Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Flotros 20mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film-coated tablet contains 20 mg of trospium chloride.

Excipients with known effect: 1 film-coated tablet contains 93.333 mg lactose-monohydrate.
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet

Round, white film-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

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

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

In patients with severe kidney dysfunction (creatinine clearance between 10 and 30 mL/min/1.73 m^2) the recommended dose is 1 film-coated tablet once a day or every second day (corresponding to 20 mg 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.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
Flotros 20 mg is contraindicated in patients with urinary retention, severe gastrointestinal dysfunctions (including toxic megacolon and severe colitis ulcerosa), myasthenia gravis, narrow-angle glaucoma and tachyarrhythmias.

4.4 Special warnings and precautions for use

Flotros 20 mg should only 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
- with reflux oesophagitis

- 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)

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.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Pharmacodynamic Interactions:

The following 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 gastrointestinal 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. For 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 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 Flotros 20 mg should be made taking into account the benefit of breast-feeding to the child and the benefit of Flotros 20 mg 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			tachy-arrythmia
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
Gastro-intestinal disorders	dry mouth	dyspepsia, constipation, abdominal pain, nausea	flatulence, diarrhoea			
Renal and urinary disorders				micturition disorders (e.g. formation of residual urine), urinary retention		
Skin and subcutaneous tissue disorders				rash	angio-oedema	pruritus, urticaria, Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN)
Musculo-skeletal and connective tissue disorders				myalgia arthralgia		
General disorders			chest pain			asthenia
Immune system disorders						anaphylaxis
Investigations						mild to moderate increase in serum transaminase

	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)
						levels
Psychiatric disorders						Hallucination, confusion, agitation*

*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 Terrace, IRL - Dublin 2;Tel: +353 1 6764971;Fax: +353 1 6762517; Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

After the administration of a maximum individual dose of 360 mg of 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. active charcoal)
- Local administration of pilocarpine in glaucoma patients
- Catheterisation in patients with urine retention
- Administration of a parasympathomimetic (e.g. neostigmine) in the case of severe symptoms
- Administration of beta-blockers in cases of insufficient response, pronounced tachycardia and/or circulatory instability (e.g. initially 1 mg of propranolol intravenously with ECG and blood pressure monitoring).

5 PHARMACOLOGICAL PROPERTIES

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 M_1, M_2 and M_3 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, the 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 20 mg of trospium chloride twice a day showed an increase of QT>60msec 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

After the oral application of trospium chloride the maximum blood level values are reached after 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 is 9.6 ± 4.5% (mean value ± standard deviation). At steady state the intraindividual variability is 16%, the interindividual variability is 36%.
The bioavailability of trospium chloride is reduced by the simultaneous intake of food, particularly food with a high fat content. After a meal that is rich in fat the mean C_{max} and AUC value falls to 15 - 20 % of the values in a fasting 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. Plasma protein binding is 50 - 80 %.

Pharmacokinetic data do not indicate any significant differences in elderly patients or any differences between the sexes.

In a study conducted on patients with severe impairment to kidney function (creatinine clearance 8 -32 ml/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.

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 hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Silica, colloidal anhydrous
Cellulose, microcrystalline
Lactose monohydrate
Povidone K 25
Sodium starch glycolate (type A)
Magnesium stearate

Tablet film:
Hypromellose
Cellulose, microcrystalline
Stearic acid (Ph. Eur.)
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 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/PVDC/Aluminium blisters or PVC/Aluminium blisters.
Original packs of 10, 20, 30, 50, 60 and 100 film-coated tablets.
Hospital packs of 500 (10 x 50) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pfleger Arzneimittel GmbH
Dr Robert Pfleger Straße 12
Germany

8 MARKETING AUTHORISATION NUMBER

PA22747/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 1 May 2009

Date of last renewal: 10 October 2013

10 DATE OF REVISION OF THE TEXT

May 2019