SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Trospium chloride 20mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect:

Each film-coated tablet contains 10 mg of lactose monohydrate and 18.5 mg of sucrose.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Brownish yellow to light brown round, biconvex film-coated tablets, debossed with “L” on one side and “l” on other side

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

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

In patients with severe kidney dysfunction (creatinine clearance between 10

and 30mL/min/1.73m2) the recommended dose is 1 film-coated tablet once a day or every second day (corresponding to 20mg of trospium chloride every day or every second day).

The necessity of continuing the treatment should be reassessed at regular intervals of 3-6 months.

As no corresponding data is available, the use of this product in children under the age of 12 is not recommended.

Method of administration

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

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

Trospium chloride should be used with caution in patients:

- with obstructions to the gastrointestinal tract such as pyloric stenosis,
- with urinary obstructions, with the risk of formation of residual urine,
- with autonomous neuropathy,
- with hiatus hernia,
- in whom an accelerated pulse rate is undesirable, e.g. patients with hyperthyroidism, coronary diseases and congestive heart failure,
- slight to moderate liver insufficiency,
- with renal insufficiency (trospium chloride is mainly excreted via the kidney. A considerable rise in plasma levels has been observed in patients with severe impairment to kidney function. See section 4.2).

Hepatic impairment

As no results of clinical trials are available with respect to patients with severe liver dysfunction, the treatment of these patients with trospium chloride is discouraged.

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

Trospium chloride film-coated tablets contain lactose monohydrate and sucrose.

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 sucrose-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:
- Increase in the effect of substances with anticholinergic properties (amantadine, tricyclic antidepressants, quinidine, antihistamines, disopyramide),
- Reinforcement of the tachycardic effect of ß sympathomimetics and
- Weakening of the effect of prokinetics (e.g. metoclopramide, cisapride).

As trospium chloride may influence gastro-intestinal motility and secretion, the possibility
of changes to the absorption of other medications administered simultaneously cannot be ruled out.

Pharmacokinetic interactions:

Inhibition of the absorption of trospium chloride by medications containing guar, cholestyramine and colestipol cannot be ruled out. Fr this reason the simultaneous administration of these medications with trospium chloride is not recommended.

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 effect on their metabolic activity was found. As trospium chloride is only slightly metabolised and ester hydrolysis is the only relevant metabolic route, metabolic interactions are not to be expected.

4.6 Fertility, pregnancy and lactation

For trospium chloride no clinical data on exposed pregnancies are available.

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).

Caution should be exercised when prescribing to pregnant women.

It is unknown whether trospium chloride is excreted in human breast milk.
Animal studies have shown excretion of trospium chloride in breast milk of rats.
A decision on whether to continue/ discontinue breast-feeding or to continue/ discontinue therapy with Trospium chloride film-coated tablets should be made taking into account the benefit of breast-feeding to the child and the benefit of Trospium chloride film-coated tablets to the woman.

4.7 Effects on ability to drive and use machines

Disturbance of visual accommodation is the main reason for the impaired ability to operate a motor vehicle or machinery.

However, investigations into other parameters for measuring the ability to drive a motor vehicle (visual orientation, general ability to react, reaction under stress, concentration and motor coordination) have not revealed any negative effects of trospium chloride.

4.8 Undesirable effects

During treatment with trospium chloride, anticholinergic side effects may occur such as dryness of the mouth, dyspepsia and constipation .

	Very common (≥1/10)	*Common (≥1/100 to <1/10)*	*Uncommon (≥1/1,000 to <1/100)*	*Rare (≥1/10,000 to <1/1,000)*	*Very Rare (<1/10,000) Not known (cannot be estimated from the available data)*	
Cardiac disorders				Tachycardia	Tachyarrhythmia	
Nervous system disorders					Headache Dizziness	
Eye disorders				disorders of accommodation (this applies in particular to patients who are hypermetropic and whose vision has not been adequately corrected)		
Respiratory, thoracic and mediastinal disorders					Dyspnoea	
Gastrointestinal disorders	Dry mouth	Dyspepsia, Constipation, Abdominal pain, Nausea	Flatulence, Diarrhoea			
Renal and urinary				Micturition disorders (e.g.		

disorders				formation of residual urine), Urinary retention		
Skin and subcutaneous disorders				Rash	Angio-oedema	
Muscoskeletal and connective tissue disorders					Myalgia, Arthralgia	
General disorders				Asthenia, Chest pain	anaphylaxis	
Hepatobiliary disorders						Mild to moderate increase in serum transaminase levels

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 the national reporting system Yellow Card Scheme www.mhra.gov.uk/yellowcard.

4.9 Overdose

After administration of a maximum individual dose of 360 mg trospium chloride, excessive dryness of the mouth, tachycardia and micturition problems have been observed in healthy probands. There have been no known cases of severe overdose or intoxication with trospium chloride. The expected symptoms of intoxication with trospium chloride are exacerbated anticholinergic symptoms.

In the case of intoxication the following measures should be taken:
- gastrolavage and resorption reduction (e.g. activated charcoal)
- local administration of pilocarpine in glaucoma patients
- catheterisation in patients with urinary retention
- Administration ofa parasympathomimetic agent (e.g. neostigmine) in the case of severe symptoms
- administration of beta blockers in the cases of insufficient response, pronounced tachycardia and/or circulatory instability (e.g. initially 1 mg propranolol intravenously ECG and blood pressure monitoring).

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: urological spasmolytic agent, ATC code: G04BD09.

Trospium chloride is a quaternary derivative of nortropane and therefore belongs to the class of parasympatholytics or anticholinergics. The substance competes in a concentration-dependent manner with acetylcholine, the body's own transmitter on postsynaptic parasympathic binding sites.

Trospium chloride displays a high level of affinity to muscarinic receptors of the so-called M1, M2 and M3 subtype and binds only to a negligible degree to nicotine 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 bronchial secretion of saliva and sweat, as well as the accommodation ability of the eyes.. No central effects have so far been observed.

A long term study with 20mg of trospium chloride twice a day showed an increase of QT > 60 ms in 3/197(1.5%) of the patients involved in the study. The clinical relevance of this is unclear. The routine determination of cardiac safety in two further placebo-controlled clinical studies lasting three months do not provide any indications of such an effect of trospium chloride: in the first study an increase of QTcF>=60 msec in 4/258 (1.6%) of the patients treated with trospium chloride was observed, in comparison to 9/256 (3.5%) in the placebo group. Comparable figures were also found in the second study with 8/326 (2.5%) in the patients treated with trospium chloride in comparison to 8/325 (2.5%) in the placebo group..

5.2 Pharmacokinetic properties

Absorption
After oral administration of trospium chloride, maximum blood levels values are reached at 4-6 hours.
Following a single dose of 20mg the maximum plasma level is about 4ng/ml. Within the tested interval, 20 to 60mg 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 is 9.6 ± 4.5% (mean value ± standard deviation). At steady state the intraindividual variability is 16%, the interindividual variability is 36%.

Trospium chloride exhibits diurnal variability in exposure with a decrease of both C_{max} and AUC for evening relative to morning doses.

Distribution, Metabolism and Excretion
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%.

Renal impairment
In a study conducted on patients with severe impairment to kidney function (creatinine clearance 8 - 32ml/min) the average AUC was increased fourfold and the Cmax twofold. In comparison to healthy individuals the half life was extended twofold. There are no known studies that have been conducted on patients with a lesser degree of kidney function impairment.

Hepatic impairment
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

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

Trospium chloride passes into the placenta and mother's milk in the rat.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Cellulose Microcrystalline

Lactose monohydrate

Maize starch

Povidone

Croscarmellose sodium

Silica Colloidal Anhydrous

Magnesium Stearate

Coating:

Sucrose

Copovidone

Titanium Dioxide (E171)

Macrogol 6000

Macrogol 400

Talc

Hypromellose (E464)

Iron Oxide Yellow (E172)

Iron Oxide Red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 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/PVDC-Aluminium blisters in cartons of 30, 50, 60, 100 film-coated tablets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Glenmark Pharmaceuticals Europe Limited
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Harrow, Middlesex HA3 0BU, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0108

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/02/2018

10 DATE OF REVISION OF THE TEXT

16/04/2015