# TOLTERODINE TARTRATE 1 MG AND 2 MG FILM-COATED TABLETS
PL 30306/0411-12

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Actavis Group PTC ehf, Marketing Authorisations for the medicinal products Tolerodine Tartrate 1 mg and 2 mg Film-Coated Tablets (PL 30306/0411-12) on 27 June 2012. These medicines are only available on prescription from your doctor.

Tolterodine Film-Coated Tablets contain the active ingredient tolterodine. This belongs to a class of medicinal products called antimuscarinics.

Tolterodine is used for the treatment of the symptoms of overactive bladder syndrome. If you have overactive bladder syndrome, you may find that you are unable to control urination or that you need to rush to the toilet with no advanced warning and/or go to the toilet frequently.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Tolerodine tartrate 1 mg and 2 mg Film-Coated Tablets (PL 30306/0411-12) outweigh the risks; hence Marketing Authorisations have been granted.
TOLTERODINE TARTRATE 1 MG AND 2 MG FILM-COATED TABLETS
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Actavis Group PTC ehf, Marketing Authorisations for the medicinal products, Tolerodine Tartrate 1 mg and 2 mg Film-Coated Tablets (PL 30306/0411-12), on 27 June 2012. These products are prescription only medicines (POM).

These are simple, abridged, ‘informed consent’ applications made under Article 10c of EC Directive 2001/83 (as amended). These applications cross-refer to the Marketing Authorisations for Tolerodine 1 mg and 2 mg Film-Coated Tablets (PL 24668/0179-0180) authorised to Caduceus Pharma Limited) on 24 February 2011 in the UK.

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

The MHRA consider that the pharmacovigilance system described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan. As the applications are for products that are identical to already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, routine pharmacovigilance activities are proposed and a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

No new data were submitted nor was it necessary for these simple applications, as the data are identical to that of the previously granted cross-reference products. A Public Assessment Report is available for the cross reference products Tolerodine 1 mg and 2 mg Film-Coated Tablets (PL 24668/0179-0180) authorised to Caduceus Pharma Limited) on 24 February 2011.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 30306/0411-12
PROPRIETARY NAME: Tolterodine Tartrate 1 mg and 2 mg Film-Coated Tablets
ACTIVE: Tolterodine Tartrate
COMPANY NAME: Actavis Group PTC
E.C. ARTICLE: Article 10c of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION
These are simple, informed consent applications for Tolterodine Tartrate 1 mg and 2 mg Film-Coated Tablets submitted under Article 10c of Directive 2001/83/EC. The proposed Marketing Authorisation Holder is Actavis Group PTC ehf., Reykjavíkurvegi 76-78, 220 Hafnarfjörður, Iceland.

The applications cross-refer to Tolterodine 1 mg and 2 mg Film-Coated Tablets (PL 24668/0179-0180) authorised to Caduceus Pharma Limited since 24 February 2011. The current applications are considered valid.

2. MARKETING AUTHORISATION APPLICATION FORM
2.1 Name
The proposed names of the products are Tolterodine Tartrate 1 mg and 2 mg Film-Coated Tablets. The products have been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
Each 1 mg tolterodine tartrate in the 1mg film-coated tablets is equivalent to 0.68 mg tolterodine base; each 2 mg tolterodine tartrate film-coated tablet contains 1.37 mg of the active ingredient tolterodine. The medicinal product is licensed for marketing in either blister strips or tablet containers. The blister strips are composed of aluminium, polyvinylchloride (PVC) and polyvinylidene chloride (PVdC); the tablet containers are composed of high density polyethylene with a low density polyethylene sealed cap and a desiccant (silica gel). Both blister strips and tablet containers are packed with the Patient Information Leaflet (PIL) into cardboard outer cartons, in pack sizes of 4, 7, 10, 14, 20, 28, 30, 42, 50, 56, 60, 90, 100, 280, 500, 560 tablets. The approved shelf-life (2 years) is satisfactory with the storage conditions of “Store below 30°C”. The storage conditions for these products are identical to the details registered for the cross-reference product.

2.3 Legal status
This product is a prescription only (POM) medicine.

2.4 Marketing authorisation holder/Contact Persons/Company
The proposed Marketing Authorisation Holder is Actavis Group PTC ehf., Reykjavíkurvegi 76-78, 220 Hafnarfjörður, eland

The Qualified Person (QP) responsible for pharmacovigilance is stated and their curriculum vita has been included.
2.5 Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference products and evidence of GMP compliance has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in-line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference products.

2.10 TSE Compliance
The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed products. None of the excipients are sourced from genetically modified organisms. This is consistent with the cross-reference products.

3. EXPERT REPORT
A satisfactory quality overall summary has been prepared by an appropriately qualified expert. The CV of the expert was provided.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product name. The licensed products are white, round, biconvex, 5.5 mm film-coated tablets marked with “T1” or “T2” on one side respective of the strength of tablet. This is identical to that of the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
The approved SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET (PIL)/CARTON
PIL
The PIL is satisfactory and in line with the approved SmPC and has been prepared in the user-tested format.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Labelling
Mock-ups of the labelling have been provided and are satisfactory. The approved artwork is comparable to the artwork registered for the cross-reference products and complies with statutory requirements.
7. CONCLUSIONS
The data submitted with these applications are acceptable. Marketing Authorisations were, therefore, granted.
NON-CLINICAL ASSESSMENT

These are simple, abridged, ‘informed consent’ applications made under Article 10c of EC Directive 2001/83 (as amended). These applications are identical to the reference products, Tolterodine 1 mg and 2 mg Film-Coated Tablets (PL 24668/0179-0180) authorised to Caduceus Pharma Limited) on 24 February 2011 in the UK, therefore, no new non-clinical data has been supplied with these applications and none are required.

A non-clinical overview report has been written by a suitably qualified person and is satisfactory. The CV of the non-clinical expert has been supplied.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environment Risk Assessment (ERA). As this application is identical to already authorised reference products, it is not expected that the environmental exposure to tolterodine tartrate will increase following the marketing approval of the proposed product.
CLINICAL ASSESSMENT

These are simple, abridged, ‘informed consent’ applications made under Article 10c of EC Directive 2001/83 (as amended), cross-referring to Tolterodine 1 mg and 2 mg Film-Coated Tablets (PL 24668/0179-0180) authorised to Caduceus Pharma Limited since 24 February 2011 in the UK.

No new clinical data has been supplied with these applications and none are required. A clinical overview has been written by a suitably qualified person and is satisfactory. The CV of the clinical expert has been supplied.

The Marketing Authorisation Holder (MAH) has provided adequate justification for not submitting a Risk Management Plan (RMP). As these applications are identical to already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The MAH has provided a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
These applications are considered identical to the previously granted licences for Tolterodine 1 mg and 2 mg Film-Coated Tablets (PL 24668/0179-0180) authorised to Caduceus Pharma Limited since 24 February 2011. The current applications are considered valid.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPC, PIL and labelling are satisfactory, and consistent with those for the cross-reference products.

The applicant has submitted results of PIL user testing. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Mock-ups of the labeling have been provided and are satisfactory. The labeling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT
The quality of the products are acceptable and no new non-clinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. The benefit; risk ratio is, therefore, considered to be positive.
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STEPS TAKEN FOR ASSESSMENT

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<td>1</td>
<td>The MHRA received the marketing authorisation application on 20 December 2011.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 21 March 2012.</td>
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<td>3</td>
<td>Following assessment of the application the MHRA requested further information relating to the quality dossier on 30 March 2012.</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 18 May 2012.</td>
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<tr>
<td>5</td>
<td>The application was determined on 27 June 2012.</td>
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TOLTERODINE TARTRATE 1 MG AND 2 MG FILM-COATED TABLETS
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STEPS TAKEN AFTER ASSESSMENT

<table>
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<th>Application type</th>
<th>Scope</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Tolterodine tartrate 1 mg and 2 mg Film-Coated Tablets (PL 30306/0411-412) is as follows: Differences between the two are highlighted in yellow.

1 NAME OF THE MEDICINAL PRODUCT
Tolterodine tartrate 1 mg Film-coated Tablets
Tolterodine tartrate 2 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film-coated tablet contains tolterodine tartrate 1 mg corresponding to 0.68 mg tolterodine.
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 tablets
Tolterodine tartrate 1 mg: White, round, biconvex, 5.5 mm film-coated tablets marked with “T1” on one side.
Tolterodine tartrate 2 mg: White, round, biconvex, 5.5 mm film-coated tablets marked with “T2” on one 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 patients:
Tolterodine is not recommended for use in children due to a lack on insufficient data on efficacy (see section 5.1).

Method of administration:
The tablets are for oral use and should be swallowed whole.

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
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 drugs 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).

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) 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 drugs metabolised by these isoenzymes is not expected when dosed in combination with tolterodine.
4.6 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 is not recommended during pregnancy.

Breastfeeding
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 list 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.

Estimated frequency of events is as follows: Very common (≥1/10); Common (≥1/100, <1/10); uncommon (≥1/1000, <1/100); not known (cannot be estimated from the available data).

Infections and infestations
Common: Bronchitis

Immune system disorders
Uncommon: Hypersensitivity not otherwise specified
Not known: Anaphylactoid reactions

Psychiatric disorders
Uncommon: Nervousness
Not known: Confusion, hallucinations, disorientation

Nervous system disorders
Very Common: Headaches
Common: Dizziness, somnolence, paresthesia
Uncommon: Memory impairment

Eye disorders
Common: Dry eyes, abnormal vision including abnormal accommodation
**Ear and labyrinth disorders**
*Common:* Vertigo

**Cardiac disorders**
*Common:* Palpitations
*Uncommon:* Tachycardia, cardiac failure, arrhythmia

**Vascular disorders**
*Not known:* Flushing

**Gastrointestinal disorders**
*Very Common:* Dry mouth
*Common:* Dyspepsia, constipation, abdominal pain, flatulence, vomiting, diarrhoea
*Uncommon:* Gastroesophageal reflux

**Skin and subcutaneous tissue disorders**
*Common:* Dry skin
*Not known:* Angioedema

**Renal and urinary disorders**
*Common:* Dysuria, urinary retention

**General disorders and administration site conditions**
*Common:* Fatigue, chest pain, peripheral oedema

**Investigations**
*Common:* 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).

## 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 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 excitement: 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

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.

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.

<table>
<thead>
<tr>
<th>Variable</th>
<th>4-week studies</th>
<th>12-week studies</th>
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<tr>
<td></td>
<td>Tolterodine 2 mg b.i.d.</td>
<td>Placebo</td>
</tr>
<tr>
<td>Number of micturitions per 24 hours</td>
<td>2 mg b.i.d.</td>
<td>Placebo</td>
</tr>
<tr>
<td>n=392</td>
<td>n=189</td>
<td>*</td>
</tr>
<tr>
<td>Number of incontinence episodes per 24 hours</td>
<td>n=288</td>
<td>n=151</td>
</tr>
<tr>
<td>Mean volume voided per micturition (ml)</td>
<td>n=385</td>
<td>n=185</td>
</tr>
<tr>
<td>Number of patients with no or minimal bladder problems after treatment (%)</td>
<td>n=394</td>
<td>n=190</td>
</tr>
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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 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.

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 (Cmax) of three times that obtained with the highest therapeutic dose of Protol SR capsules.

**Paediatric population**

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). Steady state concentrations are reached within 2 days after administration of the tablets.

**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 [14C]-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 \( \leq \) 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 patients

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 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 (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

Tablet core:

- Magnesium stearate
- Silica colloidal, anhydrous
- Sodium starch glycolate, type B
Calcium hydrogen phosphate, dihydrate
Cellulose, microcrystalline
Coating:
Silica colloidal, anhydrous
Polyethylene glycol 400
Polyethylene glycol 8000
Hypromellose (E 464)
Hydroxypropyl cellulose (E 463)
Titanium dioxide (E 171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
Aluminium/PVC/PVdC blister packs.
Tablet containers (HDPE) with a sealed cap (LDPE) and a desiccant (silica gel).
Pack sizes:
Blister packs: 4, 7, 10, 14, 20, 28, 30, 42, 50, 56, 60, 90, 100, 280, 500, 560 tablets
Tablet container: 4, 7, 10, 14, 20, 28, 30, 42, 50, 56, 60, 90, 100, 280, 500, 560 tablets
Not all pack sizes may be marketed

6.6 Special precautions for disposal
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Actavis Group PTC ehf.
Reykjavikurvegi 76-78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER(S)
PL 30306/0411

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
27/06/2012

10 DATE OF REVISION OF THE TEXT
27/06/2012
Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.
- The full name of this medicine is Tolterodine tartrate 1mg and 2mg Film-coated Tablets but within the leaflet it will be referred to as Tolterodine tablets.

What is in this leaflet

1. What Tolterodine tablets are and what they are used for
2. What you need to know before you take Tolterodine tablets
3. How to take Tolterodine tablets
4. Possible side effects
5. How to store Tolterodine tablets
6. Contents of the pack and other information

1. What Tolterodine tablets are and what they are used for

The active substance in Tolterodine tablets is tolterodine. Tolterodine belongs to a class of medicinal products called antimuscarinics.

Tolterodine is used for the treatment of the symptoms of overactive bladder syndrome. If you have overactive bladder syndrome, you may find that:

- you are unable to control urination
- you need to rush to the toilet with no advance warning and/or go to the toilet frequently.
- have a heart condition such as:
  - an abnormal heart tracing (ECG)
  - a slow heart rate (bradycardia)
  - relevant pre-existing cardiac diseases (weak heart muscle (cardiomyopathy), reduced blood flow to the heart (myocardial ischaemia), irregular heartbeat (arrhythmia) and heart failure)
  - have abnormally low levels of potassium (hypokalaemia), calcium (hypocalcaemia) or magnesium (hypomagnesaemia) in your blood
  - are taking any medicine for the treatment of an irregular heartbeat (arrhythmia) (see 'Other medicines and Tolterodine tablets').

Talk to your doctor or pharmacist before taking Tolterodine tablets if you think any of these apply to you.

Other medicines and Tolterodine tablets

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Tolterodine, the active substance of Tolterodine tablets, may interact with other medicinal products.

It is not recommended to use Tolterodine tablets in combination with

- some antibiotics (containing e.g. erythromycin, clarithromycin)
- medicinal products used for the treatment of fungal infections (containing e.g. ketoconazole, itraconazole)
- medicinal products used for the treatment of HIV

Tolterodine tablets should be used with caution when taken in combination with

- medicines that affect the passage of food (containing e.g. metoclopramide and cisapride)
- medicines for the treatment of irregular heartbeat (containing e.g. amiodarone, sotalol, quinidine, procainamide) (see 'Warnings and precautions')
- other medicines with antimuscarinic (medicines with a similar mode of action to tolterodine) or cholinergic (medicines with an opposite mode of action to tolterodine) properties. Ask your doctor if you are unsure.

Tolterodine tablets with food and drink

Tolterodine tablets can be taken before, after or during a meal.
What you need to know before you take Tolterodine tablets

Do not take Tolterodine tablets if you
- are allergic to tolterodine or any of the other ingredients of this medicine (listed in section 6).
- are unable to pass urine from the bladder (urinary retention).
- have uncontrolled narrow angle glaucoma (increase in intraocular pressure).
- suffer from excessive weakness of the muscles (myasthenia gravis).
- suffer from ulceration and inflammation of the colon (severe ulcerative colitis).
- suffer from acute dilatation of the colon (a toxic megacolon).

Warnings and precautions
Take special care with Tolterodine tablets if you
- have difficulties in passing urine and/or a poor stream of urine.
- have a gastrointestinal disease that affects the passage and/or digestion of food.
- suffer from kidney problems (renal insufficiency).
- have a liver condition.
- suffer from neurological disorders that affect your blood pressure, bowel or sexual function (any neuropathy of the autonomic nervous system).
- have herniation of an abdominal organ (hiatal hernia).
- ever experience decreased bowel movements or suffer from severe constipation (decreased gastro-intestinal motility).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
You should not use Tolterodine tablets when you are pregnant. Tell your doctor immediately if you are pregnant, think you are pregnant or are planning to become pregnant.

Breast-feeding
It is not known if tolterodine is excreted in the mother’s breast milk. Breast-feeding is not recommended during administration of Tolterodine tablets.

Driving and using machines
Tolterodine tablets may make you feel dizzy, tired or affect your sight; your ability to drive or operate machinery may be affected.

How to take Tolterodine tablets

Dosage
Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 2mg tablet twice daily, except for patients who have a kidney or a liver condition or troublesome side effects in which case your doctor may reduce your dose to one 1mg tablet twice daily.

The tablets are for oral use and should be swallowed whole.

Use in children
Tolterodine tablets is not recommended for children.

Duration of treatment
Your doctor will tell you how long your treatment with Tolterodine tablets will last. Do not stop treatment early because you do not see an immediate effect. Your bladder will need some time to adapt. Finish the course of tablets prescribed by your doctor. If you have not noticed any effect by then, talk to your doctor.

The benefit of the treatment should be re-evaluated after 2 or 3 months.

If you take more Tolterodine tablets than you should
If you or somebody else takes too many tablets, contact your doctor, accident and emergency department or pharmacy at once.

If you forget to take Tolterodine tablets
Do not take a double dose to make up for a forgotten one. If you have forgotten to take a dose at the usual time, you can take it as soon as you remember unless it is almost time for your next dose. In that case you should not take the forgotten dose but follow the normal dose schedule.

If you stop taking Tolterodine tablets
Always consult your doctor if you are thinking of stopping the treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

Uncommon (occurs in less than 1 in 100 patients) side effects are:
- Allergic reactions
- Nervousness
- Increased heart rate
- Heart failure
- Irregular heartbeat
- Heart burn
- Memory impairment.

Additional reactions reported include severe allergic reactions, confusion, hallucinations (seeing, hearing, feeling, tasting or smelling things that are not there), disorientation, flushing and angioedema.

There have also been reports of worsening symptoms of dementia in patients being treated for dementia.

If you get any side effects, talk to your doctor or pharmacist. This includes any side effects not listed in this leaflet.

How to store Tolterodine tablets

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.

Store below 30°C.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.
Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You should see your doctor immediately or go to the casualty department if you experience symptoms of angioedema, such as:
- Swollen face, tongue or pharynx
- Difficulty to swallow
- Hives and difficulty in breathing.

You should also seek medical attention if you experience a hypersensitivity reaction (for example itching, rash, hives, difficulty breathing). This occurs uncommonly (occurs in less than 1 in 100 patients).

Tell your doctor immediately or go to the casualty department if you notice any of the following:
- Chest pain, difficulty breathing or getting tired easily (even at rest), difficulty breathing at night, swelling of the legs. These may be symptoms of heart failure. This occurs uncommonly (occurs in less than 1 in 100 patients).

The following side effects have been observed during treatment with Tolterodine tablets with the following frequencies.

Very Common (occurs in more than 1 in 10 patients) side effects are:
- Dry mouth
- Headache.

Common (occurs in less than 1 in 10 patients) side effects are:
- Bronchitis
- Dizziness
- Sleeplessness
- Sensation of pins and needles in the fingers and toes
- Dry eyes
- Blurred vision
- Spinning sensation
- Aware of the heartbeat (palpitations)
- Bad digestion (dyspepsia)
- Constipation
- Abdominal pain
- Excessive amounts of air or gases in the stomach or the intestine
- Being sick (vomiting)
- Diarrhoea
- Dry skin
- Painful or difficult urination
- Inability to empty the bladder
- Tiredness
- Chest pain
- Extra fluid in the body causing swelling (e.g. in the ankles)
- Increased weight.

Contents of the pack and other information

What Tolterodine tablets contain

- The active substance in Tolterodine Tartrate 1mg Film-Coated Tablets is 1mg of tolterodine tartrate, equivalent to 0.68 mg of tolterodine.
- The active substance in Tolterodine Tartrate 2mg Film-Coated Tablets is 2mg of tolterodine tartrate, equivalent to 1.37 mg of tolterodine.
- The other ingredients are: magnesium stearate, silica colloidal anhydrous, sodium starch glycolate type B, calcium hydrogen phosphate dihydrate, cellulose microcrystalline, polyethylene glycol 400, polyethylene glycol 8000, hypromellose (E 464), hydroxypropyl cellulose (E 463), titanium dioxide (E 171).

What Tolterodine tablets look like and contents of the pack

Film-coated tablets, 1mg: White, round, biconvex, 5.5 mm film-coated tablets marked with “T1” on one side.
2mg: White, round, biconvex, 5.5 mm film-coated tablets marked with “T2” on one side.

Pack sizes: Blister packs 56 tablets

Marketing Authorisation Holder
Actavis Group PTC ehf.
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220 Hafnarfjörður
Iceland

Manufacturer
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If you would like a leaflet with larger text, please contact 01271 311257.
TOLTERODINE TARTRATE 1 MG AND 2 MG FILM-COATED TABLETS
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