1. NAME OF THE MEDICINAL PRODUCT

DETRUSITOL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: tolterodine tartrate

Each film-coated tablet for oral administration contains tolterodine tartrate 1 mg or 2 mg corresponding to 0.68 mg and 1.37 mg tolterodine, respectively.

3. PHARMACEUTICAL FORM

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Tolterodine is indicated for the treatment of overactive bladder with symptoms of urinary urgency, frequency, and/or urge incontinence.

4.2 Posology And Method Of Administration

Adults (including the Elderly)
The recommended total daily dose is 4 mg. Dosage with tolterodine tablets is 2 mg twice daily. The total daily dose may be reduced to 2 mg, based on individual tolerability.

Use in Children
Safety and effectiveness in children have not yet been established.

Use in Impaired Renal Function
The recommended total daily dose is 2 mg (i.e., tolterodine tablets 1 mg twice daily) for patients with impaired renal function **(see Section 4.4 – Special Warnings and Precautions for Use)**.

Use in Impaired Hepatic Function
The recommended total daily dose is 2 mg (i.e., tolterodine tablets 1 mg twice daily) for patients with impaired hepatic function **(see Section 4.4 – Special Warnings and Precautions for Use)**.

Use with Potent CYP3A4 Inhibitors

The recommended total daily dose is 2 mg (i.e., tolterodine tablets 1 mg twice daily) for patients receiving concomitant ketoconazole or other potent CYP3A4inhibitors **(see Section 4.4 – Special Warnings and Precautions for Use, CYP3A4 inhibitors, and Section 4.5 – Interactions with Other Medicinal Products and Other Forms of Interaction).**

4.3 Contraindications

Tolterodine is contraindicated in patients with:
- Known hypersensitivity to tolterodine or any component of the product
- Urinary retention
- Uncontrolled narrow angle glaucoma

4.4 Special Warnings And Special Precautions For Use

Tolterodine shall be used with caution in the following patients:
- At risk for urinary retention
- At risk for decreased gastrointestinal motility
- With impaired renal function **(see Section 4.2 – Posology and Method of Administration, Use in Impaired Renal Function, and Section 5.2 Pharmacokinetic Properties ,*Specific patient groups*)**
- With impaired hepatic function **(see Section 4.2 – Posology and Method of Administration, Use in Impaired Hepatic Function, and Section 5.2 – Pharmacokinetic Properties *Specific patient groups*)**
- With myasthenia gravis

In a study of the effect of tolterodine immediate-release tablets on the QT interval, the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PM) than extensive metabolizers (EMs) (**see Section 5.1 – Pharmacodynamic Properties**).

The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin. However, the confidence intervals overlapped.

These observations should be considered in clinical decisions to prescribe tolterodine immediate-release tablets for patients with:

- Congenital or documented acquired QT prolongation
- Patients who are taking Class IA (e.g., quinidine, procainamide) or Class III (e.g.,amiodarone, sotalol) antiarrhythmic medications

CYP3A4 inhibitors

The recommended total daily dose of tolterodine is 2 mg for patients on concomitant medication with potent CYP3A4 inhibitors, such as macrolide antibiotics (e.g., erythromycin and clarithromycin) or azole antifungal agents (e.g., ketoconazole, itraconazole and miconazole). **(see Section 4.2 – Posology and Method of Administration, Use with Potent CYP3A4 Inhibitors, and Section 4.5 – Interactions with Other Medicinal Products and Other Forms of Interaction).**

4.5 Interaction With Other Medicinal Products And Other Forms Of Interaction

Pharmacokinetic interactions are possible with other drugs metabolized by or inhibiting cytochrome P450 2D6 (CYP2D6) or CYP3A4. Concomitant treatment with fluoxetine does not result in a clinically significant interaction.

Ketoconazole, a potent inhibitor of CYP3A4, significantly increased plasma concentrations of tolterodine when coadministered to poor metabolisers (i.e., persons devoid of CYP2D6 metabolic pathway). For patients receiving ketoconazole or other potent CYP3A4 inhibitors, the recommended total daily dose is 2 mg **(see Section 4.2 – Posology and Method of Administration, Use with Potent CYP3A4 Inhibitors, and Section 4.4 – Special Warnings and Precautions for Use – CYP3A4 inhibitors**).

Clinical studies have shown no interactions with warfarin or combined oral contraceptives (ethinyl estradiol/levonorgestrel).

A clinical study with marker drugs for the major P450 isoenzymes has not shown any evidence that the activity of CYP2D6, 2C19, 2C9, 3A4 or 1A2 will be inhibited by tolterodine.

4.6 Pregnancy and Lactation

Pregnancy

There are no studies in pregnant women. Therefore, tolterodine should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Lactation

Use of tolterodine during lactation should be avoided since no data on excretion into breast milk in humans are available.

4.7 Effects On Ability To Drive And Use Machines

The ability to drive and use machinery may be negatively affected. Patients should be advised to exercise caution.

4.8 Undesirable Effects

Tolterodine may cause mild-to-moderate antimuscarinic effects, like dryness of the mouth, dyspepsia, and reduced lacrimation.

Clinical Trials: Adverse events considered potentially drug-related from studies of tolterodine tablets are provided below.

Infections and Infestations: bronchitis

Immune System Disorders: allergic reactions

Psychiatric Disorders: confusion

Nervous System Disorders: dizziness, headache, somnolence

Eye Disorders: abnormal vision (including abnormal accommodation), dry eyes

Ear and Labyrinth Disorders: vertigo

Vascular Disorders: flushed skin

Gastrointestinal Disorders:dry mouth, abdominal pain, constipation, dyspepsia, flatulence, gastroesophageal reflux

Skin and Subcutaneous Tissue Disorders: dry skin

Renal and Urinary Disorders: dysuria, urinary retention

General Disorders and Administration Site Conditions: chest pain, fatigue

Investigations: increased weight

The following adverse events were reported during POST-MARKETING SURVEILLANCE:

Immune System Disorders: anaphylactoid reactions

Psychiatric Disorders: disorientation, hallucinations

Nervous System Disorders: memory impairment

Cardiac Disorders: tachycardia, palpitations

Gastrointestinal Disorders: diarrhea

Skin and Subcutaneous Tissue Disorders: angioedema

General Disorders and Administration Site Conditions: peripheral edema

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.

4.9 Overdose

The highest dose of tolterodine given to human volunteers was 12.8 mg as single dose. The most severe adverse event observed were accomodation disturbances and micturition difficulties.

Overdosage with tolterodine can potentially result in severe central antimuscarinic effects and should be treated accordingly.

In the event of tolterodine overdose, standard supportive measures for managing QT prolongation should be adopted (**see Section 4.4 – Special Warnings and Precautions for Use, and Section 5.1 – Pharmacodynamic Properties**).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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 – Pharmacokinetic Properties, *Metabolism***).

Effect of the treatment can be expected within 4 weeks.

A total of 710 pediatric patients (486 on tolterodine extended-release capsules, 224 on placebo) aged 5-10 with urinary frequency and urge incontinence were studied in two phase 3 randomized, placebo-controlled, double-blind, 12-week studies. The percentage of patients with urinary tract infections was higher in patients treated with tolterodine extended-release capsules (6.6%) compared to patients who received placebo (4.5%). Aggressive, abnormal and hyperactive behavior and attention disorders occurred in 2.9% of children treated with tolterodine extended-release capsules compared to 0.9% of children treated with placebo.

Table 1. *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 2mg b.i.d.	Placebo	Statistical significance vs. placebo	tolterodine 2mg 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 urodynamic positive (motor urgency) or a urodynamic negative (sensory urgency) group. Within each group, the

patients were randomized 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 effect of 2 mg BID and 4 mg BID of tolterodine immediate-release (tolterodine IR) tablets on the QT interval was evaluated in a 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg QD) study in healthy male (N=25) and female (N=23) volunteers aged 18-55 years. There was an approximately equal representation of CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs). The 4 mg BID dose of tolterodine IR (two times the highest recommended dose) was chosen because this dose results in tolterodine exposure similar to that observed upon co-administration of tolterodine 2 mg BID with potent CYP3A4 inhibitors in patients who are CYP2D6 poor metabolizers (**see Section 4.4 – Special Warnings and Precautions for Use, and Section 4.9 – Overdose).**

Table 2 summarizes the mean change from baseline to steady state in corrected QT interval (Fridericia's QTcF and population-specific QTcP) relative to placebo at the time of peak tolterodine (1 hour) and moxifloxacin (2 hour) concentrations. QT interval was measured manually and by machine, and data from both are presented. The reason for the difference between machine and manual read of QT interval is unclear

Table 2: Mean (CI) change in QTc from baseline to steady state (Day 4 of dosing) at T_{max} (relative to placebo)

Drug/Dose ***D***	**N**	**QTcF (msec) (manual)**	**QTcF (msec) (machine)**	**QTcP (msec) (manual)**	**QTcP (msec) (machine)**
Tolterodine 2 mg BID[1]	48	5.01 (0.28, 9.74)	1.16 (-2.99, 5.30)	4.45 (-0.37, 9.26)	2.00 (-1.81, 5.81)
Tolterodine 4 mg BID[1]	48	11.84 (7.11, 16.58)	5.63 (1.48, 9.77)	10.31 (5.49, 15.12)	8.34 (4.53, 12.15)
Moxifloxacin 400 mg QD [2]	45	19.26[3] (15.49, 23.03)	8.90 (4.77, 13.03)	19.10[3] (15.32, 22.89)	9.29 (5.34, 13.24)

[1]At Tmax of 1 hr; 95% Confidence Interval
[2]At Tmax of 2 hr; 90% Confidence Interval
[3]The effect on QT interval with 4 days of moxifloxacin dosing in this QT trial may be greater than typically observed in QT trials.

The QT effect of tolterodine immediate-release tablets appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day. The effect of tolterodine 8 mg/day was not as large as that observed after four days of therapeutic dosing with the active control moxifloxacin.

There appeared to be a greater QTc interval increase in PMs than in EMs after tolterodine treatment in this study **(see Section 4.4 – Special Warnings and Precautions for Use, and Section 4.9 – Overdose)**.

5.2 Pharmacokinetic Properties

Pharmacokinetic characteristics: 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 to 3 hours in extensive and about 10 hours in poor metabolizers (devoid of CYP2D6). Steady state concentrations are reached within 2 days after administration of the tablets.

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

Absorption: After oral administration tolterodine is subject to CYP2D6 catalyzed 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 metabolizers, the majority of the patients, and 65% in poor metabolizers (devoid of CYP2D6).

Distribution: Tolterodine and the 5-hydroxymethyl metabolite bind primarily to alpha-1-acid glycoprotein. The unbound fractions are 3.7% and 36%, respectively. The volume of distribution of tolterodine is 113 L.

Metabolism: Tolterodine is extensively metabolized 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 metabolizers) 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 metabolizers. The systemic clearance of tolterodine in extensive metabolizers is about 30 L/h. In poor metabolizers 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 metabolizers 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.

Excretion: The excretion of radioactivity after administration of [^{14}C]- tolterodine is about 77% in urine and 17% in feces. 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 hepatic 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 – Posology and Method of Administration, Use in Impaired Hepatic Function, and 4.4 – Special Warnings and Precautions for Use)** .

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 Posology and Method of Administration – Use in Impaired Renal Function and 4.4 Special Warnings and Precautions for Use**).

5.3 Preclinical Safety Data

In toxicity, genotoxicity, and carcinogenicity 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.

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

Studies in pregnant mice have shown that high doses of tolterodine cause reduced fetal weight, embryolethality and increased incidence of fetal malformations.

Tolterodine, as well as its active human metabolites prolong action potential duration (90% repolarization) in canine purkinje fibers (14 - 75 times therapeutic levels) and block the K+-current in cloned human ether-a-go-go-related gene (hERG) channels (0.5 - 9.8 times therapeutic levels). In dogs prolongation of the QT interval has been observed after application of tolterodine and its human metabolites (3.1 - 42 times therapeutic levels).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Core:

Cellulose, microcrystalline
Calcium hydrogen phosphate dihydrate
Sodium starch glycollate (Type B)
Magnesium stearate
Colloidal anhydrous silica

Film coating:

Coating granules containing
Hypromellose
Cellulose, microcrystalline
Stearic acid
Titanium dioxide

6.2 Incompatibilities

Not Applicable.

6.3 Shelf-life

Refer to EXP date on outer carton.

6.4 Special Precautions for Storage

Store below 25^0C.

6.5 Nature and Contents of Container

Tablets are packed in blister package made of PVC/PVDC and aluminium foil with a heat seal coating of PVDC.

Pack sizes:
Detrusitol tablets of 1 and 2 mg are available in blisters of 2x14 and 4x14 tablets.

6.6 Instructions for Use and Handling

No special requirements.

7. MANUFACTURER

Pfizer Italia S.r.l.
Ascoli Piceno
Italy

Reference: Detrusitol-SIN-0408
Based on CDS 756, 11 Apr 2008

Date of H SA Approval: