140.00 mm 140.00 mm

Oedema lower limb

Influenza like illness EYE DISORDERS

Vision blurred

GENERAL DISORDERS AND ADMINISTRATION SITE DISORDERS

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS

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

Flatulence, gastro-oesophaegeal reflux diseases, throat irritation, eructation, dry throat.

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

The following adverse reactions have been spontaneously reported during worldwide post-approval use of Solifenacin Succinate®. The adverse reactions reported are presented below according to System Organ Class and frequency. Adverse event frequencies are defined as follows: Very common (0.1%, <10%), common (0.1%, <1%),

10%), common (1%, <10%), uncommon (0.1%, <1%), rare >0.01%, <0.1%) and very rare (<0.01%), not known (cannot be estimated from the available data).

Very rare: Torsade de Pointes, atrial fibrillation, palpitations, tachycardia.

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

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

General disorders and administration site conditions: Very rare: Peripheral oedema.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS

RENAL AND URINARY DISORDERS

Urinary retention 0.6

Depression NOS 0.8 VASCULAR DISORDERS

Gastro-intestinal disorders:

Infections and infestations:

Renal and urinary disorders

Peripheral swelling

Vascular disorders: Hot flushes.

Cardiac disorders

Hepatobiliary disorders

Immune System Disorders:

Very rare: Anaphylactic reaction

Very rare: Muscular weakness

Renal and urinary disorders

LIST OF EXCIPIENTS:

SHELF LIFE: 24 month.

MANUFACTURED BY: Umedica Laboratories Pvt. Ltd Plot No. 221, Ilnd Phase, GID Vapi – 396 195, Gujarat, India

MANUFACTURED FOR:

SYNERRV (S) PTE. LTD. 68 Circular Road, #02-01, Singapore (049422)

DATE OF REVISION: December 2021

PRESENTATION

Very rare: Electrocardiogram QT prolonged.

Nervous system disorders: Very rare: Dizziness, headache, somnolence.

Very rare: Renal impairment, urinary retention.

Respiratory, thoracic and mediastinal disorders: Very rare: dysphonia, nasal dryness.

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

Post marketing pharmacovigilance data confirmed QT prolongation associated with therapeutic doses of solifenacin succinate in cases with known risk factors (see PRECAUTIONS).

OVERDOSE:
Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects (headache, dry mouth, dizziness, drowsiness and should be treated accordingly. The highest solifenacin succinate dose given to human single patient was 280 mg in

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

Treatment of overdosage:

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

STORAGE: Store below 30°C. Store in the original package in order to

PRESENTATION:
10 tablets packed in one Alu./PVC Blister, Such 3 blisters are packed in one carton along with pack insert (3x10's Blister).

10 tablets packed in one Alu./PVC Blister, Such 10 blisters are packed in one carton along with pack insert (10x10's Blister).

70.00 mm

ohydrate, Corn starch, Hydroxypropyl methyl cellulose, earate. Hypromellose, Talc, Polyethylene Glycol, Titanium

a 5 hour period, resulting in mental status changes not req

Musculoskeletal and connective tissue disorders:

Metabolism and nutrition disorders: Very rare: Decreased appetite, hyperkala

Post Marketing Experience:

Nervous system disorders: Somnolence, dysgeusia, syncope.

General disorders and administration site disorders Thirst, suprapubic pain, chest tightness.

Difficulty in micturation, bladder pain, micturition urgency. Respiratory, thoracic and mediastinal disorders:

Musculoskeletal and connective tissue disorders:

Skin and subcutaneous tissue disorders:

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

Freatment Least Squares Means of Change from Baseline QTc (Bazett ANCOVA Model

Dose (mg)	Bazett Method		Friderica Method		
	Estimate	95% Confidence Interval	Estimate	95% Confidence Interval	
10	0.8	(-2.1, 3.6)	-0.6	(-3.3, 2.0)	
20	5.4	(2.6, 8.3)	2.5	(-0.2, 5.2)	
30	5.5	(2.5, 8.5)	1.3	(-1.5, 4.2)	
40	-0.1	(-3.4, 3.1)	-4.7	(-7.8, -2.0)	
There were	no QTc into	ervals >500 m	sec; increa	ses of >60 msec	

occurred in 1 subject (on 30 mg), while change <60 msec but >30 msec occurred in 34 subjects (11 changes on 10 mg, 20 changes on 20 mg, 27 changes on 30 mg, 9 changes on 40 mg).

27 changes on 30 mg, 9 changes on 40 mg). The second study was a double blind, multiple dose, placebo and positive controlled (moxifloxacin 400 mg) study in 76 female volunteers aged 19 to 79 years. This second QT study was a dedicated thorough QT study with the subjects 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. 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 chosen for use in this study because this dose results in a solifenacir exposure that covers the exposure 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 he study, baseline ECG measurements were separated from the fina QT assessment (of the 30 mg dose level) by 33 days.

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

QTc changes in msec (90% Confidence Interval) from baseline at Tmax (relative to placebo)

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

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

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

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

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

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

INDICATIONS:

Solifenacin Succinate is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency or increased urinary frequency.

POSOLOGY AND METHOD OF ADMINISTRATION: Adults, including the elderly: The recommended dose is 5 mg Solifenacin succinate film-coated

ablet once daily. If needed, the dose may be increased to 10 mg Solifenacin succinate film-coated tablet once daily.

Children and adolescents: Solifenacin succinate is not indicated for treatment of OAB in the

pediatric population Special populations:

00.

No dose adjustment is necessary for patients with mild to moderate renal impairment (creatinine clearance >30 ml/min). Patients with severe renal impairment (creatinine clearance 30 ml/min) should be treated with caution and receive no more than 5 mg once daily.

Patients with hepatic impairment No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate hepatic impairment (Child-Pugh B) should be treated with caution and receive no more than 5 mg once daily. Solifenacin Succinate is not recommended for patients with severe hepatic impairment (Child-Pugh C).

nedication: maximum dose of Solifenacin Succinate should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4-inhibitors e.g. ritonavir, nelfinavir, itraconazole, cyclosporin, macrolide antibiotics (see also INTERACTIONS WITH

Method of administration: Solifenacin Succinate should be taken orally and should be swallowed whole with liquids. It can be taken with or without food.

CONTRAINDICATIONS: Solifenacin is contraindicated in

- patients with urinary retention. patients with uncontrolled narrow-angle glaucoma.
- patients who have demonstrated hypersensitivity to the drug substance or other components of the product.
- severe gastro-intestinal condition (including toxic megacolon and gastric retention).

- gastric retentuon).

 myasthenia gravis.

 patients undergoing haemodialysis.

 patients with severe hepatic impairment.

 patients with severe renal impairment or moderate hepatic impairment and who are on treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole.

- WARNING AND PRECAUTIONS
- Solifenacin Succinate should be used with caution in patients with
- clinically significant bladder outflow obstruction at risk of urinary
- stro-intestinal obstructive disorders
- gastro-intestinal obstructive disorders.

 risk of decreased gastro-intestinal motility.

 in patients being treated for narrow-angle glaucoma.

 hiatus hernia/gastro-oesophagal reflux and/or who are concurrently
 taking medicinal products that can cause or exacerbate oesophagitis.

 autonomic neuropathy.

 known risk factors for QT prolongation, such as pre-existing long QT

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

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

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

Hepatic Impairment:

Doses of Solifenacin Succinate greater than 5 mg are not recommended. ended in patients with moderate hepatic impairment (Child-Pugh B). Solifenacin Succinate is not recommended for patients with severe nepatic impairment (Child-Pugh C).

70.00 mm

rolongation and Torsade de Pointes: rolongation and Torsade de Pointes have been observed in nts with known risk factors for these conditions. As with other drugs in this class, caution is advised in patients with

As will other origis in time class, caucion is advised in patients with known risk factors for QT-prolongation, (i.e. history of QT prolongation, long QT syndrome, hypokalaemia, bradycardia, coadministration of drugs known to prolong the QT interval) and relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure) (see CLINICAL TRIALS and INTERACTIONS WITH OTHER DRUGS).

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

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

Use in Pregnancy (Category B3):
Solifenacin (and/or its metabolites) has been shown to cross the placenta in pregnant mice. No embryotoxicity or teratogenicity was observed in mice treated with 1.2 times exposure at the maximum recommended human dose (MRHD). In one of two studies, higher doses (3.6 times exposure at the MRHD) resulted in maternal toxicity and reduced fetal body weight. No embryotoxic effects were observed in rabbits up to 1.8 times exposure at the MRHD. Use in Pregnancy (Category B3):

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

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

Use in Lactation:
Solifenacin is excreted into the breast milk of mice. There were no significant adverse effects at 1.2 times exposure at the maximum recommended human dose (MRHD) in a pre- and postnatal study in mice. Pups of female mice treated at 3.6 times exposure at the MRHD showed reduced body weights, postpartum pup mortality or delays in the onset of reflex and physical development during the lactation period. It is expected that solifenacin is excreted in human milk and solifenacin should not be administered during breast-feeding.

<u>Carcinogenicity:</u> No significant increase in tumors was found following the administratior olifenacin to male and female mice for 104 weeks up to 5 and 9 times xposure at the maximum recommended human dosa (MPHD) respectively, and male and female rats for 104 weeks at doses that resulted in <1 times exposure at the MRHD.

cin was not mutagenic in the in vitro Salmonella typhimurium or chia 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. INTERACTION WITH OTHER MEDICINAL PRODUCTS:

In vitro studies have demonstrated that at therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver

Effect of other medicinal products on the pharmacokinetics of

Notified the solution of the AUC of solifenacin of the AUC of solifenacin. Is a substrate of CYP3A4. Inducers or inhibitors of CYP3A4 may alter solifenacin pharmacokinetics. Simultaneous administration of ketoconazole (200 mg/day), a potent CYP3A4 inhibitor, resulted in a two-fold increase of the AUC of solifenacin, while ketoconazole at a dose of 400 mg/day resulted in a three-fold increase of the AUC of solifenacin. Therefore, the maximum dose of Solifenacin 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, cyclosporin, macrolide antibiotics).

The effects of enzyme induction on the pharmacokinetics of solifenacin and its metabolites have not been studied as well as the effect of higher affinity CYP3A4 substrates on solifenacin exposure. Since solifenacin is metabolised by CYP3A4, pharmacokinetic interactions are possible with other CYP3A4 substrates with higher affinity (e.g. verapamil, diltiazem) and CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepin).

Effect of solifenacin on the pharmacokinetics of other medicinal

ntake of Solifenacin Succinate showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinyl oestradiol/levonorgestrel).

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

Intake of Solifenacin Succinate showed no effect on the pharma-

Drugs which prolong the QT/QTc interval:

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

is in the eluenty.

To do sage adjustment based on patient age is required. Studies in the lderly have shown that C_{min} AUC and t_{min} values were 20-25% higher s compared to the younger volunteers (18-55 years). No overall ifferences were observed in the safety of solifenacin between older nd younger patients treated for 4 to 12 weeks with 5 to 10 mg

Effects on ability to drive and use machines:
Since solifenacin, like other anticholinergics may cause blurred vision, and fatigue, the ability to drive and use machines may be negatively

Influenza

Arthralgia

Neck pain

Sinusitis NOS

Pharyngitis NOS

NERVOUS SYSTEM DISC

MUSCULOSKELET AL AN

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

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

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
GASTROINTESTINAL DIS	ORDERS		
Dry mouth	4.2	10.9	27.6
Constipation	2.9	5.4	13.4
Nausea	2.0	1.7	3.3
Dyspepsia	1.0	1.4	3.9
Diarrhoea NOS	2.1	0.7	1.9
Vomiting NOS	0.9	0.2	1.1
Abdominal pain upper	1.0	1.9	1.2
	1.2	0.2	0.6

70.00 mm

4.2	10.9	27.6	1
2.9	5.4	13.4	1
2.0	1.7	3.3	1
1.0	1.4	3.9	1
2.1	0.7	1.9	1
0.9	0.2	1.1	1
1.0	1.9	1.2	1
1.2	0.2	0.6	1
ATIONS			
2.8	2.8	4.8	
2.0	0.9	1.5	
1.3	2.2	0.9]
1.2	0.9	1.0	
2.7	0.9	1.0	1
1.0	0.3	1.1	1
1.1	0.7	0.7	1
RDERS]
4.5	1.9	1.8]
1.8	1.9	1.8	
		DISORDERS	
2.2	0.7	1.2	
1.8	0.5	1.5]
0.5	0.3	0.1	1

Synerry Solifenacin

NAME AND STRENGTH OF ACTIVE INGREDIENTS:

PRODUCT DESCRIPTION:

Light yellow round shaped, 7.5 mm, biconvex film coated tablets, debossed with "SOL" on one side and "5" on other side.

Pharmacotherapeutic group: Urinary antispasmodics
ATC code: G04B D08.

Mechanism of Action olifenacin is a competitive muscarinic receptor antagonist. Muscarini receptors play an important role in several major cholinergic mediated functions, including contractions of urinary bladder smooth muscle and

Pharmacokinetics:

After intake of Solifenacin tablets, maximum solifenacin plasma concentrations (Cmax) are reached after 3 to 8 hours and at steady

The apparent volume of distribution of solifenacin fol administration is about 600 L. Solifenacin is to a great extent (approximately 98%) bound to plasma proteins, primarily α 1-acid

Solifenacin is extensively metabolized in the liver. The primary pathway for elimination is by way of CYP3A4; however, alternate metabolic pathway exist. The primary metabolic routes of solifenacin are through N-oxidation of the quinuclidin ring and 4R-hydroxylation of tetrahydroisoguinoline ring. One pharm logically active metal (4R-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 4R-hydroxy-N oxide of solifenacin) have been found in human plasma after ora

Excretion:

After a single administration of 10 mg [14C-labelled]-solifenacin, about 70% of the radioactivity was detected in urine and 23% in faeces over 26 days. In urine, approximately 11% of the radioactivity is recovered as unchanged active substance; about 18% as the N-oxide metabolite, 9% as the 4R-hydroxy-N-oxide metabolite and 8% as the 4R-hydroxy metabolite (active metabolite). The systemic clearance of solifenacin is about 9.5 L/h. The elimination half-life of solifenacin following chronic dosing is approximately 45 - 68 hours.

Pharmacokinetics are linear in the therapeutic dose range.

Renal impairment:
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 t1/2 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_c-<30 ml/min) (see PRECAUTIONS and DOSAGE ADMINISTRATION).

Hepatic impairment:
Solifenacin Succinate should be used with caution in patients with hepatic impairment. There is a 2-fold increase in the t1/2 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-

solitenacin Succinate is not recommended for patients with severe hepatic impairment (Child-Pugh C) (see PRECAUTIONS and DOSAGE ADMINISTRATION).

CLINICAL TRIALS:

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

As shown in the table below, both the 5 mg and 10 mg doses of As slifenacin 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. After 12 weeks of treatment approximately

50% of patients suffering from incontinence before treatment were fre of incontinence episodes, and in addition 35% of patients achieved a micturition frequency of less than 8 micturitions per day. All patients completing the 12-week studies were eligible to enter an open labor long term extension study and 81% of patients enrolling completed the additional 40-week treatment period demonstrating a maintenance of effect. Treatment of the symptoms of overactive bladder also results in a benefit on a number of Quality of Life measures, such as general health perception, inco limitations, social limitations, emotions, symptom severity, severit measures and sleep/energy

Results (pooled data) of four controlled Phase 3 studies with a treatment duration of 12 weeks

	Placebo	Solifenacin succinate 5 mg film- coated tablet o.d.	Solifenacin succinate 10 mg film- coated tablet o.d.
No. of micturitions/24 h			
Mean baseline	11.9	12.1	11.9
Mean reduction from			
baseline	1.4	2.3	2.7
% change from baseline	(12%) 1138	(19%) 552	(23%) 1158
n Diff. vs placebo (95% CI) ¹	1130	0.9 (0.6;1.3)	1.3(1.0;1.6)
p-value*		<0.001	<0.001
No. of urgency episodes/2	4 h		
Mean baseline	6.3	5.9	6.2
Mean reduction from	2.0	2.9	3.4
baseline	(000/)		/==a/\
% change from baseline	(32%) 1124	(49%) 548	(55%) 1151
Diff. vs placebo (95% CI) ¹	1144	1.1 (0.7:1.5)	1.5 (1.2;1.8)
p-value*		<0.001	<0.001
No. of incontinence episod	es/24 h		
Mean baseline	2.9	2.6	2.9
Mean reduction from baseline	1.1	1.5	1.8
% change from baseline	(38%)	(58%)	(62%)
n Diff. vs placebo (95% CI) ¹	781	314	778 0.7 (0.5;1.0)
p-value*		0.7 (0.4:1.1) <0.001	<0.001
No. of nocturia episodes/2	4 h		
Mean baseline	1.8	2.0	1.8
Mean reduction from	0.4	0.6	0.6
baseline			
% change from baseline	(22%)	(30%)	(33%)
n Diff. vs placebo (95% CI) ¹	1005	494 0.1 (0.0;0.3)	1035 0.2 (0.0;0.3)
p-value*		0.025	0.025
Volume voided/micturition			
Mean baseline	166 ml	146 ml	163 ml
Mean increase from	9 ml	32 ml	43 ml
baseline % change from baseline	(5%)	(21%)	(26%)
n 1135	552	1156	(20/0)
Diff. vs placebo (95% CI) ¹		25 (19;32)	34 (29;39)
p-value*		<0.001	<0.001
No. of pads/24 h			
Mean baseline	3.0	2.8	2.7
Mean reduction from	0.8	1.3	1.3
baseline	(270/)	(469/)	(400/)
% change from baseline n	(27%) 238	(46%) 236	(48%) 242
Diff. vs placebo (95% CI) ¹	200	0.6 (0.2;0.9)	0.7 (0.3;1.0)
p-value*		<0.001	<0.001

XXXXXX

PHARMACOLOGICAL PROPERTIES: PHARMACODYNAMICS PROPERTIES:

stimulation of the salivary secretion.

concentrations (Cmax) are reached after 3 to 8 nours and at steady state ranged from 32.3 to 69.9 ng/ml for the 5 and 10 mg Solifenacin tablets, respectively. The tmax is independent of the dose. The Cmax and area under the curve (AUC) increase in proportion to the dose between 5 to 40 mg. Absolute bioavailability is approximately 90%. Food intake does not affect the Cmax and AUC of solifenacin.

Dose Proportionality

Pugh B).

The pharmacokinetics of solifenacin have not been established in children and adolescents.

	Placebo	Solifenacin succinate 5 mg film- coated tablet o.d.	Solifenacin succinate 10 mg film- coated tablet o.d.
o. of micturitions/24 h			
ean baseline ean reduction from	11.9	12.1	11.9
seline change from baseline ff. vs placebo (95% CI) ¹	1.4 (12%) 1138	2.3 (19%) 552 0.9 (0.6;1.3)	2.7 (23%) 1158 1.3(1.0;1.6)
/alue*		<0.001	<0.001
o. of urgency episodes/2	4 h		
ean baseline ean reduction from	6.3 2.0	5.9 2.9	6.2 3.4
seline change from baseline	(32%) 1124	(49%) 548	(55%) 1151
ff. vs placebo (95% CI) ¹ value*		1.1 (0.7:1.5) <0.001	1.5 (1.2;1.8) <0.001
o. of incontinence episoo	les/24 h		
ean baseline	2.9	2.6	2.9
ean reduction from seline	1.1	1.5	1.8
change from baseline	(38%) 781	(58%) 314	(62%) 778
ff. vs placebo (95% CI) ¹ value*		0.7 (0.4:1.1) <0.001	0.7 (0.5;1.0) <0.001
o. of nocturia episodes/2	4 h		
ean baseline ean reduction from seline	1.8 0.4	2.0 0.6	1.8 0.6
change from baseline	(22%) 1005	(30%) 494	(33%) 1035
ff. vs placebo (95% CI)¹ value*		0.1 (0.0;0.3) 0.025	0.2 (0.0;0.3) 0.025
lume voided/micturition			
ean baseline ean increase from seline	166 ml 9 ml	146 ml 32 ml	163 ml 43 ml
change from baseline	(5%) 552	(21%) 1156	(26%)
ff. vs placebo (95% CI)¹ value*		25 (19;32) <0.001	34 (29;39) <0.001
o. of pads/24 h			
ean baseline ean reduction from	3.0 0.8	2.8 1.3	2.7 1.3
seline change from baseline	(27%)	(46%)	(48%)
ff. vs placebo (95% CI)1	238	236 0.6 (0.2;0.9) <0.001	242 0.7 (0.3;1.0) <0.001

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.

70.00 mm

Note to Printer

Return the original approved artwork along with the sample.

For any clarification, please contact Packaging Development Department.

The overprinting area should be unvarnished.

* P-value for the pair wise comparison to placebo 1 As estimated from the statistical model

UMEDICA LABORATORIES PVT. LTD. SPECIFICATION FOR ARTWORK APPROVAL Format No.: FM/PDD/002-01-04 Ref. SOP No.: PDD/002 Artwork/SAP Code No.: XXXXXX Old Version/SAP Code No.: Specification Version: 01 **Product Name** : Synerry Solifenacin Company Name/Country : Singapore - (Synerry) (Solifenacin Succinate 5 mg film-coated Tablets) Pack Style : 3x10T & 10x10T Component Type : Package Insert : New develop Package Insert Artwork as per Singapore country requirement. Description **Specifications** : LxH Site : Umedica Full Size / Size : 140x400 MM Type / Blister / Strip Size / Adhesive / Tube Type : Front-Back Sachet Size/Pocket Size/Fold Size/Release Paper: 70x25 MM Size - Catch Cover / Foil / BOPP : — Space between Labels **Transparent Paper Thickness** GSM of Paper / GSM of Aluminum Foil: 40 GSM Type of Paper / GSM : Bible Paper Thickness of Foil Type of Foil / Fold / Coating GSM Cylinder Lamination / Varnish / Material Grade : — Repeat/Tolerence Partition / Plate Size / Total GSM / Sealing / Embossing / Core Diameter GSM/BF of Printed Shipper Paper Grade / Flute Type / PLY of Shipper (Top/Middle/Bottom and Flute layer BLACK or as per Sample **Printing Colour** Approved by Export/Marketing [Approval attached with ADF] CHECKLIST FOR CHECKING ARTWORK & SPECIFICATION Artwork Approved b and printing colours specifica-specifica-requirement Popular training and printing colours specification Popular training and printing Sign with Date Rx/ (Qty.) / / Code PDD RA Department

Machine proof must be verified against the approved hard copy in Light, Standard and Dark shade should be certified and signed by an authorized person.

Any deviation must be brought to the notice of the Packaging Development Department immediately in the writing.

QA