



**SOLIFENACIN SUCCINATE TABLETS 10 MG**

**MODULE 1**

**ADMINISTRATIVE INFORMATION AND PRESCRIBING INFORMATION**

**1.3 LABELLING AND PACKAGING**

**1.3.1 PACKAGE INSERT**

**1.3.1 Package insert****1. Name of the medicinal product**

**INN Name:** Solifenacin succinate tablets 10 mg.

**Trade Name:** Solifenacin succinate

**Strength:** 10mg

**Pharmaceutical form:** Tablets

**2. Qualitative and quantitative composition****GOAB 10 (Solifenacin Succinate Tablets 10mg)**

Each film coated tablet contains 10 mg solifenacin succinate

Excipient(s): lactose monohydrate

**3. Pharmaceutical form**

Solifenacin succinate film-coated tablet:

**GOAB 10 (Solifenacin Succinate Tablets 10mg)**

White to off white color, round, biconvex tablets debossed “V” on one side and “19”.

**4. Clinical particulars****4.1 Therapeutic indications**

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

**4.2 Posology and method of administration**

Adults, including the elderly

Posology

The recommended dose is 5 mg solifenacin succinate tablets once daily. If needed, the dose may be increased to 10 mg solifenacin succinate tablets once daily.

Paediatric population

The safety and efficacy of solifenacin succinate tablets in children have not yet been established. Therefore, solifenacin succinate tablets 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 5 mg once daily.

**Module 1- Administrative information and product information**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 tablets should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4-inhibitors e.g. ritonavir, nelfinavir, itraconazole.

Method of administration

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

**4.3 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.

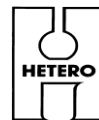
- Patients hypersensitive to the active substance or to any of the excipients
- Patients undergoing hemodialysis
- Patients with severe hepatic impairment
- Patients with severe renal impairment or moderate hepatic impairment and who are on treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole.

**4.4 Special warnings and precautions for use**

Other causes of frequent urination (heart failure or renal disease) should be assessed before treatment with solifenacin succinate tablets. If urinary tract infection is present, an appropriate antibacterial therapy should be started.

Solifenacin succinate tablets 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.

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- Moderate hepatic impairment (Child-Pugh score of 7 to 9;), and doses should not exceed 5 mg 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.

QT prolongation and torsade de pointes have been observed in patients with risk factors, such as preexisting long QT syndrome and hypokalemia. Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor over activity.

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

Angioedema with airway obstruction has been reported in some patients on solifenacin succinate tablets.

If angioedema occurs, solifenacin succinate tablets should be discontinued and appropriate therapy and/or measures should be taken.

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

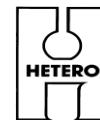
The maximum effect of solifenacin succinate tablets can be determined after 4 weeks at the earliest.

#### **4.5 Drug Interactions**

##### 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 tablets, 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.

**Module 1- Administrative information and product information**Pharmacokinetic interactions

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 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 solifenacin succinate tablets should be restricted to 5 mg, 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, 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 (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 tablets showed no effect on the pharmacokinetics of digoxin.

**4.6 Fertility, Pregnancy and Lactation****Pregnancy**



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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.

### **Breast-feeding**

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 solifenacin succinate should therefore be avoided during breast-feeding.

### **4.7 Effects on 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.

### **4.8 Undesirable Effects**

#### Summary of the safety profile

Due to the pharmacological effect of solifenacin, solifenacin succinate tablets 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. It occurred in 11% of patients treated with 5 mg once daily, in 22% of patients treated with 10 mg once daily and in 4% of placebo-treated patients. The severity of dry mouth was generally mild and did only occasionally lead to discontinuation of treatment. In general, medicinal product compliance was very high (approximately 99%) and approximately 90% of the patients treated with Solifenacin Succinate tablets completed the full study period of 12 weeks treatment.

MedDRA system organ class	Verycommon >1/10	Common >1/100, <1/10	Uncommon > 1/1000, 1/100	Rare > 1/10000, <1/1000	Very rare <1/10000	Notknown (cannot be estimated from the available data)
Infections and infestations			Urinary tract infection Cystitis			



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Immunesystem disorders						Anaphylactic reaction*
Metabolism and nutrition disorders						Decreased appetite* Hyperkalaemia*
Psychiatric disorders					Hallucinations* Confusional state*	Delirium
Nervoussystem disorders			Somnolence Dysgeusia	Dizzines, Headach*		
Eyedisorders		Blurred vision	Dry eyes			Glaucoma*
Cardiac disorders						Torsade de Pointes* Electrocardiogram QT prolonged* Atrial fibrillation* Palpitations* Tachycardia*
Respiratory, thoracic And mediastinal disorders			Nasal dryness			Dysphonia*



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Gastrointestinal disorders	Dry mouth	Constipation Nausea Dyspepsia Abdominal pain	Gastro-oesophageal reflux diseases Dry throat	Colonic Obstructin Faecal impaction, vomiting*		Ileus* Abdominal discomfort*
Hepatobiliary disorders						Liver disorder* Liver function test abnormal*
Skin and subcutaneous tissue disorders			Dry skin	Pruritus*, Rash*	Erythema multiforme* Urticarial* Angioedema*	Exfoliative dermatitis*
Musculoskeleton and connective tissue disorders						Muscle weakness*
Renal and urinary disorders			Difficulty in micturition	Urinary retention		Renal impairment*
General disorders And administration Site conditions			Fatigue Peripheral oedema			

\*observed post-marketing

**4.9 Overdose**Symptoms



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Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects. The highest dose of solifenacin succinate accidentally given to a single patient was 280 mg in a 5 hour period, resulting in mental status changes 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 catheterisation.
- Mydriasis: treat with pilocarpine eye drops and/or place patient in 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).

**5. PHARMACOLOGICAL PROPERTIES****5.1 Pharmacodynamic properties**

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.


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Pharmacodynamic effects

Treatment with solifenacin succinate tablets doses of 5 mg and 10 mg daily was studied in several double blind, randomised, controlled clinical trials in men and women with overactive bladder.

As shown in the table below, both the 5 mg and 10 mg doses of solifenacin succinate tablets 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. A long-term open label study demonstrated that efficacy was maintained for at least 12 months. 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. 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 treatment duration of 12 weeks.*

	<b>Placebo</b>	<b>Solifenacin succinate tablets 5mg o.d.</b>	<b>Solifenacin succinate tablets 10mg o.d.</b>	<b>Tolterodine 2mg b.i.d</b>
<b>No. of micturitions/24 h</b>				
Mean baseline	11.9	12.1	11.9	12.1
Mean reduction from baseline	1.4	2.3	2.7	1.9
% change from baseline	(12%)	(19%)	(23%)	(16%)
n	1138	552	1158	250
p-value*		<0.001	<0.001	0.004
<b>No. of urgency episodes / 24 h</b>				
Mean baseline	6.3	5.9	6.2	5.4
Mean reduction from baseline	2.0	2.9	3.4	2.1
% change from baseline	(32%)	(49%)	(55%)	(39%)



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n		548	1151	250
p-value*	1124	<0.001	<0.001	0.031
<b>No. of incontinence episodes/24 h</b>				
Mean baseline	2.9	2.6	2.9	2.3
Mean reduction from baseline	1.1	1.5	1.8	1.1
% change from baseline	(38%)	(58%)	(62%)	(48%)
n		314	778	157
p-value*	781	<0.001	<0.001	0.009
<b>No. of nocturia episodes/24 h</b>				
Mean baseline	1.8	2.0	1.8	1.9
Mean reduction from baseline	0.4	0.6	0.6	0.5
% change from baseline	(22%)	(30%)	(33%)	(26%)
n		494	1035	232
p-value*	1005	0.025	<0.001	0.199
<b>Volume voided/micturition</b>				
Mean baseline	166 ml	146 ml	163 ml	147 ml
Mean reduction from baseline	9 ml	32 ml	43 ml	24 ml
% change from baseline	(5%)	(21%)	(26%)	(16%)
n	1135	552	1156	250
p-value*		<0.001	<0.001	<0.001
<b>No. of pads/24 h</b>				
Mean baseline	3.0	2.8	2.7	2.7
Mean reduction from baseline	0.8	1.3	1.3	1.0
% change from baseline	(27%)	(46%)	(48%)	(37%)


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n	238	236	242	250
p-value		<0.001	<0.001	0.010

Note: In 4 of the pivotal studies, solifenacin succinate tablets 10 mg and placebo were used. In 2 out of the 4 studies also solifenacin succinate tablets 5 mg was used and one of the studies included tolterodine 2 mg bid.

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

## 5.2 Pharmacokinetic properties

### Absorption

After intake of solifenacin succinate tablets \* P-value for the pair wise comparison to placebo tablets, maximum solifenacin plasma concentrations ( $C_{max}$ ) are reached after 3 to 8 hours. The  $t_{max}$  is independent of the dose. The  $C_{max}$  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  $C_{max}$  and  $AUC_{max}$  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  $\alpha$ -acid 1 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 (Nglucuronide, N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been identified in plasma in addition to solifenacin.

### Elimination

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14 After a single administration of 10 mg [ C-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-Noxide metabolite and 8% as the 4R-hydroxy metabolite (active metabolite).

Linearity/non-linearity

Pharmacokinetics is linear in the therapeutic dose range.

Other special populations***Elderly***

No dosage adjustment based on patient age is required. Studies in elderly have shown that the exposure to solifenacin, expressed as the AUC, after administration of solifenacin succinate (5 mg and 10 mg once daily) was similar in healthy elderly subjects (aged 65 through 80 years) and healthy young subjects (aged less than 55 years). The mean rate of absorption expressed as  $t$  was slightly slower in the elderly and the max terminal half-life was approximately 20% longer in elderly subjects. These modest differences were considered not clinically significant.

The pharmacokinetics of solifenacin has 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 C of solifenacin in mild and moderate renally impaired patients, was not significantly max different from that found in healthy volunteers. In patients with severe renal impairment (creatinine clearance  $\leq 30$  ml/min) exposure to solifenacin was significantly greater than in the controls with increases in C of about 30%, AUC of more than 100% and  $t$  of more than 60%. A statistically significant max  $\frac{1}{2}$  relationship was observed between creatinine clearance and solifenacin clearance.

Pharmacokinetics in patients undergoing hemodialysis has not been studied.

***Hepatic impairment***

In patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) the C is not affected, AUC max increased with 60% and  $t$  doubled. Pharmacokinetics of solifenacin in patients with severe hepatic  $\frac{1}{2}$  impairment has not been studied.

**Module 1- Administrative information and product information****5.3 Preclinical safety data**

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, fertility, embryofetal development, genotoxicity, and carcinogenic potential. In the pre- and postnatal development study in mice, solifenacin treatment of the mother during lactation caused dose-dependent lower postpartum survival rate, decreased pup weight and slower physical development at clinically relevant levels. Dose related increased mortality without preceding clinical signs occurred in juvenile mice treated from day 10 or 21 after birth with doses that achieved a pharmacological effect and both groups had higher mortality compared to adult mice. In juvenile mice treated from postnatal day 10, plasma exposure was higher than in adult mice; from postnatal day 21 onwards, the systemic exposure was comparable to adult mice. The clinical implications of the increased mortality in juvenile mice are not known.

**6. Pharmaceutical particulars****6.1 List of excipients**

Tablet core:

Corn starch, lactose monohydrate, hypromellose, magnesium stearate.

Tablet coating:

Hypromellose, titanium dioxide, macrogol, talc.

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

24 Months

**6.4 Special precautions for storage**

Store below 30°C.

**6.5 Nature and contents of container**

10's Blister Pack



**Module 1- Administrative information and product information**

**6.6 Special precautions for disposal and other handling**

Not Applicable

**7. Marketing authorization holder**

(Company) Name : Hetero Labs Limited,  
Address : 7-2-A2, Hetero Corporate, Industrial Estate, Sanath Nagar,  
Hyderabad, Telangana, Pin Code - 500018  
Country : INDIA  
Telephone : +91-40-23704923/24/25  
Tele fax : +91-40-23704926/23714250

**8. MARKETING AUTHORISATION NUMBER(S)**

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

**10. DATE OF REVISION OF THE TEXT**