Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Detrusitol SR 2mg Prolonged Release Capsules.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 2mg tolterodine tartrate corresponding to 1.37mg tolterodine.

Each 2mg prolonged release capsule contains a minimum of 61.52mg of Sucrose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Prolonged release capsule, hard

Blue green, two-piece prolonged release capsules with “2” printed on one half and a symbol on the other half.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Detrusitol SR is indicated for the treatment of urge incontinence and/or increased urinary frequency associated with urgency as may occur in patients with unstable bladder.

4.2 Posology and method of administration

Adults (including the elderly):

The recommended dose is 4 mg once daily except in patients with impaired liver function or severely impaired renal function (GFR $\leq$ 30 ml/min) for whom the recommended dose is 2 mg once daily *(see sections 4.4 and 5.2).* In case of troublesomeside-effects the dose may be reduced from 4 mg to 2 mg once daily.

The prolonged-release capsules can be taken with or without food and must be swallowed whole.
The effect of treatment should be re-evaluated after 2-3 months *(see section 5.1).*

Children:

Safety and effectiveness in children have not yet been established. Therefore Detrusitol SR prolonged-release capsules are not recommended for children, until more information is available.

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 impairment *(see sections 4.2 and 5.2)*
- Hepatic disease *(see sections 4.2 and 5.2)*
- Autonomic neuropathy
- Hiatus hernia
- Risk of decreased gastrointestinal motility

Caution should be used in patients with known risk factors for QT-prolongation (i.e. hypokalaemia, bradycardia and concurrent administration of drugs known to prolong QT interval) and relevant pre-existing cardiac diseases (i.e. myocardial ischaemia, arrhythmia, congestive heart failure). *(See section 5.3).*

As with all treatments for unstable bladder, organic reasons for urge and frequency should be considered before treatment.

The combination of tolterodine with strong inhibitors of CYP3A4 is not recommended *(see Section 4.5. Interactions).*

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine**.**

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (erythromycin and clarithromycin), antifungal agents (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) does not result in a clinically significant interaction since tolterodine and its CYP2D6-dependent metabolite, 5-hydroxymethyl tolterodine are equipotent.

Drug interaction studies have shown no interactions with warfarin or combined oral contraceptives (ethinyl estradiol/levonorgestrel).
A clinical study has indicated that tolterodine is not a metabolic inhibitor of CYP2D6, 2C19, 3A4 or 1A2. Therefore an increase of plasma levels of drugs metabolised by the isoenzyme systems is unexpected when dosed in combination with tolterodine.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of tolterodine in pregnant women.
Studies in animals have shown reproductive toxicity *(see section 5.3).* Thepotential risk for humans is unknown. Consequently, Detrusitol SR is not recommended during pregnancy.

Lactation
No data concerning the excretion of tolterodine into human milk are available. 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 reflectsthe data obtained with Detrusitol in clinical trials and from post marketing experience. The most commonly reported adverse reaction was dry mouth, which occurred in 23.4 % of patients treated with Detrusitol SR and in 7.7 % of placebo-treated patients.

	Common (>1/100,<1/10)	Uncommon (>1/1000,<1/100)	Rare (>1/10,000,<1/1000)
Eye disorders	Dry eyes, abnormal vision (including abnormal accommodation)		
General disorders and administration site conditions	Fatigue, headache, chest pain	Oedema, Peripheral oedema	
Gastrointestinal disorders	Dyspepsia, constipation, abdominal pain, flatulence, vomiting		
Immune system disorders		Hypersensitivity not otherwise specified	
Nervous system disorders	Dizziness, somnolence, paresthesia		
Psychiatric disorders	Nervousness	Confusion	Hallucinations
Renal and urinary disorders		Urinary retention	
Cardiac disorders			Tachycardia
Skin and subcutaneous tissue disorders	Dry skin		

Other adverse effects reported with the use of tolterodine are anaphylactoid reaction including angiodema (very rare) and cardiac failure (very rare). Palpitations and arrhythmia (rare) are known adverse effects for this drug class.

4.9 Overdose

The highest dose given to human volunteers of tolterodine tartrate is 12.8 mg as single dose of the immediate release formulation. The most severe adverse events observed were 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 catheterisation
- Mydriasis: treat with pilocarpine eye drops and/or place patient in dark room

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 5.2).*
Effect of the treatment can be expected within 4 weeks.

In the Phase III program, the primary endpoint was reduction of incontinence episodes per week and the secondary endpoints were reduction of micturitions per 24 hours and increase of mean volume voided per micturition. These parameters are presented in the following table.

Effect of treatment with Detrusitol SR 4 mg once daily after 12 weeks, compared with placebo. Absolute change and percentage change relative to baseline. Treatment difference Detrusitol vs. placebo: Least Squares estimated mean change and 95% confidence interval.

	Detrusitol SR 4 mg once daily (n=507)	**Placebo (n=508)**	**Treatment difference vs. placebo: Mean change and 95% CI**	**Statistical significance vs. placebo (p-value)**
Number of incontinence episodes per week	-11.8 (-54%)	-6.9 (-28%)	-4.8 (-7.2; -2.5)*	<0.001
Number of micturitions per 24 hours	-1.8 (-13%)	-1.2 (-8%)	-0.6 (-1.0; -0.2)	0.005
Mean volume voided per micturition (ml)	+34 (+27%)	+14 (+12%)	+20 (14; 26)	<0.001

(*) 97.5% confidence interval according to Bonferroni

After 12 weeks of treatment 23.8% (121/507) in the Detrusitol SR group and 15.7% (80/508) in the placebo group reported that they subjectively had no or minimal bladder problems.

The effect of tolterodine was evaluated in patients, examined with urodynamic assessment at baseline and, depending on the urodynamic result, they were allocated to a urodynamic positive (motor urgency) or a urodynamic negative (sensory urgency) group. Within each group, the patients were randomised to receive either tolterodine or placebo. The study could not provide convincing evidence that tolterodine had effects over placebo in patients with sensory urgency.

Clinical effects of tolterodine on QT interval were investigated in a variety of clinical studies. The clinical trial information is based on ECGs that were obtained from over 600 treated patients, and which included the elderly and patients with pre-exisiting cardiovascular disease. The changes in QT intervals did not significantly differ between placebo and treatment groups. Overall, there does not appear to be a significant change in QT interval.

5.2 Pharmacokinetic properties

Pharmacokinetic characteristics specific for this formulation:
Tolterodine prolonged-release capsules give a slower absorption of tolterodine than the immediate-release tablets do. As a result, the maximum serum concentrations are observed 4 (2-6) hours after administration of the capsules. The apparent half-life for tolterodine given as the capsule is about 6 hours in extensive and about 10 hours in poor metabolisers (devoid of CYP2D6). Steady state concentrations are reached within 4 days after administration of the capsules.
There is no effect of food on the bioavailability of the capsules.

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

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

Elimination:
Tolterodine is 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 is 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 is about 30 L/h. In poor metabolisers the reduced clearance leads to significantly higher serum concentrations of tolterodine (about 7-fold) and negligible concentrations of the 5-hydroxymethyl metabolite are observed.

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 are similar irrespective of phenotype.

The excretion of radioactivity after administration of [^{14}C]-tolterodine is 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 account for about 51% and 29% of the urinary recovery, respectively.
The pharmacokinetics is 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 is found in subjects with liver cirrhosis *(see section 4.2 and 4.4).* Impaired renal function: The mean exposure of unbound tolterodine and its 5-hydroxymethyl metabolite is doubled in patients with severe renal impairment (inulin clearance GFR $\geq$ 30 ml/min). The plasma levels of other metabolites were markedly (up to 12-fold) increased in these patients. The clinical relevance of the increased exposure of these metabolites is unknown. There is no data in mild to moderate renal impairment *(see section 4.2 and 4.4).*

5.3 Preclinical safety data

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

Reproduction studies have been performed in mice and rabbits.
In mice, there was no effect of tolterodine on fertility or reproductive function. Tolterodine produced embryo death and malformations at plasma exposures (C_{max} or AUC) 20 or 7 times higher than those seen in treated humans.

Tolterodine, as well as its active human metabolites prolong action potential duration (90% repolarisation) in canine purkinje fibres (14-75 times therapeutic levels) and block the K+ -current in cloned human either-a-go-go related gene (hERG) channels (0,5 – 26,1 times therapeutic levels). In dogs prolongation of the QT interval has been observed after application of tolterodine and its human metabolites (3, 1-61,0 times therapeutic levels). The clinical relevance of these findings is unknown. In clinical trials, overall there does not appear to be a significant changes in QT interval.

In rabbits no malformative effect was seen, but the studies were conducted at 20 or 30 times higher plasma exposure (Cmax or AUC) then those expected in treated humans.

In dogs a slight prolongation of the QT interval has been observed at high concentrations of tolterodine or its main metabolite (50-100 times therapeutic levels). In clinical trials, no QT interval prolongation has been found in a large and representative patient sample on recommended doses of tolterodine tablets.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Maize starch
Ethylcellulose
Medium chain triglycerides
Oleic acid
Hypromellose
Gelatin
Shellac glaze
Titanium dioxide (E171)
Indigo carmine (E132)
Propylene glycol
Simeticone
Yellow iron oxide (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf-life expiry date of this product is the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

Do not store above 30°C.
Store in original package.

6.5 Nature and contents of container

Blister pack of 28 capsules contained in an outer cardboard carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co. Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA 0465/080/004

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