For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only OR for Specialist Use only

Bispec – 5 (Solifenacin Succinate Tablets 5mg)
Bispec – 10 (Solifenacin Succinate Tablets 10mg)

Solifenacin Succinate

COMPOSITION

Bispec – 5

Each film coated tablet contains:
Solifenacin Succinate …….5 mg
(Corresponding to Solifenacin 3.8 mg)
Colour: Yellow oxide of iron & Titanium dioxide

Bispec – 10

Each film coated tablet contains:
Solifenacin Succinate …….10 mg
(Corresponding to Solifenacin 7.5 mg)
Colour: Red oxide of iron & Titanium dioxide

DOSAGE FORM

Film coated tablets

PRODUCT DESCRIPTION

Bispec – 5

Light yellow coloured, round, biconvex, film coated tablets debossed with ‘C’ and ‘259’ on one side and plain on the other.

Bispec – 10

Light pink colored, round, biconvex film coated tablets debossed with 'C' and '261' on one side and plain on the other.

PHARMACOLOGY

Pharmacodynamics

Pharmacotherapeutic group: Urinary antispasmodics,
ATC code: G04B DO8.

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. 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

After intake of solifenacin 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 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.

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 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).

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 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

No significant impact on the pharmacokinetic of solifenacinin mild and moderate renally impaired patients. However, in patients with severe renal impairment (creatinine clearance ≤ 30 ml/min) exposure to solifenacin was significantly greater.

Pharmacokinetics in patients undergoing haemodialysis have not been studied.

Hepatic impairment

In patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) the C_{max} is not affected, AUC increased with 60% and $t_{½}$ doubled. Pharmacokinetics of solifenacin in patients with severe hepatic impairment have not been studied.

INDICATION

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

DOSAGE AND METHOD OF ADMINISTRATION

Posology

Adults, including the elderly

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

Paediatric population

The safety and efficacy of solifenacin in children have not yet been established. Therefore, solifenacin 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 (*see Pharmacokinetic*).

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 5 mg once daily (*see Pharmacokinetic*).

Potent inhibitors of cytochrome P450 3A4

The maximum dose of solifenacin should be limited to 5 mg when treated simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4-inhibitors e.g. ritonavir, nelfinavir, itraconazole (*see Drug Interactions*).

Method of administration

Solifenacin 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.
- Patients undergoing haemodialysis (*see Pharmacokinetic*).
- Patients with severe hepatic impairment (*see Pharmacokinetic*).
- Patients with severe renal impairment or moderate hepatic impairment and who are on treatment with a potent CYP3A4 inhibitor, e.g. ketoconazole (see *Drug Interactions*).

WARNINGS AND PRECAUTIONS

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

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; *see Dosage and Method of Administration and, Pharmacokinetic*), and doses should not exceed 5 mg for these patients.
- Moderate hepatic impairment (Child-Pugh score of 7 to 9; *see Dosage and Method of Administration and, Pharmacokinetic*), and doses should not exceed 5 mg for these patients.
- Concomitant use of a potent CYP3A4 inhibitor, e.g. ketoconazole (*see Dosage and Method of Administration, and Drug Interactions*).
- 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 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) (*see Drug Interactions and Pharmacodynamics*). Appropriate Investigations (e.g. ECG) should be considered in patients with risk factors for QTc prolongation.

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, 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 solifenacin should be restricted to 5 mg, when used simultaneously with ketoconazole or therapeutic doses of other potent CYP3A4 inhibitors (e.g. ritonavir, nelfinavir, itraconazole) (*see Dosage and Method of Administration*). Simultaneous treatment of solifenacin and a potent CYP3A4 inhibitor is contra-indicated in patients with severe renal impairment or moderate hepatic impairment.

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 showed no pharmacokinetic interaction of solifenacin on combined oral contraceptives (ethinylestradiol/levonorgestrel).

Warfarin

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

Digoxin

Intake of solifenacin 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.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy

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. The use of solifenacin should therefore be avoided during breast-feeding.

UNDESIRABLE EFFECTS

Summary of the safety profile

Due to the pharmacological effect of solifenacin, 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 was dry mouth. 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.

Tabulated list of adverse reactions

MedDRA 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 Hyperkalaemia
Psychiatric disorders					Hallucinations Confusional state	Delirium
Nervous system disorders			Somnolence Dysgeusia	Dizziness, Headache		
Eye disorders		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
Gastrointestinal disorders	Dry mouth	Constipation Nausea Dyspepsia Abdominal pain	Gastro-oesophageal reflux diseases Dry throat	Colonic obstruction 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, Urticaria, Angioedema	Exfoliative dermatitis
Musculoskeletal and connective						Muscular weakness

tissue disorders						
Renal and urinary disorders			Difficulty in micturition	Urinary retention		Renal impairment
General disorders and administration site conditions			Fatigue Peripheral oedema			

OVERDOSE

Symptoms

Overdosage with solifenacin succinate can potentially result in severe anticholinergic effects.

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).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE

Since solifenacin, like other anticholinergics may cause blurred vision, and uncommonly somnolence and fatigue (see *Undesirable Effects*), the ability to drive and use machines may be negatively affected.

INCOMPATIBILITY

Not applicable.

STORAGE AND HANDLING INSTRUCTION

Store below 30°C

SHELF LIFE

24 months

PACKAGING INFORMATION

Bispec – 5 (Solifenacin Succinate Tablets 5 mg) is packed in carton containing plain aluminium blister foil with NC coated with 3 ply Alu-Alu laminated film. Blister of 10 tablets each.

Bispec – 10 (Solifenacin Succinate Tablets 10 mg) is packed in carton containing plain aluminium blister foil with NC coated with 3 ply Alu-Alu laminated film. Blister of 10 tablets each.

MANUFACTURED BY

CIPLA LTD.
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PRODUCT REGISTRATION HOLDER

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