DETRUSITOL SR®

Tolterodine tartrate (extended-release)

1. NAME OF THE MEDICINAL PRODUCT

DETRUSITOL SR®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: tolterodine tartrate

Each extended-release capsule for oral administration contains tolterodine tartrate 4 mg corresponding to 2.74 mg tolterodine, respectively.

3. PHARMACEUTICAL FORM

Extended-release capsules

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

DETRUSITOL SR® 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

General: DETRUSITOL SR® capsules can be taken with or without food and must be swallowed whole (see Section **5.2. Pharmacokinetic Properties, *Pharmacokinetic characteristics***).

Adults (including the Elderly): The recommended total daily dose is 4 mg. Dosage with DETRUSITOL SR® capsules is 4 mg once 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 been established.

Use in Impaired Renal Function: The recommended total daily dose of DETRUSITOL SR® is 2 mg once 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 of DETRUSITOL SR® is 2 mg once 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 of DETRUSITOL SR® is 2 mg once daily for patients receiving concomitant ketoconazole or other potent CYP3A4 inhibitors, (see

Sections **4.4. Special Warnings and Precautions for Use, CYP3A4 inhibitors,** and **4.5. Interactions with Other Medicinal Products and Other Forms of Interaction**).

4.3. CONTRAINDICATIONS

DETRUSITOL SR® (tolterodine tartrate) is contraindicated in patients with:
- Known hypersensitivity to tolterodine or any other component of the product
- Urinary retention
- Uncontrolled narrow angle glaucoma

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

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 Sections **4.2. Posology and Method of Administration,** Use with Potent CYP3A4 Inhibitors, and **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 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 Sections **4.2. Posology and Method of Administration,** Use with Potent CYP3A4 Inhibitors, and **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, 3A4 or 1A2 will be inhibited by tolterodine.

4.6. FERTILITY, 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

DETRUSITOL SR® (tolterodine tartrate) 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 DETRUSITOL SR® (tolterodine tartrate) capsules are provided below.

- Infections and Infestations: sinusitis
- 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
- Renal and Urinary Disorders: dysuria, urinary retention
- General Disorders and Administration Site Conditions: fatigue

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 DETRUSITOL SR® (tolterodine tartrate) given to human volunteers was 12.8 mg as single dose. The most severe adverse events observed were accommodation disturbances and micturition difficulties.

Overdosage with DETRUSITOL SR® (tolterodine tartrate) can potentially result in severe central antimuscarinic effects and should be treated accordingly.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

DETRUSITOL SR® (tolterodine tartrate) 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 metabolizers 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.

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

Table 1: *Effect of treatment with tolterodine extended-release 4 mg once daily after 12 weeks, compared with placebo. Absolute change and percentage change relative to baseline. Treatment difference tolterodine extended-release vs. placebo: Least Squares estimated mean change and 95% confidence interval.*

	Tolterodine extended-release 4 mg once daily (n=507)	**Placebo (n=508)**	**Treatment difference vs. placebo: Mean change and 95% CI**	**Statistical significance vs. Placebo (p-value)**
Number of incontinence episodes per week	-11.8 (-54%)	-6.9 (-28%)	-4.8 (-7.2; -2.5)*	<0.001

Number of micturitions per 24 hours	-1.8 (-13%)	-1.2 (-8%)	-0.6 (-1.0; -0.2)	0.005
Mean volume voided per micturition (ml)	+34 (+27%)	+14 (+12%)	+20 (14; 26)	<0.001

** 97.5% confidence interval according to Bonferroni*

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

The effect of tolterodine was evaluated in patients, examined with urodynamic assessment at baseline and, depending on the urodynamic result, they were allocated to a urodynamic positive (motor urgency) or a urodynamic negative (sensory urgency) group. Within each group, the patients were 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 Sections **4.4. Special Warnings and Precautions for Use** and **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	***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 Sections **4.4. Special Warnings and Precautions for Use** and **4.9. Overdose)**.

5.2. PHARMACOKINETIC PROPERTIES

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

Absorption: After oral administration tolterodine is subject to CYP2D6 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 Sections **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 Sections **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 (23 - 123 times therapeutic levels) and block the K+-current in cloned human ether-a-go-go-related gene (hERG) channels (0.8 – 14.7 times therapeutic levels). In dogs prolongation of the QT interval has been observed after application of tolterodine and its human metabolites (5.1 - 62.7 times therapeutic levels).

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Prolonged release capsule contents:
Sugar spheres (containing sucrose and maize starch)
Hypromellose
Surelease E-7-9010 clear:
Ethylcellulose
Medium Chain Triglycerides
Oleic acid
Prolonged release capsule shell contents:
Gelatin

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF-LIFE

2 years

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C
Avoid exposure to heat, sunlight and moisture
Keep all medicines out of the reach of children

6.5. NATURE AND CONTENTS OF CONTAINER

DETRUSITOL SR® (tolterodine tartrate) is available in bottle of 30's.

DETRUSITOL SR/LPD/PK-01
According to CDS dated 11 April 2008; Supersedes CDS dated 23 February 2007

Imported & Marketed by:

Pfizer Pakistan Limited
B-2, Site, Karachi

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*