SUMMARY OF PRODUCT CHARACTERISTICS

ROLITEN TABLETS 2 MG
(Tolterodine Tartrate Tablets)

1. Name of the medicinal product
ROLITEN TABLETS 2 MG

2. Qualitative and quantitative composition

ROLITEN TABLETS 2 MG
Each film-coated tablet contains:
Tolterodine Tartrate …….2 mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

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 syndrome.

4.2 Posology and method of administration

ROLITEN TABLETS 2 MG may not be suitable for all dosages and therefore, other suitable available strengths and/or dosage forms of tolterodine should be used in such cases.

Adults (including elderly)
The recommended dose is 2 mg twice daily.

Impaired liver function or severely impaired renal function
In patients with impaired liver function or severely impaired renal function (GFR$\leq$30 ml/min) the recommended dose is 1 mg twice daily (see section **4.4**).

Troublesome side effects
In case of troublesome side effects the dose may be reduced from 2 mg to 1 mg twice daily.

The effect of treatment should be re-evaluated after 2-3 months.

Paediatric patients
Efficacy of tolterodine has not been reported in children. Therefore, tolterodine is not recommended for children.

Method of administration
For oral use, should be swallowed whole

Roliten can be taken with or without food

4.3 Contraindications

Tolterodine is contraindicated in patients with

- Urinary retention
- Uncontrolled narrow angle glaucoma
- Myasthenia gravis
- Known hypersensitivity to tolterodine or excipients
- Severe ulcerative colitis
- Toxic megacolon

4.4 Special warnings and precautions for use

Tolterodine shall be used with caution in patients with
- Significant bladder outlet obstruction at risk of urinary retention
- Gastrointestinal obstructive disorders, e.g. pyloric stenosis
- Renal impairement (see section **4.2**)
- Hepatic disease. (see sections **4.2** and **5.2**)
- Autonomic neuropathy
- Hiatus hernia
- Risk for decreased gastrointestinal motility

Multiple oral total daily doses of immediate release 4 mg (therapeutic) and 8 mg (supratherapeutic) tolterodine have been reported to prolong the QTc interval. The clinical relevance of these findings is unclear and will depend on individual patient risk factors and susceptibilities present.

Tolterodine should be used with caution in patients with risk factors for QT-prolongation including:
- Congenital or documented acquired QT prolongation
- Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia
- Bradycardia

- Relevant pre-existing cardiac diseases (i.e. cardiomyopathy, myocardial ischaemia, arrhythmia, congestive heart failure)
- Concomitant administration of drugs known to prolong QT-interval including Class IA (e. g. quinidine, procainamide) and Class III (e. g. amiodarone, sotalol) anti-arrhythmics

This especially holds true when taking potent CYP3A4 inhibitors.

Concomitant treatment with potent CYP3A4 inhibitors should be avoided (see section **4.5**).
As with all treatments for symptoms of urgency and urge incontinence, organic reasons for urge and frequency should be considered before treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (e.g. erythromycin and clarithromycin), antifungal agents (e.g. ketoconazole and itraconazole) and antiproteases is not recommended due to increased serum concentrations of tolterodine in poor CYP2D6 metabolisers with (subsequent) risk of overdosage (see section **4.4**).

Concomitant medication with other drugs that possess antimuscarinic properties may result in more pronounced therapeutic effect and side-effects. Conversely, the therapeutic effect of tolterodine may be reduced by concomitant administration of muscarinic cholinergic receptor agonists.

The effect of prokinetics like metoclopramide and cisapride may be decreased by tolterodine.

Concomitant treatment with fluoxetine (a potent CYP2D6 inhibitor) has been reported to result in no clinically significant interaction since tolterodine and its CYP2D6-dependent metabolite, 5-hydroxymethyl tolterodine are equipotent.

No interactions with warfarin or combined oral contraceptives (ethinyl estradiol/levonorgestrel) has been reported.

Tolterodine has not been reported to be a metabolic inhibitor of CYP2D6, 2C19, 2C9, 3A4 or 1A2. Therefore an increase of plasma levels of drugs metabolised by these isoenzymes is not expected when dosed in combination with tolterodine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate reported data from the use of tolterodine in pregnant women.

Reported studies in animals have shown reproductive toxicity (see section **5.3**). The potential risk for humans is unknown.

Consequently, tolterodine is not recommended during pregnancy.

Breast-feeding
No data concerning the excretion of tolterodine into human milk have been reported. Tolterodine should be avoided during lactation.

4.7 Effects on ability to drive and use machines

Since this drug may cause accommodation disturbances and influence reaction time, the ability to drive and use machines may be negatively affected.

4.8 Undesirable effects

Due to the pharmacological effect of tolterodine it may cause mild to moderate antimuscarinic effects, like dryness of the mouth, dyspepsia and dry eyes.

The table below reflects the data reported with tolterodine. The most commonly reported adverse reaction was dry mouth, which occurred in 35% of patients treated with tolterodine tablets and in 10% of placebo treated patients. Headaches were also reported very commonly and occurred in 10.1% of patients treated with tolterodine tablets and in 7.4% of placebo treated patients.

Table: Adverse events associated with Tolterodine Tartrate reported in clinical trials and post marketing experience

	Very Common (≥1/10)	**Common** (≥1/100 and <1/10)	**Uncommon** (≥1/1000 and<1/100)	**Not known** (cannot be estimated from the available data)
Infections and infestations		Bronchitis		
Immune system disorders			Hypersensitivity not otherwise specified	Anaphylactoid reactions
Psychiatric disorders			Nervousness	Confusion, hallucinations, disorientation
Nervous system disorders	Headaches	Dizziness, somnolence, paresthesia	Memory impairment	
Eye disorders		Dry eyes, abnormal vision including abnormal accommodation		

	Very Common (≥1/10)	**Common** (≥1/100 and <1/10)	**Uncommon** (≥1/1000 and<1/100)	**Not known** (cannot be estimated from the available data)
Ear and labyrinth disorders		Vertigo		
Cardiac disorders		Palpitations	Tachycardia, cardiac failure, arrhythmia	
Vascular disorders				Flushing
Gastrointestinal disorders	Dry mouth	Dyspepsia, constipation, abdominal pain, flatulence, vomiting, diarrhoea	Gastroesophageal reflux	
Skin and subcutaneous tissue disorders		Dry skin		Angioedema
Renal and urinary disorders		Dysuria, urinary retention		
General disorders and administration site conditions		Fatigue, chest pain, peripheral oedema		
Investigations		Increased weight		

Cases of aggravation of symptoms of dementia (e.g. confusion, disorientation, delusion) have been reported after tolterodine therapy was initiated in patients taking cholinesterase inhibitors for the treatment of dementia.

Paediatric patients
Diarrhoea and abnormal behaviour have been reported higher in paediatric patients with urinary tract infections treated with tolterodine than placebo.

4.9 Overdose

The highest dose reported to be given to human volunteers of tolterodine L-tartrate is 12.8 mg as a single dose. The most severe adverse events that has been reported are accommodation disturbances and micturition difficulties.
In the event of tolterodine overdose, treat with gastric lavage and give activated charcoal. Treat symptoms as follows:

- Severe central anticholinergic effects (e.g. hallucinations, severe excitation): treat with physostigmine
- Convulsions or pronounced excitation: treat with benzodiazepines
- Respiratory insufficiency: treat with artificial respiration

- Tachycardia: treat with beta-blockers
- Urinary retention: treat with catheterization
- Mydriasis: treat with pilocarpine eye drops and/or place patient in dark room

An increase in QT interval has also been reported at a total daily dose of 8 mg immediate release tolterodine (twice the recommended daily dose of the immediate release formulation and equivalent to three times the peak exposure of the prolonged release capsule formulation) administered over four days. In the event of tolterodine overdose, standard supportive measures for managing QT prolongation should be adopted.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Urinary antispasmodics

ATC code: G04B D07

Tolterodine is a competitive, specific muscarinic receptor antagonist with a selectivity for the urinary bladder over salivary glands *in vivo*. One of the tolterodine metabolites (5-hydroxymethyl derivative) exhibits a pharmacological profile similar to that of the parent compound. In extensive metabolisers this metabolite contributes significantly to the therapeutic effect (see section **5.2**).

Effect of the treatment can be expected within 4 weeks.

5.2 Pharmacokinetic properties

Pharmacokinetic characteristics specific for this formulation: Tolterodine has been reported to be rapidly absorbed. Both tolterodine and the 5-hydroxymethyl metabolite has been reported to reach maximal serum concentrations 1-3 hours after dose. The half-life for tolterodine given as the tablet has been reported to be 2-3 hours in extensive and about 10 hours in poor metabolisers (devoid of CYP2D6). Steady state concentrations has been reported to reach within 2 days after administration of the tablets.

Food has been reported to not influence the exposure to the unbound tolterodine and the active 5-hydroxymethyl metabolite in extensive metabolisers, although the tolterodine levels increase when taken with food. Clinically relevant changes are likewise not expected in poor metabolisers.

Absorption: After oral administration tolterodine is subject to CYP2D6 catalysed first-pass metabolism in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically equipotent metabolite. The absolute bioavailability of tolterodine has been

reported to be 17% in extensive metabolisers, the majority of the patients, and 65% in poor metabolisers (devoid of CYP2D6).

Distribution: Tolterodine and the 5-hydroxymethyl metabolite has been reported to bind primarily to orosomucoid. The unbound fractions are 3.7% and 36%, respectively. The volume of distribution of tolterodine has been reported to be 113 litres.

Elimination: Tolterodine has been reported to be extensively metabolised by the liver following oral dosing. The primary metabolic route is mediated by the polymorphic enzyme CYP2D6 and leads to the formation of the 5-hydroxymethyl metabolite. Further metabolism leads to formation of the 5-carboxylic acid and N-dealkylated 5-carboxylic acid metabolites, which account for 51 % and 29 % of the metabolites recovered in the urine, respectively. A subset (about 7%) of the population has been reported to be devoid of CYP2D6 activity. The identified pathway of metabolism for these individuals (poor metabolisers) is dealkylation via CYP3A4 to N-dealkylated tolterodine, which does not contribute to the clinical effect. The remainder of the population is referred to as extensive metabolisers. The systemic clearance of tolterodine in extensive metabolisers has been reported to be about 30 L/h. In poor metabolisers the reduced clearance has been reported to lead to significantly higher serum concentrations of tolterodine (about 7-fold) and negligible concentrations of the 5-hydroxymethyl metabolite has been reported.

The 5-hydroxymethyl metabolite is pharmacologically active and equipotent with tolterodine. Because of the differences in the protein-binding characteristics of tolterodine and the 5-hydroxymethyl metabolite, the exposure (AUC) of unbound tolterodine in poor metabolisers is similar to the combined exposure of unbound tolterodine and the 5-hydroxymethyl metabolite in patients with CYP2D6 activity given the same dosage regimen. The safety, tolerability and clinical response has been reported to be similar irrespective of phenotype.

The excretion of radioactivity after administration of [^{14}C]-tolterodine has been reported to be about 77% in urine and 17% in faeces. Less than 1% of the dose is recovered as unchanged drug, and about 4% as the 5-hydroxymethyl metabolite. The carboxylated metabolite and the corresponding dealkylated metabolite has been reported to account for about 51% and 29% of the urinary recovery, respectively.

The pharmacokinetics has been reported to be linear in the therapeutic dosage range.

Specific patient groups

Impaired liver function: About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite has been reported to be found in subjects with liver cirrhosis (see sections **4.2** and **4.4**).

Impaired renal function: The mean exposure of unbound tolterodine and its 5-hydroxymethyl metabolite has been reported to be doubled in patients with severe renal impairment (inulin clearance GFR ≤ 30 ml/min). The plasma levels of other metabolites has been reported to markedly (up to 12-fold) increased in these patients. The clinical relevance of the increased exposure of these metabolites is unknown. There is no reported data in mild to moderate renal impairment (see sections **4.2** and **4.4**).

Paediatric patients
The exposure of the active moiety per mg dose has been reported to be similar in adults and adolescents. The mean exposure of the active moiety per mg dose has been reported to be approximately two-fold higher in children between 5-10 years than in adults (see sections **4.2** and **4.4**).

5.3 Preclinical safety data

In reported toxicity, genotoxicity, carcinogenicity and safety pharmacology studies no clinically relevant effects have been reported, except those related to the pharmacological effect of the drug.

Reproduction studies have been reported in mice and rabbits.

In mice, no effect of tolterodine on fertility or reproductive function has been reported. Tolterodine has been reported to produce embryo death and malformations at plasma exposures (C_{max} or AUC) 20 or 7 times higher than those seen in treated humans.

In rabbits, no malformative effect has been reported, but the studies were reported to be conducted at 20 or 3 times higher plasma exposure (C_{max} or AUC) than those expected in treated humans.

Tolterodine, as well as its active human metabolites has been reported to prolong action potential duration (90% repolarisation) in canine purkinje fibres (14 - 75 times therapeutic levels) and block the K+-current in cloned human ether-a-go-go-related gene (hERG) channels (0.5 – 26.1 times therapeutic levels). In dogs prolongation of the QT interval has been reported after application of tolterodine and its human metabolites (3.1 – 61.0 times therapeutic levels). The clinical relevance of these findings is unknown.

6. Pharmaceutical particulars

6.1 List of excipients
Microcrystalline cellulose, dibasic calcium phosphate dehydrate, sodium starch glycollate, colloidal anhydrous silica, magnesium stearate, opadry OY-S-58910 white, purified water

6.2 Incompatibilities

6.3 Shelf life

6.4 Special precautions for storage

6.5 Nature and contents of container

6.6 Special precautions for disposal and other handling

7. Marketing authorisation holder

8. Marketing authorisation number(s)
A4-1498

9. Date of first authorisation/renewal of the authorisation
Date of first authorisation 29-02-2008

10. Date of revision of the text
August 2020

REFERENCE
Summary of Product Characteristics of Detrusitol 2 mg film-coated tablets, Upjohn UK Limited, UK, July 2020

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