Clinical QT Interval Data:

Two dedicated QT studies have been performed with solifenacin.

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

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

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

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

The second study was a double blind, multiple dose, placebo and positive controlled (moxifloxacin 400 mg) study in 76 female volunteers aged 19 to 79 years. This second QT study was a dedicated thorough QT study with the subjects 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 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 the study, baseline ECG measurements were separated from the final QT assessment (of the 30 mg dose level) by 33 days.

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

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

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

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

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

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

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

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

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

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

Co-medication:
The 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 OTHER DRUGS).

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).
- 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 retention.
- 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:
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.

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

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).

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

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

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

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

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

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

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

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

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

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

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

microsomes. Therefore, solifenacin succinate is not likely to interact with the CYP mediated metabolism of co-administered drugs.

Effect of other medicinal products on the pharmacokinetics of solifenacin

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

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

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

Digoxin:
Intake of Solifenacin Succinate showed no effect on the pharmacokinetics of digoxin.

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

Use in children:
Solifenacin succinate is not indicated for treatment of OAB in the pediatric population.

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

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 affected.

SIDE EFFECTS:
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.

Numbers(%) of patients with treatment-emergent adverse events reported by 1% or more patients: controlled phase 3 studies (all combined)

SYSTEM ORGAN CLASS MedDRA Preferred Term	Placebo (%)	Solifenacin Succinate 5 mg (%)	Solifenacin Succinate 10 mg (%)
Number of patients	1216	578	1233
Number of patients with treatment-emergent AE	634	265	773
GASTROINTESTINAL DISORDERS			
Dry mouth	4.2	10.9	27.6
Constipation	2.9	5.4	13.4
Nausea	2.0	1.7	3.3
Dyspepsia	1.0	1.4	3.9
Diarrhoea NOS	2.1	0.7	1.9
Vomiting NOS	0.9	0.2	1.1
Abdominal pain upper	1.0	1.9	1.2
Abdominal pain NOS	1.2	0.2	0.6
INFECTIONS AND INFESTATIONS			
Urinary tract infection NOS	2.8	2.8	4.8
Upper respiratory tract infection NOS	2.0	0.9	1.5
Influenza	1.3	2.2	0.9
Sinusitis NOS	1.2	0.9	1.0
Nasopharyngitis	2.7	0.9	1.0
Pharyngitis NOS	1.0	0.3	1.1
Bronchitis	1.1	0.7	0.7
NERVOUS SYSTEM DISORDERS			
Headache	4.5	1.9	1.8
Dizziness	1.8	1.9	1.8
MUSCULOSKELET AL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia	2.2	0.7	1.2
Back pain	1.8	0.5	1.5
Neck pain	0.5	0.3	0.1
GENERAL DISORDERS AND ADMINISTRATION SITE DISORDERS			
Fatigue	1.1	1.0	2.1
Oedema lower limb	0.7	0.3	1.1
Influenza like illness	0.5	0.3	0.3
EYE DISORDERS			
Vision blurred	1.8	3.8	4.8
Dry Eye NOS	0.6	0.3	1.6
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough	0.2	0.2	1.1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Rash	1.0	0	0.6
RENAL AND URINARY DISORDERS			
Urinary retention	0.6	0	1.4
Dysuria	0.4	0.3	0.7
PSYCHIATRIC DISORDERS			
Insomnia	1.2	0.3	1.1
Depression NOS	0.8	1.2	0.8
VASCULAR DISORDERS			
Hypertension NOS	0.6	1.4	0.5

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

Gastro-intestinal disorders:
Flatulence, gastro-oesophageal reflux diseases, throat irritation, eructation, dry throat.

Infections and infestations:
Cystitis.

Nervous system disorders:
Somnolence, dysgeusia, syncope.

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

Renal and urinary disorders:
Difficulty in micturation, bladder pain, micturition urgency.

Respiratory, thoracic and mediastinal disorders:
Nasal dryness.

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

Musculoskeletal and connective tissue disorders:
Peripheral swelling.

Skin and subcutaneous tissue disorders:
Dry skin.

Vascular disorders:
Hot flushes.

Post Marketing Experience:
The following adverse reactions have been spontaneously reported during worldwide post-approval use of Solifenacin Succinate®. The adverse reactions reported are presented below according to System Organ Class and frequency.

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

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

Eye disorders:
Very rare: glaucoma.

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

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

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

Immune System Disorders:
Very rare: Anaphylactic reaction.

Investigations:
Very rare: Electrocardiogram QT prolonged.

Metabolism and nutrition disorders:
Very rare: Decreased appetite, hyperkalaemia.

Musculoskeletal and connective tissue disorders:
Very rare: Muscular weakness.

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

Psychiatric disorders:
Very rare: Hallucinations, delirium, confusional state.

Renal and urinary disorders:
Very rare: Renal impairment, urinary retention.

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

Skin and subcutaneous tissue disorders:
Very rare: Pruritus, rash, urticaria, angioedema, erythema multiforme, exfoliative dermatitis.

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 blurred vision) and should be treated accordingly. The highest solifenacin succinate dose given to human single patient was 280 mg in a 5 hour period, resulting in mental status changes not requiring hospitalization.

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 30ºC. Store in the original package in order to protect from light.

LIST OF EXCIPIENTS:
Lactose monohydrate, Corn starch, Hydroxypropyl methyl cellulose, Magnesium stearate. Hypromellose, Talc, Polyethylene Glycol, Titanium dioxide, Red iron oxide.

SHELF LIFE: 24 month.

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).

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

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

DATE OF REVISION: December 2021

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Synerrv Solifenacin

NAME AND STRENGTH OF ACTIVE INGREDIENTS:
Each tablet contains 10 mg Solifenacin Succinate Ph. Eur.

PRODUCT DESCRIPTION:
Light pink round shaped, biconvex film coated tablets, debossed with "SOL" on one side and "10" on other side.

PHARMACOLOGICAL PROPERTIES:
PHARMACODYNAMICS PROPERTIES:
Pharmacotherapeutic group: Urinary antispasmodics,
ATC code: G04B D08.
Mechanism of Action
Solifenacin is a competitive muscarinic receptor antagonist. Muscarinic receptors play an important role in several major cholinergic mediated functions, including contractions of urinary bladder smooth muscle and stimulation of the salivary secretion.

Pharmacokinetics:
Absorption:
After intake of Solifenacin tablets, maximum solifenacin plasma concentrations (Cmax) are reached after 3 to 8 hours and at steady state ranged from 32.3 to 69.9 ng/ml for the 5 and 10 mg Solifenacin tablets, respectively. The 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.

Distribution:
The apparent volume of distribution of solifenacin following intravenous administration is about 600 L. Solifenacin is to a great extent (approximately 98%) bound to plasma proteins, primarily α1-acid glycoprotein.

Metabolism:
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 4*R*-hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (4*R*-hydroxy solifenacin), occurring at low concentrations and unlikely to contribute significantly to clinical activity, and three pharmacologically inactive metabolites (*N*-glucuronide and the *N*-oxide and 4*R*-hydroxy-*N*-oxide of solifenacin) have been found in human plasma after oral dosing.

Excretion:
After a single administration of 10 mg [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 4*R*-hydroxy-*N*-oxide metabolite and 8% as the 4*R*-hydroxy metabolite (active metabolite). The systemic clearance of solifenacin is about 9.5 L/h. The elimination half-life of solifenacin following chronic dosing is approximately 45 - 68 hours.

Dose Proportionality:
Pharmacokinetics are linear in the therapeutic dose range.

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_{cr} <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-Pugh B).

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

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

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

As shown in the table below, both the 5 mg and 10 mg doses of Solifenacin 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 free of incontinence episodes, and in addition 35% of patients achieved a micturition frequency of less than 8 micturitions per day. All patients completing the 12-week studies were eligible to enter an open label, long term extension study and 81% of patients enrolling completed the additional 40-week treatment period demonstrating 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, incontinence impact, role limitations, physical limitations, social limitations, emotions, symptom severity, severity measures and sleep/energy.

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

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

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

Not all parameters and treatment groups were evaluated in each individual study. Therefore, the numbers of patients listed may deviate per parameter and treatment group.

* P-value for the pair wise comparison to placebo

1 As estimated from the statistical model

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	**: Synerrv Solifenacin (Solifenacin Succinate 10 mg film-coated Tablets)**	**Company Name/Country**	**: Singapore - (Synerrv)**
Component Type	**: Package Insert**	**Pack Style**	**: 3x10T & 10x10T**
Description	**: New develop Package Insert Artwork as per Singapore country requirement.**		

Specifications	**: LxH**	**Site**	**: Umedica**
~~Full Size~~ / Size	**: 140x400 MM**	**Type / ~~Blister~~ / ~~Strip Size~~ / ~~Adhesive~~ / ~~Tube Type~~**	**: Front-Back**
Size - Catch Cover / Foil / BOPP	**: —**	**~~Sachet Size/Pocket Size/~~Fold Size/~~Release Paper~~**	**: 70x25 MM**
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	**: —**		
Printing Colour	**: BLACK**		**or as per Sample**
Approved by Export/Marketing	**:**		**[Approval attached with ADF]**

CHECKLIST FOR CHECKING ARTWORK & SPECIFICATION

Brand Name and Generic Name(As per IP/BP/USP/ In-house Pharma-copeia)	Dosage Form and strength	Prefix Rx/ XRx	Mfg. Lic. No. / Code	Regulatory Agency Approval	Packing (Qty.) / Presentation	Dosage details if required	Size / Design	Composition /Label Claim	Schedule 'H','H1','G' or 'X' etc warning for local product / Red line for oral products	Item Code	QR Code/ Barcode (1D / 2D) as per requirement	Material and printing colours specifica-tion	Storage Condition as per pharmaco-peia/Buyer requirement/ Registration	Registration No. / Other requirement	Mfg. Name and Address, (Tel. No. and e-mail in the insert)	Marketed by / Distributors Name	Route of Admin. [in case of Inj./ Multidose Vial matter	Adequate Space (Batch details/2D barcode/ Embossing for Overprinting	Artwork Approved by Sign with Date
																			PDD Department
																			PPIC/Packing Department
																			QC Department
																			RA Department
																			QA Department

Note to Printer:
- Return the original approved artwork along with the sample.
- The overprinting area should be unvarnished.
- 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.
- For any clarification, please contact Packaging Development Department.