

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trosmolyt 20mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The active ingredient is trospium chloride. Each film-coated tablet contains 20 mg trospium chloride.

For the full list of excipients, see section 6.1.

3

PHARMACEUTICAL FORM

Round, light Yellow-Brown, biconvex coated tablet

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

Posology

One film-coated tablet twice daily (equivalent to 40 mg of trospium chloride per day).

Patients with renal impairment:

In patients with severe renal impairment (creatinine clearance between 10 and 30 mL/min/1.73 m²) the recommended dosage is: One film-coated tablet per day or every second day (equivalent to 20 mg of trospium chloride per day or every second day).

Trosmolyt 20mg film-coated tablets are contraindicated in children aged under 12 years.

Method of administration

The film-coated tablet should be swallowed whole with a glass of water before meals on an empty stomach.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per coated tablet, that is to say it is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

The following potential pharmacodynamic interactions may occur:

Potential of the effect of drugs 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 gastrointestinal 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 Fertility, pregnancy and lactation

Pregnancy

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).

For Trosmolyt 20mg film-coated tablets no clinical data on exposed pregnancies are available.

Breast-feeding

In rats, placental transfer and passage into the maternal milk of trospium chloride occurs.

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).

Adverse events are listed below by system organ class and frequency.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1000$) and very rare ($< 1/10,000$).

The following table lists possibly related drug reactions reported for patients treated with Trosmolyt 20mg film-coated tablets:

	Very common	Common	Uncommon	Rare	Very Rare	Not known (cannot be estimated from the available data)
Cardiac disorders			Tachycardia			Tachyarrhythmia
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)
Musculoskeletal and connective tissue disorders				Myalgia Arthralgia		
General disorders and administration site conditions			Chest pain			Asthenia
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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il>

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.

Tropium 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 tropium 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, tropium 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 tropium chloride has been proven not to affect cardiac repolarisation, but has been shown to have a consistent and dose dependent heart rate accelerating effect.

A long term clinical trial with tropium 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 tropium chloride: In the first study an increase of QTcF >= 60 msec was seen in 4/258 (1.6%) in tropium-treated patients vs. 9/256 (3.5%) in placebo-treated patients. Corresponding figures in the second trial were 8/326 (2.5%) in tropium-treated patients vs. 8/325 (2.5%) in placebo-treated patients.

5.2 Pharmacokinetic properties

After oral administration of tropium 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 tropium chloride (1 coated tablet Tropium 20 mg) is $9.6 \pm 4.5\%$ (mean value \pm standard deviation). At steady state the intra-individual variability is 16%, the inter-individual variability is 36%.

Simultaneous intake of food, especially high fat diets, reduces the bioavailability of tropium 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

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose
Croscarmellose Sodium
Povidone K-25

Magnesium Stearate
Coating blend:
Hypromellose 2910
Titanium Dioxide
Polydextrose
Talc
Maltodextrin
Medium Chain Triglycerides
Iron Oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 25C

6.5 Nature and contents of container

PVC foiled aluminum blister.
Pack sizes approved: 30, 50, and 100 film-coated tablets. Not all
pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

CTS CHEMICAL INDUSTRIES LTD
3 HAKIDMA ST., KIRYAT-MALACHI, ISRAEL

8 MARKETING AUTHORISATION NUMBER(S)

159-44-35071-00

9 DATE OF REVISION OF THE TEXT

Revised in 03/2024 according to the MoH guidelines.

