## 1. NAME OF THE MEDICINAL PRODUCT

# Spasmo-lyt **20 mg**, coated tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is trospium chloride. Each coated tablet contains 20 mg trospium chloride.
Excipients: includes 7mg lactose monohydrate, 39mg sucrose and 19mg wheat starch per coated tablet.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Coated tablet.
Brownish-yellow, glossy coated, biconvex tablets.

## 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 (e.g. idiopathic or neurologic detrusor overactivity).

### 4.2 Posology and method of administration

One coated tablet twice daily (equivalent to 40 mg of trospium chloride per day).
In patients with severe renal impairment (creatinine clearance between 10 and 30 mL/min/1.73 $m^2$) the recommended dosage is: One coated tablet per day or every second day (equivalent to 20 mg of trospium chloride per day or every second day).
The coated tablet should be swallowed whole with a glass of water before the meals on empty stomach.
The need for continued treatment should be reassessed at regular intervals of 3-6 months.
Since no data are available the use in children under 12 years of age is contraindicated.

### 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.

As there are no data in patients with severe hepatic impairment, treatment of these patients with trospium chloride is not recommended. In patients with mild to moderate liver impairment caution should be exercised.

Trospium chloride is mainly eliminated by renal excretion. Marked elevations in the plasma levels have been observed in patients with severe renal impairment. Therefore in this population but also in patients with mild to moderate renal impairment caution should be exercised (see section 4.2).
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.
**Spasmo-lyt** *20 mg contains lactose-monohydrate, sucrose and wheat starch.*
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Patients with rare hereditary problems of fructose intolerance or sucrase-isomaltase insufficiency should not take this medicine.
Patients with wheat allergy (different from coeliac disease) should not take this medicine. Apart from that, trospium chloride is suitable for people with coeliac disease.

## 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 drugs with anticholinergic action (such as amantadine, tricyclic antidepressants), enhancement of the tachycardic action of ß-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 drugs may be altered.

Pharmacokinetic interactions:
An inhibition of the absorption of trospium chloride with drugs like guar, colestyramine and colestipol cannot be excluded. Therefore the simultaneous administration of these drugs with trospium chloride is not recommended.
Metabolic interactions of trospium chloride have been investigated in vitro on cytochrome P450 enzymes involved in drug metabolism (P450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4). No influence on their metabolic activities was 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.
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.

## 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.
For **Spasmo-lyt** 20 mg no clinical data on exposed pregnancies are available.
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 such as dry mouth, dyspepsia and constipation mainly reflect the typical anticholinergic properties of the active ingredient.

In Phase-III clinical studies, dry mouth was very common and occurred in approximately 18% of patients treated with trospium chloride and in approximately 6% treated with placebo (total of 1931 patients of which 911 received placebo).

The following table lists possibly related drug reactions reported for patients treated with **Spasmo-lyt** 20 mg:

| | Very common (>1/10) | Common (≥1/100,<1/10) | Un-common (≥1/1000, <1/100) | Rare (≥1/10.000, <1/1000) | Very Rare (<1/10.000) | Not known (cannot be estimated from the available data) |
|---|---|---|---|---|---|---|
| Cardiac disorders | | | Tachycardia | | | Tach-yarrhythmia |
| Nervous system disorders | | | Headache | Dizziness | | Hallucination* confusion* agitation* |
| Eye disorders | | | | Vision disorders | | |
| Respiratory, thoracic and mediastinal disorders | | | | | | Dyspnoea |
| Gastrointestinal disorders | Dry mouth | Dyspepsia Constipation Abdominal pain Nausea | Flatulence Diarrhoea | | | |
| Renal and urinary disorders | | | | Micturition disorders Urinary retention | | |
| Skin and subcutaneous disorders | | | | Rash | Angio-oedema | Pruritus Urticaria Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN) |
| Muscoskeletal and connective tissue disorders | | | | Myalgia Arthralgia | | |
| General | | | Chest pain | | | Asthenia |

| | Very common (>1/10) | Common (≥1/100,<1/10) | Un-common (≥1/1000, <1/100) | Rare (≥1/10.000, <1/1000) | Very Rare (<1/10.000) | Not known (cannot be estimated from the available data) |
|---|---|---|---|---|---|---|
| disorders and administration site conditions | | | | | | |
| Immune system disorders | | | | | | Anaphylaxis |
| Investigations | | | | | | Mild to moderate increase in serum transaminase levels |

*These adverse effects occurred mostly in elderly patients and can be facilitated by neurological diseases and/or concomitant intake of other anticholinergic drugs (see section 4.5).

### 4.9 Overdose

After the administration of a maximum single dose of 360 mg trospium chloride to healthy volunteers, dryness of the mouth, tachycardia and disorders of micturition were observed to an increased extent. No manifestations of severe overdosage or intoxication in humans have been reported to date. Increased anticholinergic symptoms are to be expected as signs of intoxication.
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 nortropane and therefore belongs to the class of parasympatholytic or anticholinergic drugs, 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 $M_1$-, $M_2$- and $M_3$-subtypes and demonstrates negligible affinity to nicotinic receptors.
Consequently, the anticholinercic 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 occular 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 a consistent and dose dependant heart rate accelerating effect.

A long term clinical trial with Trospium chloride 20 mg 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 does not support such an influence of trospium chloride: In the first study an increase of QTcF >= 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.

## 5.2 Pharmacokinetic properties

After oral administration of trospium chloride maximum plasma levels are reached at 4-6 hours. Following a single dose of 20 mg the maximum plasma level is about 4 ng/mL. Within the tested interval, 20 to 60 mg as a single dose, the plasma levels are proportional to the administered dose. The absolute bioavailability of a single oral dose of 20 mg of trospium chloride (1 coated tablet **Spasmo-lyt** 20 mg) is 9.6 ± 4.5% (mean value ± standard deviation). At steady state the intraindividual variability is 16%, the interindividual variability is 36%.
Simultaneous intake of food, especially high fat diets, reduces the bioavailability of trospium chloride. After a high-fat meal mean $C_{max}$ and AUC are reduced to 15-20% of the values in the fasted state.
Trospium chloride exhibits diurnal variability in exposure with a decrease of both $C_{max}$ and AUC for evening relative to morning doses.
Most of the systemically available trospium chloride is excreted unchanged by the kidneys, though a small portion (10% of the renal excretion) appears in the urine as the spiroalcohol, a metabolite formed by ester hydrolysis. The terminal elimination half-life is in the range of 10-20 hours. No accumulation occurs. The plasma protein binding is 50-80%.
Pharmacokinetic data in elderly patients suggests no major differences. There are also no gender differences.
In a study in patients with severe renal impairment (creatinine clearance 8-32 mL/min) 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 results of a study with mildly and moderately hepatically impaired patients do not suggest a need for dose adjustment in patients with hepatic impairment, and are consistent with the limited role of hepatic metabolism in the elimination of trospium chloride.
The Blood Brain Barrier permeability of trospium chloride is virtually absent due to its chemical properties (low lipophilicity as a quaternary amine).

## 5.3 Preclinical safety data

Preclinical data 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

Tablet core:

Wheat starch
Microcrystalline cellulose
Lactose monohydrate
Povidone (K 29-32)
Croscarmellose sodium

Stearic acid
Silica colloidal anhydrous
Talc

Tablet coat:

Sucrose
Carmellose sodium
Talc
Silica colloidal anhydrous
Calcium carbonate E 170
Macrogol 8000
Titanium dioxide E 171
Iron oxide yellow E 172
Beeswax white
Carnauba wax

Note for diabetics: 1 coated tablet corresponds to 0.06 g carbohydrate (equivalent to 0.005 bread units***)***.

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

### 6.5 Nature and contents of container

PVC foiled aluminium blister
Pack sizes approved 30, 50, 100
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. MANUFACTURER

Madaus GmbH, 51101 Cologne, Germany

## 8. MARKETING AUTHORISATION NUMBER

**145 82 33117**

**9. Authorization Holder**

MegaPharm Ltd.
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**The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in April 2011**