Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Trospium Chloride 20mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each coated tablet contains 20 mg trospium chloride.

Excipient: Each tablet contains 71 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Coated Tablet.

Yellow, round 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 meals on an empty stomach.

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

Since no data are available, use in children under 12 years of age is contra-indicated.

4.3 Contraindications

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

Trospium chloride is also contra-indicated 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 gastro-intestinal 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 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.

Trospium Chloride tablets contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption 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 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 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, cholestyramine 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 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 Fertility, pregnancy and lactation

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

For Trospium Chloride 20 mg tablets no clinical data on exposed pregnancies are available.

Caution should be exercised when prescribing to pregnant or breast-feeding 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 Trospium Chloride 20 mg Film-Coated Tablets:

	Very common (>1/10)	Common (≥1/100,<1/10)	Uncommon (≥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			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)
Muscoskeletal and connective tissue disorders				Myalgia Arthralgia		
General			Chest pain			Asthenia

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).

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terace, IRL – Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: http://www.hpra.ie/, E-mail: medsafety@hpra.ie

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)
- ocal 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 G04BD15.

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 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 gastro-intestinal 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 dependent 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 do 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 versus 9/256 (3.5%) in placebo-treated patients. Corresponding figures in the second trial were 8/326 (2.5%) in trospium-treated patients versus 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 4ng/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 Trospium Chloride 20 mg tablets) is 9.6 ± 4.5% (mean value ± 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 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 8-32ml/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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Lactose monohydrate
Microcrystalline cellulose
Povidone K30
Sodium starch glycolate
Magnesium stearate

Film-Coat:
Macrogol 400
Hypromellose
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

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.

Packs of 20 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Teva B.V.,
Swensweg 5,
2031GA Haarlem,
Netherlands.

8 MARKETING AUTHORISATION NUMBER

PA1986/062/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 17th June 2011

Date of Last Renewal: 6th April 2016

10 DATE OF REVISION OF THE TEXT

July 2018