[PFI1]PT. PFIZER INDONESIA
Local Product Document

Product Document Title: Tolterodine L-Tartrate~~Tolterodine~~[PFI2]
Trade Name: DETRUSITOL
Product Document No.:756
Date: April 11, 2008
Supercedes: February 23, 2007

[FN3] **Pada proses pembuatannya bersinggungan dengan bahan bersumber babi**

QUALITATIVE AND QUANTITATIVE COMPOSITION

Tolterodine L-tartrate 2 mg corresponding 1.37 mg tolterodine (rINN) respectively,[FN4]

PHARMACEUTICAL FORM

Film Coated Tablet

CLINICAL PARTICULARS

Therapeutic Indications

For the treatment of overactive bladder with symptoms of urinary urgency, frequency, or urge incontinence.

Posology and methods of administration

The recommended dose is 2 mg b.i.d. The dose may be reduced from 2 mg to 1 mg b.i.d., based on individual tolerability.

Safety and effectiveness in children have not yet been established. Therefore, Detrusitol is not recommended for children until more information is available.

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 – **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 – **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 CYP3A4 inhibitors (see Section – **Special Warnings and Precautions for Use, CYP3A4 inhibitors**, and Section – **Interactions with Other Medicinal Products and Other Forms of Interaction**).

After 6 months the need for further treatment should be considered.

Contraindications

Detrusitol is contraindicated in patients with:

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

Special Warnings and Special Precautions for Use

Detrusitol shall be used with caution in patients with:

- Significant bladder outlet obstruction at risk for urinary retention.
- Gastrointestinal obstructive disorders, e.g. pyloric stenosis.
- Renal disease. (see Section – **Posology and Method of Administration, Use in Impaired Renal Function**, and Section **Pharmacokinetic Properties, *Specific patient groups*)**
- Hepatic disease. (see Section – **Posology and Method of Administration, Use in Impaired Hepatic Function,** and Section – **Pharmacokinetic Properties, *Specific patient groups*)**
- Autonomic neurophaty.
- Hiatus hernia.
- Organic reason for urgency and frequency and should be considered before treatment.
- 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 – **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 extended-release capsules 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

Patients on concomitant medication with potent CYP3A4 inhibitors, such as macrolide antibiotics (erythromycin and clarithromycin) or antifungal agents (ketoconazole, itraconazole and miconazole) should be treated with caution until further data are available.

Interaction with other medicaments and other forms of interaction

Concomitant medication with other drugs that possess antimuscarinic properties may result in more pronounced therapeutic effect and adverse-effects. Conversely, the therapeutic effect of Detrusitol may be reduced by concomitant administration of muscarinic receptor agonists. The effect of prokinetics like metoclopramide and cisapride on GI tract (increased lower esophageal sphincter pressure and improved gastroduodenal coordination) may be decreased by Detrusitol.

Pharmacokinetic interactions are possible with other drugs metabolized by or inhibiting cytochrome P450 2D6 (CYP2D6) or CYP3A4. However, concomitant treatment with fluoxetine (a potent CYP2D6 inhibitor which is metabolised to norfluoxetine, a CYP3A4 inhibitor) result in only minor increase in the combined exposure of unbound Detrusitol and the equipotent 5-hydroxymethyl metabolite. This does not result in a clinically significant interaction.

Ketoconazole, a potent inhibitor of CYP3A4, significantly increased plasma concentrations of tolterodine when coadministered to poor metabolizers (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 – **Posology and Method ofAdministration, Use with Potent CYP3A4 Inhibitors** and Section – **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 Detrusitol.

Pregnancy and lactation

No pregnant women have been included in the clinical studies. Therefore, Detrusitol should be used during pregnancy only after consideration of the potential benefits for the mother in the relation to the potential risk for the fetus.

Women of fertile age should be considered for treatment only if using adequate contraception.

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

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.

Undesirable Effects

Tolterodine it 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 and capsules 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.

Overdose

The highest dose tolterodine given to human volunteers is 12.8 mg as single dose. The most severe adverse events observed were accommodation disturbances and micturition difficulties.

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

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. If the daylight is unpleasant place patient in dark room.

Pharmacologicy

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 – **Pharmacokinetic Properties**).

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

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		
	Detrusitol 2 mg b.i.d.	Placebo	Statistical significance vs. placebo	Detrusitol 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 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 – **Special Warnings and Precautions for Use**, and Section – **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	**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 T_{max} of 1 hr; 95% Confidence Interval
[2]At T_{max} 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 – **Special Warnings and Precautions for Use**, and Section – **Overdose**).

Pharmacokinetic properties

Tolterodine is rapidly absorbed. Both tolterodine and the 5-hydroxymethyl metabolite reach maximal serum concentrations 1-3 hours after dose. The average peak serum concentrations of tolterodine and the metabolite increase proportionally in the dose interval 1 to 4 mg. Tolterodine is mainly metabolized by the polymorphic enzyme CYP2D6 leading to the formation of a pharmacologically active 5-hydroxymethyl metabolite. The systemic serum clearance of tolterodine in extensive metabolisers about 30 L/h and the terminal half life is 2 to 3 hours. The half life of the hydroxymethyl metabolite is 3 – 4 hours. In poor metabolisers (deficient of CYP2D6) tolterodine is dealkylated via CYP3A isoenzymes whereby N-dealkalylated tolterodine is formed. This metabolite does not contribute to the clinical effect. The reduced clearance and prolonged half life (about 10 hours) of the parent compound in poor metabolisers lead to increased concentration of tolterodine (about 7 fold) associated with undetectable concentrations of the 5-hydroxymethyl metabolite. As a result, the exposure (AUC) of unbound tolterodine in poor metabolisers is similar to the combined exposure of unbound tolterodine and 5-hydroxymethyl metabolite in patients with CYP2D6 activity given the same dosage regimen. The safety, tolerability and clinical response are similar irrespective of phenotype. Steady state concentrations are reached within 2 days.

The absolute bioavailability of tolterodine is 65% in poor metabolisers (devoid of CYP2D6) and 17% in extensive metabolisers (the majority of the patients).

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.

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.

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 excreted 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.

About 2-fold higher exposure of unbound tolterodine and the 5-hydroxymethyl metabolite is found in liver cirrhosis subjects.

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

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.

Reduced foetal weight, embryolethality and increased incidence of foetal malformations have been observed in pregnant mice treated with high doses. No effect were observed at a systemic exposure (measured as C_{max} or UAC for unbound tolterodine and its major active metabolite) 9 – 50 times higher than in humans after the highest recommended dose.

In conscious dogs, a slight prolongation (10% to 20%) of the QT interval has been observed at a toxic dose (4.5 mg/kg/day) of tolterodine. This dose results in very high serum consentrations both of tolterodine and its major active metabolite. No QT interval prolongation has been found in clinical studies with tolterodine.

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 Detrusitol cause reduced foetal weigt, embryolethality and increased incidence of foetal 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).

Pharmaceutical Particulars

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:
Methylhydroxypropylcellulose (Hypromellose)
Cellulose, microcrystalline
Stearic acid
Titanium dioxide

Incompatibilities

No incompatibilities are known.

Store at temperature below 25°C.

Nature and content of container

Tablets are packed in either blister package made of PVC/PVDC and aluminium foil with a heat seal coating of PVDC or plastic containers made of polyethylene provided with screw caps of polypropylene.

How Supplied

Detrusitol Tablets 2 mg (white, round, biconvex film-coated tablets engraved with arcs and below the letters DT) in carton containing 2 blisters @ 14 tablets.

Reg. No. DKI0054200117B1

HARUS DENGAN RESEP DOKTER

Imported by
PT. Pfizer Indonesia
PO BOX 2706
Jakarta, Indonesia

Manufactured by
Pfizer Italia S.r.l., ~~-~~ Ascoli, [ZH5]Italy