Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Tolterodine Tartrate 2 mg Film-coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains tolterodine tartrate 2 mg corresponding to 1.37 mg tolterodine.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet

White to off white, round, approximately 6.35 mm in diameter, biconvex, film-coated tablet, debossed S042 on one side and plain 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 syndrome.

4.2 Posology and method of administration

Posology

Adults (including elderly):

The recommended dose is 2 mg twice daily except in patients with impaired liver function or severely impaired renal function (GFR≤30 ml/min) for whom the recommended dose is 1 mg twice daily (see section 4.4). 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 (see section 5.1).

Paediatric population:
Efficacy of Tolterodine Tartrate tablets has not been demonstrated in children (See section 5.1). Therefore, Tolterodine Tartrate tablets is not recommended for children.

4.3 Contraindications

Tolterodine is contraindicated in patients with

- Urinary retention
- Uncontrolled narrow angle glaucoma
- Myasthenia gravis
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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 section 4.2)
- Hepatic disease (see section 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 shown to prolong the QTc interval (see section 5.1).

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 medicinal products known to prolong QT-interval including Class IA (e.g. quinidine, procainamide) and Class III (e.g. amiodarone, sotalol) antiarrhythmics.

This especially holds true when taking potent CYP3A4 inhibitors (see section 5.1). Concomitant treatment with potent CYP3A4 inhibitors should be avoided (see section 4.5).

Urinary retention
As with all treatments for symptoms of urgency and urge incontinence, organic reasons for urge and frequency should be considered before treatment.

Excipient information
This medicine contains less than 1 mmol sodium (23 mg) per tablet. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant systemic medication with potent CYP3A4 inhibitors such as macrolide antibiotics (e.g. erythromycin and claritromycin), 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 medicinal products that possess antimuscarinic properties may result in more pronounced therapeutic effect and side effects of tolterodine. 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, 2C9, 3A4 or 1A2. Therefore an increase of plasma levels of medicinal products metabolised by these isoenzymes is not expected 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). The potential risk for humans is unknown. Consequently, Tolterodine tartrate film-coated tablets are not recommended during pregnancy.

Breast-feeding:

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 medicinal product may cause accommodation disturbances and influence reaction time, the ability to drive and use machines may be negatively affected.

4.8 Undesirable effects

Summary of the safety profile
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 obtained with tolterodine in clinical trials and from postmarketing experience. The most commonly reported adverse reaction was dry mouth, which occurred in 35% of patients treated with tolterodine tartrate tablets and in 10% of placebo treated patients. Headaches were also reported very commonly and occurred in 10.1% of patients treated with tolterodine tartrate tablets and in 7.4% of placebo treated patients.

Tabulated list of adverse reactions
The adverse drug reactions listed in the table below are presented by System Organ Class (SOC) and frequency categories, defined using the following convention: 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), or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Adverse drug reactions

System organ class	**Very Common (≥1/10)**	**Common (1/100 to <1/10)**	**Uncommon (1/1000 to <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		
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 population

In two paediatric phase III randomised, placebo-controlled, double-blind studies conducted over 12 weeks where a total of 710 paediatric patients were recruited, the proportion of patients with urinary tract infections, diarrhoea and abnormal behaviour was higher in patients treated with tolterodine than placebo (urinary tract infection: tolterodine 6.8 %, placebo 3.6 %; diarrhoea: tolterodine 3.3 %, placebo 0.9 %; abnormal behaviour: tolterodine 1.6 %, placebo 0.4 %). (See section 5.1)

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
Website: www.hpra.ie

4.9 Overdose

The highest dose given to human volunteers of tolterodine L-tartrate is 12.8 mg as a single dose. The most severe adverse events observed were accomodation 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 was observed 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

Mechanism of action
Tolterodine is a competitive, specific muscarinic receptor antagonist with selectivity for the urinary bladder over salivary glands in vivo.

Pharmacodynamic effects
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).

Clinical efficacy and safety
Effect of the treatment can be expected within 4 weeks.

Effect of treatment with tolterodine 2 mg twice daily after 4 and 12 weeks, respectively, compared with placebo (pooled data). Absolute change and percentage change relative to baseline.

Variable	**4-week studies**			**12-week studies**		
	Tolterodine 2 mg b.i.d.	Placebo	Statistical significance vs. placebo	Tolterodine 2 mg b.i.d.	Placebo	Statistical significance vs. placebo
Number of micturitions per 24 hours	-1.6 (-14%) n=392	-0.9 (-8%) n=189	*	-2.3 (-20%) n=354	-1.4 (-12%) n=176	**
Number of incontinence episodes per 24 hours	-1.3 (-38%) n=288	-1.0 (-26%) n=151	n.s.	-1.6 (-47%) n=299	-1.1 (-32%) n=145	*
Mean volume voided per micturition (ml)	+25 (+17%) n=385	+12 (+8%) n=185	***	+35 (+22%) n=354	+10 (+6%) n=176	***
Number of patients with no or minimal bladder problems after treatment (%)	16% n=394	7% n=190	**	19% n=356	15% n=177	n.s.

n.s.=not significant; *=p≤0.05; **= p≤0.01; ***= p≤0.001

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 urodynamics 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.

The clinical effects of tolterodine on QT interval were studied in ECGs obtained from over 600 treated patients, including the elderly and patients with pre-existing cardiovascular disease. The changes in QT intervals did not significantly differ between placebo and treatment groups.

The effect of tolterodine on QT-prolongation was investigated further in 48 healthy male and female volunteers aged 18-55 years. Subjects were administered 2 mg BID and 4 mg BID tolterodine as the immediate release formulations. The results (Fridericia corrected) at peak tolterodine concentration (1 hour) showed mean QTc interval increases of 5.0 and 11.8 msec for tolterodine doses of 2 mg BID and 4 mg BID respectively and 19.3 msec for moxifloxacin (400 mg) which was used as an active, internal control. A pharmacokinetic/pharmacodynamic model estimated that QTc interval increases in poor metabolisers (devoid of CYP2D6) treated with tolterodine 2 mg BID are comparable to those observed in extensive metabolisers receiving 4 mg BID. At both doses of tolterodine, no subject, irrespective of their metabolic profile, exceeded 500 msec for absolute QTcF or 60 msec for change from baseline that are considered thresholds of particular concern. The 4 mg BID dose corresponds to a peak exposure (C_{max}) of three times that obtained with the highest therapeutic dose of tolterodine SR capsules.

Paediatric patients

Efficacy in the paediatric population has not been demonstrated. Two paediatric phase 3 randomised, placebo-controlled, double blind 12 week studies were conducted using tolterodine extended release capsules. A total of 710 paediatric patients (486 on tolterodine and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied. No significant difference between the two groups was observed in either study with regard to change from baseline in total number of incontinence episodes/week. (See section 4.8)

5.2 Pharmacokinetic properties

Pharmacokinetic characteristics specific for this formulation:

Tolterodine is rapidly absorbed. Both tolterodine and the 5 - hydroxymethyl metabolite reach maximal serum concentrations 1-3 hours after dose. The half-life for tolterodine given as the tablet is 2-3 hours in extensive and about 10 hours in poor metabolisers (devoid of CYP2D6). Steady state concentrations are reached within 2 days after administration of the tablets. Food does 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 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 medicinal product, 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.

Hepatic impairment

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 ≤ 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).

Paediatric population:

The exposure of the active moiety per mg dose is similar in adults and adolescents. The mean exposure of the active moiety per mg dose is approximately two-fold higher in children between 5-10 years than in adults (See sections 4.2 and 5.1).

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 medicinal product.

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 (Cmax or AUC) 20 or 7 times higher than those seen in treated humans.

In rabbits, no malformative effect was seen, but the studies were conducted at 20 or 3 times higher plasma exposure (Cmax or AUC) than those expected 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 ether-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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Cellulose, microcrystalline pH 102
Sodium starch glycolate (Type A)
Magnesium stearate
Colloidal anhydrous silica

Film coating:

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 8000
Talc (E553b)

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

2 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– Alu blister

Pack sizes:

Blister packs containing;

14 film-coated tablets (1 strip of 14)
28 film-coated tablets (2 strips of 14)
56 film-coated tablets (4 strips of 14)
20 film-coated tablets (2 strips of 10)
50 film-coated tablets (5 strips of 10)
100 film-coated tablets (10 strips of 10)
30 film-coated tablets (3 strips of 10 or 2 strips of 15)
60 film-coated tablets (6 strips of 10 or 4 strips of 15)
90 film-coated tablets (9 strips of 10 or 6 strips of 15)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
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Euro Business Park
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Cork T45 K857
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8 MARKETING AUTHORISATION NUMBER

PA2315/041/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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