Package Insert

SOLICIN-5
(Solifenacin Succinate Tablets 5 mg)

i. Name and Strength of Active Substance(s):

SOLICIN 5: Solifenacin Succinate Tablets 5 mg

ii. Product Description:

SOLICIN 5: Light yellow colored, round, biconvex, film coated tablets, debossed with "EG" on one side and "1" on other side.

List of excipients:

Tablet core
Solifenacin Succinate
Lactose monohydrate (Pharmatose 200M) DMV
Maize starch
Hydroxy Propyl Methyl Cellulose (3 cps)
Magnesium stearate

Film-coating (Opadry Yellow 2F520011)
Hypromellose (5cP) (E464)
Talc (E553b)
Titanium Dioxide (E171)
Macrogol 6000 (E1521)
Iron Oxide Yellow (E172)

iii. Pharmacodynamics/Pharmacokinetics:

PHARMACOLOGY

Pharmacotherapeutic group: Urinary antispasmodics

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 Succinate tablets, maximum solifenacin plasma concentrations (C_{max}) 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 Succinate 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 4R-hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (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 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 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.

Dose Proportionality

Pharmacokinetics are linear in the therapeutic dose range.

Renal impairment
Solifenacin Succinate Tablet 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 Tablet greater than 5 mg are not recommended in patients with severe renal impairment (CLcr <30 ml/min).

Hepatic impairment
Solifenacin Succinate Tablet 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 Tablet greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B).

Solifenacin Succinate Tablet is not recommended for patients with severe hepatic impairment (Child-Pugh C).
The pharmacokinetics of solifenacin have not been established in children and adolescents.

iv. Therapeutic Indication:

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

v. Recommended Dosage:

Adults, including the elderly
The recommended dose is 5 mg Solifenacin succinate once daily. If needed, the dose may be increased to a maximum of 10 mg Solifenacin succinate 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 Tablet is not recommended for patients with severe hepatic impairment (Child-Pugh C).

Co-medication
The maximum dose of Solifenacin Succinate Tablet 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.

vi. Method of administration:

Solifenacin Succinate Tablet should be taken orally and should be swallowed whole with liquids. It can be taken with or without food.

vii. Contraindication:

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

viii. Special Warnings and Precautions for use:

Solifenacin Succinate Tablet 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 lmpairment
Solifenacin Succinate Tablet should be used with caution in patients with reduced renal function. Solifenacin Succinate Tablet 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 Tablet greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). Solifenacin Succinate Tablet 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).

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 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.

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.

ix. Interactions with Other Medicines and Other Forms of Interaction:

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

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

Digoxin
Intake of Solifenacin Succinate Tablet 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.

<u>Use in children</u>
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 Cmax, AUC and t1/2 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.

x. Undesirable Effects /Adverse Reactions:

In the four 12-week double-blind clinical trials 3027 patients were involved (1811 on Solifenacin Succinate Tablet 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 Tablet 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 Tablet.

Numbers (%) of patients with treatment-emergent adverse events reported by 1% or more patients: controlled phase 3 studies (all combained)		
SYSTEM ORGAN CLASS MedDRA Preferred Term	**Placebo (%)**	**Solifenacin Succinate Tablet 5mg (%)**
Number of patients	1216	578
Number of Patients with treatment-mergent AE	634	265
GASTROINTESTINAL DISORDER		
Dry Mouth	4.2	10.9
Constipation	2.9	5.4
Nausea	2.0	1.7
Dyspepsia	1.0	1.4
Diarrhoea NOS	2.1	0.7
Vomiting NOS	0.9	0.2
Abdominal pain upper	1.0	1.9
Abdominal pain NOS	1.2	0.2
INFECTIONS AND INFESTATIONS		
Urinary tract infection NOS	2.8	2.8
Urinary respiratory tract infection NOS	2.0	0.9
Influenza	1.3	2.2

Sinusitis NOS	1.2	0.9
Nasopharyngitis	2.7	0.9
Pheryngitis NOS	1.0	0.3
Bronchitis	1.1	0.7
NERVOUS SYSTEM DISORDES		
Headache	4.5	1.9
Dizziness	1.8	1.9
MUSCULOSKELETAL AN CONNECTIVE TISSUE DISORDER		
Arthralgia	2.2	0.7
Back pain	1.8	0.5
Neck pain	0.5	0.3
GENERAL DISORDER AND ADMINISTRATION SITE DISORDERS		
Fatigue	1.1	1.0
Oedema lower limb	0.7	0.3
Influenza like illness	0.5	0.3
EYE DISORDERS		
Vision blurred	1.8	3.8
Dry Eye NOS	0.6	0.3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough	0.2	0.2
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	1.0	0
RENAL AND URINARY DISORDERS		
Urinary retention	0.6	0
Dysuria	0.4	0.3
PSYCHIATRIC DISORDERS		
Insomnia	1.2	0.3
Depression NOS	0.8	1.2
VASCULAR DISORDERS		
Hypertention NOS	0.6	1.4

Adverse reactions reported in the clinical trials with a frequency of occurrence less than 1% are:
Gastro-intestinal disorders: flatulence, gastro-oesophaegeal 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, micturation 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

xi. Overdose and Treatment:

Over dosage 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.

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

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

For advice on the management of an overdose, please contact the Poisons Information Centre.

xii. Storage Conditions:
Store at or below 30 °C.
Keep out of the sight and reach of children.

xiii. Dosage Forms or Presentation:
PVC/PVdC- Aluminum blisters of 30 Tablets. 3 such blister in one printed carton (3 × 10 Tablets).

xiv. Product Registrant:
ACCORD HEALTHCARE PRIVATE LIMITED.
6 Shenton Way, OUE Downtown #38-01,
Singapore, 068809

xv. Date of Revision of Package Insert:

30th March 2022