

Regurin[®] XL



Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

Regurin XL 60 mg prolonged-release capsule, hard

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release capsule, hard contains 60 mg trospium chloride.

Excipients:

Each prolonged-release capsule, hard contains 154.5 mg sucrose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release capsule, hard

The Regurin XL 60 mg prolonged-release capsule, hard has an opaque orange cap and an opaque white body imprinted with SAN 60 and contains white to off-white pellets.

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.

4.2 Posology and method of administration

One capsule once daily (equivalent to 60 mg of trospium chloride per day).

Regurin XL 60 mg should be taken with water on an empty stomach one hour before a meal.

Renal impairment:

Data on the use of Regurin XL 60 mg are not available for patients with renal impairment. Trospium chloride is mainly excreted unchanged by the kidneys. An increase in plasma levels is documented for the immediate release formulation. For the prolonged release formulation an appropriate level of dose adjustment is not known for renally impaired patients and the product is therefore not recommended for use in renally impaired patients (see section 4.4 and 5.2).

Hepatic impairment:

Data on patients with mild and moderate impairment of liver function are

only available for the immediate release formulation of trospium chloride, but not for the prolonged release formulation. These patients should be treated with caution. Regurin XL 60 mg should not be given to patients with severe hepatic impairment (see section 4.4 and 5.2).

The need for continued treatment should be reassessed at regular intervals of 3-6 months.

Regurin XL 60 mg is not recommended for use in children and adolescents below 18 years due to lack of data on safety and efficacy.

4.3 Contraindications

Trospium chloride is contraindicated in patients with urinary retention, severe gastro-intestinal condition (including toxic megacolon), myasthenia gravis, narrow-angle glaucoma, and tachyarrhythmia.

Trospium chloride is also contraindicated in patients who have demonstrated hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Trospium chloride should be used with caution by patients:

- with obstructive conditions of the gastrointestinal tract such as pyloric stenosis
- with obstruction of the urinary flow with the risk of formation of urinary retention
- with autonomic neuropathy
- with hiatus hernia associated with reflux oesophagitis
- in whom fast heart rates are undesirable e.g. those with hyperthyroidism, coronary artery disease and congestive heart failure.

Data on the use of the prolonged-release formulation of trospium chloride are not available for patients with hepatic impairment. Based on data available for the immediate release formulation of trospium chloride, Regurin XL 60 mg is not recommended for patients with severe hepatic impairment and caution should be exercised in patients with mild to moderate liver impairment (see section 4.2 and 5.2).

Trospium chloride is mainly eliminated by renal excretion. For the immediate release formulation marked elevations in plasma levels have been observed in patients with severe renal impairment and lead to dose adjustment.

For the prolonged release formulation an appropriate level of dose adjustment is not known. Therefore, it is recommended not to treat

renally impaired patients with Regurin XL 60 mg (see section 4.2 and 5.2).

Before commencing therapy organic causes of urinary frequency, urgency, and urge incontinence, such as heart diseases, diseases of the kidneys, polydipsia, or infections, or tumours of urinary organs should be excluded.

Regurin XL 60 mg contains sucrose.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions:

The following potential pharmacodynamic interactions may occur: Potentiation of the effect of medicinal products with anticholinergic action (such as amantadine, tricyclic antidepressants), enhancement of the tachycardic action of β -sympathomimetics; decrease in efficacy of pro-kinetic agents (e.g. metoclopramide).

Since trospium chloride may influence gastro-intestinal motility and secretion, the possibility cannot be excluded that the absorption of other concurrently administered medicinal products may be altered.

Pharmacokinetic interactions:

An inhibition of the absorption of trospium chloride with active substances like guar, cholestyramine and colestipol cannot be excluded. Therefore the simultaneous administration of medicinal products containing these active substances with trospium chloride is not recommended.

Though trospium chloride was shown not to affect pharmacokinetics of digoxin, an interaction with other active substances eliminated by active tubular secretion cannot be excluded.

Metabolic interactions of trospium chloride have been investigated

in vitro on cytochrome P450 enzymes involved in active substance metabolism (P450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4). No influence on their metabolic activities were observed. Since trospium chloride is metabolised only to a low extent and since ester hydrolysis is the only relevant metabolic pathway, no metabolic interactions are expected.

4.6 Pregnancy and lactation

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). In rats, placental transfer and passage into the maternal milk of trospium chloride occurs.

Clinical data on exposure during pregnancy or lactation are not available for Regurin XL 60 mg.

Caution should be exercised when prescribing to pregnant or breastfeeding women.

4.7 Effects on ability to drive and use machines

Principally, disorders of accommodation can lower the ability to actively participate in road traffic and to use machines.

However, examinations of parameters characterising the ability to participate in road traffic (visual orientation, general ability to react, reaction under stress, concentration and motor coordination) have not revealed any effects of trospium chloride.

4.8 Undesirable effects

Undesirable effects observed with trospium chloride are caused mainly by typical anticholinergic effects such as dry mouth, dyspepsia and constipation.

In two Phase 3, placebo-controlled, double-blind clinical studies 1165 patients were treated for 12 weeks with either Regurin XL 60 mg or placebo.

The following table lists possibly related adverse events reported for patients treated with Regurin XL 60 mg:

	Very common ($>1/10$)	Common ($\geq 1/100, < 1/10$)	Uncommon ($\geq 1/1000, < 1/100$)	Rare ($\geq 1/10.000, < 1/1000$)	Very Rare ($< 1/10.000$)
Cardiac disorders				Tachycardia	
Eye disorders		Dry eye			
Gastrointestinal disorders	Dry mouth	Dyspepsia Constipation Constipation aggravated Abdominal pain Abdominal distension Nausea	Flatulence	Vision disorders	
General disorders and administration site conditions				Asthenia	
Infections and infestations					Urinary tract infection
Nervous system disorders					Headache
Renal and urinary disorders				Micturition disorders Urinary retention	
Respiratory, thoracic and mediastinal disorders		Nasal dryness			
Skin and subcutaneous disorders				Rash	

In ensuing open-label phases of the two Phase 3 clinical studies the most common adverse events constipation (6.8%) and dry mouth (6.5%) were reported less frequently.

For immediate-release formulations of trospium chloride the following undesirable effects have been observed in post-marketing surveillance:

Cardiac disorders: tachyarrhythmia; Gastrointestinal disorders: diarrhoea; General disorders and administration site conditions: chest pain; Immune system disorders: anaphylaxis; Investigations: mild to moderate increase in serum transaminase levels; Musculoskeletal and connective tissue disorders: myalgia, arthralgia; Nervous system disorders: dizziness; Respiratory, thoracic and mediastinal disorders: dyspnoea; Skin and subcutaneous tissue disorders: angio-oedema, Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN).

The frequencies for the prolonged-release capsule Regurin XL 60 mg are not known.

4.9 Overdose

After administration of a maximum single dose of 360 mg trospium chloride as immediate release preparation to healthy volunteers, dryness of the mouth, tachycardia and disorders of micturition were observed to an increased extent. No manifestations of severe overdose or intoxication in humans have been reported to date. Exaggerated anticholinergic symptoms are to be expected as signs of intoxication following administration of trospium chloride as an extended release preparation as well.

In the case of intoxication the following measures should be taken:

- gastric lavage and reduction of absorption (e.g. activated charcoal)
- local administration of pilocarpine to glaucoma patients
- catheterisation in patients with urinary retention
- treatment with a parasympathomimetic agent (e.g. neostigmine) in the case of severe symptoms
- administration of beta blockers in the case of insufficient response, pronounced tachycardia and/or circulatory instability (e.g. initially 1 mg propranolol intravenously along with monitoring of ECG and blood pressure).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary Antispasmodic, ATC code: G04BD09

Trospium chloride is a quaternary derivative of nortropine and therefore belongs to the class of parasympatholytic or anticholinergic active substances, as it competes concentration-dependently with acetylcholine, the body's endogenous transmitter at postsynaptic, parasympathic binding sites.

Trospium chloride binds with high affinity to muscarinic receptors of the so called M1-, M2- and M3- subtypes and demonstrates negligible affinity to nicotinic receptors.

Consequently, the anticholinergic effect of trospium chloride exerts a relaxing action on smooth muscle tissue and organ functions mediated by muscarinic receptors. Both in preclinical as well as in clinical experiments, trospium chloride diminishes the contractile tone of smooth muscle in the gastrointestinal and genito-urinary tract.

Furthermore, it can inhibit the secretion of bronchial mucus, saliva, sweat and the ocular accommodation. No effects on the central nervous system have so far been observed.

In two specific safety studies in healthy volunteers trospium chloride has been proven not to affect cardiac repolarisation, but has been shown to have consistent and dose dependent heart rate accelerating effect.

A long term clinical trial with the immediate release formulation of trospium chloride 20mg bid found an increase of QT > 60 ms in 1.5% (3/197) of included patients. The clinical relevance of these findings has not been established. Routine safety monitoring in two other placebo-

controlled clinical trials of three months duration do not support such an influence of the immediate release formulation of trospium chloride: In the first study an increase of QTcF \geq 60 msec was seen in 4/258 (1.6%) in trospium-treated patients vs. 9/256 (3.5%) in placebo-treated patients. Corresponding figures in the second trial were 8/326 (2.5%) in trospium-treated patients vs. 8/325 (2.5%) in placebo-treated patients.

An increase in ECG heart rate of about 6 bpm was observed during two pivotal phase-III studies (IP631-018, IP631-022) in patients given the prolonged release formulation of trospium chloride (total number of patients exposed to drug substance N= 948, duration of trials = 9 months). No other significant ECG abnormality was found.

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability of a single oral dose of 20 mg of trospium chloride as immediate release formulation is $9.6 \pm 4.5\%$ (mean value \pm standard deviation).

Compared to an immediate release formulation, Regurin XL 60 mg following multiple oral dosing resulted in a further reduction of peak exposure (C_{max}) and relative overall systemic exposure (AUC) by approximately 28% and 33% respectively.

Oral administration (single and multiple dosing) of trospium chloride 60 mg prolonged release formulation as once daily dosing achieved maximum plasma levels of approximately 2 ng/ml and 1.9 ng/ml (C_{max}) respectively. Following single and multiple dosing of 20 mg of trospium chloride as immediate release formulation corresponding values revealed to be higher indicating plasma levels of 2 -4 ng/mL (C_{max}). Time to maximum concentration (T_{max}) was around 5 hrs with both preparations, whereas steady state concentration differed slightly resulting at day 8 by multiple dosing of the 60 mg prolonged release formulation.

Administration of Regurin XL 60 mg immediately after a high (50%) fat-content meal reduced the oral bioavailability of trospium chloride by 35% for AUC(0 Tlast) and by 60% for C_{max}. Other pharmacokinetic parameters such as T_{max} and t_{1/2} were unchanged in the presence of food. Coadministration with antacid, however, had no effect on the oral bioavailability of Regurin XL 60 mg.

Distribution

Protein binding ranged from 48 to 78%, depending upon the assessment method used, when a range of concentration levels of trospium chloride (0.5-100 μ g/L) were incubated in vitro with human serum.

The ratio of 3H trospium chloride in plasma to whole blood was 1.6:1. This ratio indicates that the majority of 3H trospium chloride is distributed in plasma.

Trospium chloride is highly distributed to non-CNS tissues, with an apparent volume of distribution > 600 L.

Biotransformation

Of a trospium chloride dose absorbed following oral administration, metabolites account for approximately 40% of the excreted dose. The major metabolic pathway of trospium is hypothesized as ester hydrolysis with subsequent conjugation of benzylic acid to form azoniaspironortropanol with glucuronic acid. Cytochrome P450 does not contribute significantly to the elimination of trospium. Data taken from in vitro studies of human liver microsomes, investigating the inhibitory effect of trospium on seven cytochrome P450 isoenzyme substrates (CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4), suggest a lack of inhibition at clinically relevant concentrations.

Elimination

The terminal elimination half-life was extended after multiple dosing of trospium chloride 60 mg prolonged release formulation to approximately 38.5 hours in comparison to about 20hrs after immediate release formulations. Most of the systemically available trospium chloride is excreted unchanged mainly by glomerular filtration and tubular secretion.

A small portion (10 % of the renal excretion) appears in the urine as spiroalcohol, a metabolite formed by ester hydrolysis.

Special patient groups

Pharmacokinetic data of trospium chloride in elderly patients suggest no major differences. There are also no gender differences.

Severe renal impairment may significantly alter the disposition of Regurin XL 60 mg. In a study in patients with severe renal impairment (creatinine clearance 8-32 ml/min) after administration of trospium chloride as 20 mg immediate release formulation, mean AUC was 4-fold higher, C_{max} was 2-fold higher and the mean half-life was prolonged 2-fold compared with healthy subjects.

Pharmacokinetic studies have not been done on patients with renal impairment using the prolonged-release formulation of trospium chloride.

Therefore, Regurin XL 60 mg is not recommended for patients with renal impairment (see sections 4.2 and 4.4).

After a single dose of 40mg of the immediate-release formulation of trospium chloride given to patients with mild (Child-Pugh 5-6) and moderate to severe (Child-Pugh 7-12) hepatic impairment, C_{max} was increased 12% and 63%, respectively, in comparison to healthy controls. The AUC was, however, decreased by 5% and 15%, respectively. Mean oral and mean renal clearance were 5% and 7% higher in subjects with mild and 17% and 51% higher in patients with moderate/severe hepatic impairment. Pharmacokinetic studies have not been done on patients with hepatic impairment using the prolonged-release formulation of trospium chloride.

5.3 Preclinical safety data

Preclinical data on trospium chloride reveal no special hazard to humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity, and toxicity to reproduction.

Placental transfer and passage of trospium chloride into the maternal milk occurs in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content: Sucrose
Maize starch
Methyl acrylate-methyl methacrylate-methacrylic acid-copolymer
Ammonium hydroxide
Triglycerides, medium chain
Oleic acid
Ethylcellulose
Titanium dioxide (E 171),
Hypromellose
Macrogol 400
Polysorbate 80
Triethyl citrate
Talc

Capsule Shell: Gelatin
Titanium dioxide (E 171),
Iron oxide yellow (E 172)
Iron oxide red (E 172)
Printing ink:
Shellac (20% esterified),
Iron oxide black (E 172),
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years packaged in PVC/Aclar/aluminium blister or PVC/aluminium blister

18 months packaged in PVC/PVDC/aluminium blister

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polyvinylchloride (PVC)/aluminium blister, Polyvinylchloride/
Polyvinylidenchloride (PVC/PVDC)/aluminium blister or PVC/Aclar®/
aluminium blister.

Packs of 4, 7, 10, 14, 28, 30, 56, 60, 84, 90 and 10x28 capsules.

Sample packs of 4.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

MADAUS GmbH
51101 Cologne
Germany
Tel.: 0221/8998-0
Fax: 0221 / 8998-711
e-mail: info@madaus.de

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