100.00 mm | 100.00 mm | 280.00 mm

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, severe gastro-intestinal condition (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and in patients at risk for these conditions:

- Patients hypersensitive to the active substance or to any of the excipients listed at the end of this leaflet.
- 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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Other causes of frequent urination (heart failure or renal disease) should be assessed before treatment with Synerrv Solifenacin. If urinary tract infection is present, an appropriate antibacterial therapy should be started.
Synerrv Solifenacin should be used with caution in patients with:

- Clinically significant bladder outflow obstruction at risk of urinary retention.
- Gastrointestinal obstructive disorders.
- Risk of decreased gastrointestinal motility.
- Severe renal impairment (creatinine clearance ≤ 30 ml/min), and doses should not exceed 5mg for these patients.
- Moderate hepatic impairment (Child-Pugh score of 7 to 9), and doses should not exceed
  5mg for these patients.
- Concomitant use of a potent CYP3A4 inhibitor, e.g., ketoconazole.
- Hiatus hernia/gastro-oesophageal reflux and/ or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis.
- Autonomic neuropathy.

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

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

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

The maximum effect of Synerrv Solifenacin can be determined after 4 weeks at the earliest. QT prolongation and Torsade de Pointes have been observed in patients with risk factors. 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)

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

INTERACTIONS WITH OTHER MEDICAMENTS:
Pharmacological interactions
Concomitant medication with other medicinal products with anticholinergic properties may result in more pronounced therapeutic effects and undesirable effects. An interval of approximately one week should be allowed after stopping treatment with solifenacin succinate, before commencing other anticholinergic therapy. The therapeutic effect of solifenacin may be reduced by concomitant administration of cholinergic receptor agonists.

Solifenacin can reduce the effect of medicinal products that stimulate the motility of the gastro-intestinal tract, such as metoclopramide and cisapride.

Pharmacokinetic interactions:
At therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes. Therefore, solifenacin is unlikely to alter the clearance of drugs metabolised by these CYP enzymes.

Effect of other medicinal products on the pharmacokinetics of solifenacin
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 Synerrv Solifenacin should be restricted to 5mg, when used simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g., ritonavir, nelfinavir, itraconazole).
Simultaneous treatment of solifenacin and a potent CYP3A4 inhibitor is contra-indicated in patients with severe renal impairment or moderate hepatic impairment.

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

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 (ethinylestradiol/ 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/ QT c prolongation resulting in arrythmia 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.

PREGNANCY AND LACTATION:
Pregnancy
No clinical data are available from women who became pregnant while taking solifenacin. Animal studies do not indicate direct harmful effects on fertility, embryonal / foetal development or parturition. The potential risk for humans is unknown. Caution should be exercised when prescribing to pregnant women.

Lactation
No data on the excretion of solifenacin in human milk are available. In mice, solifenacin and/or its metabolites was excreted in milk, and caused a dose dependent failure to thrive in neonatal mice. The use of Synnerv Solifenacin should therefore be avoided during breast-feeding.

Effects on The Ability to Drive and Use Machines:
Since solifenacin, like other anticholinergics may cause blurred vision, and, uncommonly, somnolence and fatigue, the ability to drive and use machines may be negatively affected.

SIDE EFFECTS:
Summary of the safety profile
Due to the pharmacological effect of solifenacin, Synerrv Solifenacin may cause anticholinergic undesirable effects of (in general) mild or moderate severity. The frequency of anticholinergic undesirable effects is dose related.
The most commonly reported adverse reaction with solifenacin succinate was dry mouth. The severity of dry mouth was generally mild and did only occasionally lead to discontinuation of treatment.

Tabulated list of adverse reactions

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not Known
Infections and infestations			Urinary tract infection Cystitis			
Immune system disorders						Anaphylactic reaction*
Metabolism and nutrition disorders						Decreased appetite* Hyper-kalaemia*
Psychiatric disorders					Hallucina-tions* Confu-sional state*	Delirium*
Nervous system disorders			Somnolence Dysgeusia	Dizzi-ness* Head ache		
Eye disorders		Blurred vision	Dry eyes			Glaucoma*
Cardiac disorders						Torsade de Pointes* Electro-cardiogram QT prolonged* Atrial fibrillation* Palpitations* Tachycardia*
Respiratory, thoracic and mediastinal disorders			Nasal dryness			Dysphonia*
Gastro-intestinal disorders	Dry mouth	Constipation Nausea Dyspepsia Abdominal pain	Gastro-oesopha geal reflux diseases Dry throat	Colonic obstruc-tion Faecal impaction Vomitting*		Ileus* Abdominal discomfort*
Hepatobiliary disorders						Liver disorder* Liver function test abnormal*
Skin and subcutaneous tissue disorders			Dry skin	Pruritus* Rash*	Erythema multi-forme* Urticaria* Angioe-dema*	Exfoliative dermatitis*
Musculo-skeletal and connective tissue disorders						Muscular weakness*
Renal and urinary disorders			Difficulty in micturation	Urinary retention		Renal impairment*
General disorders and administration site conditions			Fatigue Peripheral oedema			

*observed post-marketing

OVERDOSE:
Symptoms
Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects. The highest dose of solifenacin succinate accidentally given to a single patient was 280mg in a 5 hour period, resulting in mental status changes not requiring hospitalization.

Treatment
In the event of overdose with solifenacin succinate the patient should be treated with activated charcoal. Gastric lavage is useful if performed within 1 hour , but vomiting should not be induced.
As for other anticholinergics, symptoms can be treated as follows:

- Severe central anticholinergic effects such as hallucinations or pronounced excitation: treat with physostigmine or carbachol.
- Convulsions or pronounced excitation: treat with benzodiazepines.
- Respiratory insufficiency: treat with artificial respiration.
- Tachycardia: treat with beta-blockers.
- Urinary retention: treat with catherelisation.
- Mydriasis: treat with pilocarpine eye drops and/or place patient in a dark room.

As with other antimuscarinics, in case of overdosing, specific attention should be paid to patients with known risk for QT-prolongation (i.e., hypokalaemia, bradycardia and concurrent administration of medicinal products known to prolong QT-interval) and relevant pre-existing cardiac diseases (i.e., myocardial ischaemia, arrhythmia, congestive heart failure).

PHARMACEUTICAL PARTICULARS:
List of Excipients
Lactose monohydrate, Corn starch, Hydroxypropyl methyl cellulose, Magnesium stearate (vegetable origin), Purified water & Instacoat universal light yellow (A05G12185).

Nature and contents of container
Container
The film coated tablets are packed in PVC/ Aluminium blisters.

Pack sizes
3 x 10's and 10 x 10's (not all pack sizes may be marketed).

STORAGE :
Store below 30°C.

Manufacturer
Umedica Laboratories Pvt. Ltd.,
Plot. No. 221, IInd Phase G.I.D.C.,
Vapi, Gujarat, 396195, India

Product registration holder
Synerrv Sdn Bhd.,
SO-29-2, Menara 1, KL Eco City,
Jalan Bangsar, KG Haji Abdullah Hukum,
59200 Kuala Lumpur Malaysia.

Leaflet revision date
6th December 2024

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For the use only of a Registered Medical Practitioner or a Hospital.

Synerrv Solifenacin

PRODUCT NAME:
Synerrv Solifenacin (Solifenacin Succinate Film Coated Tablets 5mg)

COMPOSITION:
Synerrv Solifenacin (Solifenacin Succinate Film Coated Tablets 5mg):
Each tablet contains 5mg of solifenacin succinate equivalent to 3.8mg of solifenacin.

DESCRIPTION:
Synerrv Solifenacin (Solifenacin Succinate Film Coated Tablets 5mg): Light yellow round shaped, biconvex film coated tablets, debossed with "SOL" on one side and "5" on other side.

PHARMACODYNAMICS:
Pharmacotherapeutic group: Urinary antispasmodics,
ATC code: G04B D08.

Mechanism of Action
Solifenacin is a competitive, specific cholinergic-receptor antagonist.
The urinary bladder is innervated by parasympathetic cholinergic nerves. Acetylcholine contracts the detrusor smooth muscle through muscarinic receptors of which the M3 subtype is predominantly involved. In vitro and in vivo pharmacological studies indicate that solifenacin is a competitive inhibitor of the muscarinic M3 subtype receptor. In addition, solifenacin showed to be a specific antagonist for muscarinic receptors by displaying low or no affinity for various other receptors and ion channels tested.

Pharmacokinetics:
Absorption:
Maximum solifenacin plasma concentrations (Cmax) are reached after 3 to 8 hours. The tmax is independent of the dose. The Cmax and area under the curve (AUC) increase in proportion to the dose between 5 to 40mg. 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 a1-acid glycoprotein.

Biotransformation:
Solifenacin is extensively metabolised by the liver, primarily by cytochrome P450 3A4 (CYP3A4). However, alternative metabolic pathways exist, that can contribute to the metabolism of solifenacin. The systemic clearance of solifenacin is about 9.5 L/h and the terminal half-life of solifenacin is 45 - 68 hours. After oral dosing, one pharmacologically active (4R-hydroxy solifenacin) and three inactive metabolites (N-glucuronide, N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been identified in plasma in addition to solifenacin.

Elimination:
After a single administration of 10mg [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).

Linearity/non-linearity:
Pharmacokinetics are linear in the therapeutic dose range.

Other special populations:
Elderly
No dosage adjustment based on patient age is required. The mean rate of absorption expressed as tmax was slightly slower in the elderly and the terminal half-life was approximately 20% longer in elderly. These modest differences are not clinically significant.
The pharmacokinetics of solifenacin have not been established in children and adolescents.

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

Race:
The pharmacokinetics of solifenacin are not influenced by race.

Renal impairment:
The AUC and Cmax of solifenacin in mild and moderate renal impairment is not significantly different from that without renal impairment.
Pharmacokinetics in patients undergoing haemodialysis have not been studied.

Hepatic impairment:
In moderate hepatic impairment (Child-Pugh score of 7 to 9) the Cmax is not affected, AUC increased with 60% and t½ doubled. Pharmacokinetics of solifenacin in patients with severe hepatic impairment have not been studied.

Therapeutic Indication:
Symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome.

DOSAGE AND ADMINISTRATION:
Adults, including the elderly
The recommended dose is 5mg solifenacin succinate once daily . If needed, the dose may be increased to 10mg solifenacin succinate once daily.

Paediatric population
The safety and efficacy of solifenacin succinate in children have not yet been established. Therefore, solifenacin succinate should not be used in children.

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

Patients with hepatic impairment
No dose adjustment is necessary for patients with mild hepatic impairment. Patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) should be treated with caution and receive no more than 5mg once daily.

Potent inhibitors of cytochrome P450 3A4
The maximum dose of solifenacin succinate should be limited to 5mg when treated simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors e.g., ritonavir, nelfinavir, itraconazole.

Format

UMEDICA LABORATORIES PVT. LTD.

Format Name	**SPECIFICATION FOR ARTWORK APPROVAL**		
Format Number	**FM/PDD/002-01-06**	**SOP Number**	**PDD/002**

New Artwork Code No. : XXXXXX **Old Artwork Code No.:** NA **Artwork Effective Date:**

Product Name : **Synerrv Solifenacin** **Company Name/Country :** **Synerrv - Malaysia**
(Solifenacin Succinate Film Coated Tablets 5mg & 10mg)

Component Type : **Package Insert** **Pack Style** : **3×10T, 10×10T**

Description : **New development Package Insert Artwork as per export-country, Malaysia country requirement.**

Specifications : **L×H (Auto Cartonator Size)** **Site : Umedica** **Artwork Language: English**

Full Size / ~~Size~~	: 200×280 MM	**Type / ~~Blister / Strip Size / Adhesive / Tube Type~~**	: Front-Back
Size - Catch Cover / Foil / BOPP	: NA	**~~Sachet Size~~/~~Pocket Size~~/Fold Size/~~Release Paper~~**	: 100×35 MM
Space between Labels	: NA	**Transparent Paper Thickness**	: NA
GSM of Paper / ~~GSM of Aluminum Foil~~	: 40 GSM	**Type of Paper / ~~GSM~~**	: Bible Paper
Thickness of Foil	: NA	**Type of Foil / Fold / Coating GSM**	: NA
Cylinder	: NA	**Lamination / Varnish / Material Grade**	: NA
Repeat/Tolerence	: NA	**Partition / Plate Size / Total GSM /**	: NA
		Sealing / Embossing / Core Diameter	: NA
GSM/BF of Printed Shipper	: NA	**Paper Grade / Flute Type / PLY of Shipper**	: NA
(Top/Middle/Bottom and Flute layer	: NA		
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 Product Profile/Inhouse 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','Q' or 'X' etc warning for Rx products and / 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, (In case of 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/ Overprinting	Artwork Approved by Sign with Date
																				PDD Department
																				PPIC/Packing Department
																				QC Department
																				RA Department
																				QA Department

Note to Printer:

- **After receive the CDR File, Submit the print proof for approval**
- **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.**