SOLIFENACIN may cause blurred vision and drowsiness. Do not drive a car, operate any machinery, or engage in any activities that require accurate vision and full attention.

In hot weather, TARO-SOLIFENACIN can cause heat prostration (fever and heat stroke due to decreased sweating). Do not stay long in a hot environment while taking the drug. If you have any symptoms of heat prostration, keep yourself cool and drink a lot of water.

Angioedema (the symptoms include swelling of the face or tongue, difficulty breathing) and anaphylactic reactions (the symptoms include hives, difficulty breathing, abdominal cramps, rapid heartbeat and feeling faint), which could be life-threatening, have been reported in some patients taking TARO-SOLIFENACIN. If you experience any of these symptoms, stop taking TARO-SOLIFENACIN and see your doctor immediately.

INTERACTIONS WITH THIS MEDICATION

Before and while taking TARO-SOLIFENACIN you should tell your doctor about your other medications, even the medicine you bought without prescription, including vitamins and herbal supplements.

TARO-SOLIFENACIN is known to have drug interactions with the following drugs: Drugs known to prolong the QT/QTc interval and/or cause torsade de pointes, drugs that decrease electrolyte levels, anticholinergic drugs, drugs that stimulate the motility of the gut such as metoclopramide,

ketoconazole, clarithromycin, erythromycin, diclofenac, nefazodone, verapamil.

Drinking grapefruit juice with TARO-SOLIFENACIN may increase your blood level of solifenacin.

PROPER USE OF THIS MEDICATION

Usual Dose:
5 mg daily. The daily dose may be increased to 10 mg following consultation with your doctor. Swallow the tablet whole with water.

TARO-SOLIFENACIN tablets can be taken with or without food.

Overdose:

If you think you have taken too much TARO-SOLIFENACIN, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If a dose is missed, the next tablet should be taken as planned. Doses should not be doubled to make up for a missed dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

The following side effects have been reported in clinical trials with solifenacin succinate:

Most common side effects: dry mouth and constipation

Common side effects: dry eyes, urinary retention, blurred vision, nausea, abdominal pain, indigestion, urinary tract infection.

The following side effects have been reported with the use of solifenacin succinate in worldwide post-marketing experience, although the frequency of events or a causal relationship with solifenacin succinate could not always be confirmed:

acid reflux, change in sense of taste, decreased appetite, delirium, dizziness, dry skin, fast or irregular heartbeat, feeling sleepy, glaucoma, hallucination, headache, high potassium levels, hypersensitivity reactions, intestinal blockage, itchiness, kidney ailment, liver problems, muscle weakness, nasal dryness, voice disorder, severe skin scaling and redness, itching (exfoliative dermatitis), severe skin rash, itchiness and fever (erythema multiforme), swelling in the lower limbs and vomiting.

Tell your doctor or pharmacist if you have any side effects while taking TARO-SOLIFENACIN. This includes any side effects not listed above.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom/effect		Talk with your doctor or pharmacist		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Rare	Abdominal pain	√		
	Constipation for more than 3 days		√	
	Urinary retention		√	
Very rare	Swelling of the face or tongue, difficulty breathing			√
	Fast or irregular heartbeat			√
	Anaphylactic reactions (severe allergic reactions)			√

HOW TO STORE IT

Keep TARO-SOLIFENACIN and all other medications out of the reach of children.

Store between 15°C to 30°C.

Do not keep medicine that is out of date or that you no longer need.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- **Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or**
- **Calling toll-free at 1-866-234-2345.**

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance

Program does not provide medical advice.

MORE INFORMATION

This document, plus the full product monograph prepared for health professionals, can be found by contacting Sun Pharma Canada Inc., at 1-866-840-1340.

This leaflet was prepared by

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