QUEMED 5 MG TABLETS
QUEMED 10 MG TABLETS

Solifenacin succinate

DESCRIPTION
Film-coated tablet.
Quemed 5 mg: yellow round biconvex film-coated tablets, plain on both sides, diameter 6 mm, without break line.
Quemed 10 mg: pink round biconvex film-coated tablets, plain on both sides, diameter 7 mm, without break-line.

COMPOSITION
Quemed 5 mg: each film-coated tablet contains 5 mg of solifenacin succinate.
Quemed 10 mg: each film-coated tablet contains 10 mg of solifenacin succinate.

List of excipients:
Tablet core: Lactose monohydrate, Maize starch, Talc, Magnesium stearate.
Tablet coating:
Quemed 5 mg: Opadry yellow OY 32823 (Hypromellose 6cP, Titanium dioxide, Macrogol 400, Ferric oxide Yellow, Ferric oxide Red)
Quemed 10 mg: Opadry white 03B28796 (Hypromellose 6cP, Titanium dioxide, Macrogol 400), Opadry brown 02F23883 (Hypromellose 5cP, Titanium dioxide, Macrogol 6000, Ferric oxide Yellow, Ferric oxide Red)

PHARMACODYNAMICS
Pharmacotherapeutic group: Urinary antispasmodics, ATC code: G04BD08.

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 M_3 subtype is predominantly involved. Solifenacin is a competitive inhibitor of the muscarinic M_3 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.

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 α_1-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 (4*R*-hydroxy solifenacin) and three inactive metabolites (*N*-glucuronide, *N*-oxide and 4*R*- hydroxy-*N*-oxide) of solifenacin have been identified in plasma in addition to solifenacin.

Elimination
After a single administration of 10 mg [^{14}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 4*R*-hydroxy-*N*-oxide metabolite and 8% as the 4*R*-hydroxy metabolite (active metabolite).

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

Other special populations
Elderly patients
No dosage adjustment based on patient age is required.

Paediatric population
The pharmacokinetics of solifenacin has not been established in children and adolescents.

Gender
The pharmacokinetics of solifenacin is not influenced by gender.

Race
The pharmacokinetics of solifenacin is not influenced by race.

Renal impairment
No significant difference in the AUC and C_{max} of solifenacin in mild and moderate renally impaired patients. In patients with severe renal impairment (creatinine clearance ≤ 30 ml/min), exposure to solifenacin was significantly greater, with increases in C_{max} of about 30%, AUC of more than 100% and $t_{½}$ of more than 60%. There is a statistically significant relationship between creatinine clearance and solifenacin clearance.

Pharmacokinetics in patients undergoing haemodialysis has not been established.

Hepatic impairment
In patients with moderate hepatic impairment (Child-Pugh score of 7 to 9) the C_{max} is not affected, AUC increased by 60% and $t_{½}$ doubled.

Pharmacokinetics of solifenacin in patients with severe hepatic impairment has not been established.

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

RECOMMENDED DOSAGE

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, Quemed 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.

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.

Potent inhibitors of cytochrome P450 3A4

The maximum dose of Quemed 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

Quemed 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 gastrointestinal 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.
- 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 PRECAUTION

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) and doses should not exceed 5 mg for these patients.
- 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/gastroesophageal 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 pre-existing long QT syndrome and hypokalaemia..

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, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

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 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 gastrointestinal tract, such as metoclopramide and cisapride.

Pharmacokinetic interactions

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).

Simultaneous treatment of solifenacin and a potent CYP3A4 inhibitor is contraindicated 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 established 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 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.

STATEMENT ON USAGE DURING 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.

Breastfeeding
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 Quemed should therefore be avoided during breast-feeding.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS

Summary of the safety profile
Due to the pharmacological effect of solifenacin, Quemed 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 only occasionally led to discontinuation of treatment.

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

OVERDOSAGE

Symptoms

Overdose 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 hours period, resulting in mental status changes not requiring hospitalisation.

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 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).

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.

STORAGE CONDITION
Store below 30°C.

DOSAGE FORM AND PACKAGING AVAILABLE
OPA/Al/PVC/Al blister, carton.
Pack size: 30 or 100 film-coated tablets.

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PRODUCT REGISTRATION HOLDER
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