DETRUSITOL® SR 2MG
DETRUSITOL® SR 4MG

NAME OF THE MEDICINAL PRODUCT

Detrusitol® 2 mg
Detrusitol®4 mg

QUALITATIVE AND QUANTATIVE COMPOSITION

Each capsule contains 2 mg or 4mg of tolterodine L-tartrate.

Excipients with known effect:
Each capsule contains sugar spheres.

For the full list of excipients, see section Description (9) in this leaflet.

PHARMACEUTICAL FORM
Capsules slow release

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION
The recommended dose of DETRUSITOL® SR Capsules are 4 mg daily. DETRUSITOL® should be taken once daily with liquids and swallowed whole. The dose may be lowered to 2 mg daily based on individual response and tolerability, however, limited efficacy data is available for DETRUSITOL® SR 2 mg (see CLINICAL STUDIES).
For patients with significantly reduced hepatic or renal function or who are currently taking drugs that are potent inhibitors of CYP3A4, the recommended dose of DETRUSITOL® is 2 mg daily (see CLINICAL PHARMACOLOGY and PRECAUTIONS, Drug Interactions).

3 CONTRAINDICATIONS

DETRUSITOL ® SR is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. DETRUSITOL® SR is also contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients listed in section 9,, or to fesoterodine fumarate extended-release tablets which, like DETRUSITOL® SR, are metabolized to 5-hydroxymethyl tolterodine *[see **WARNINGS AND PRECAUTIONS** (4.2) (4.3) (4.4)]*.

4 WARNINGS AND PRECAUTIONS

4.1 Angioedema

Anaphylaxis and angioedema requiring hospitalization and emergency medical treatment have occurred with the first or subsequent doses of DETRUSITOL® SR. In the event of difficulty in breathing, upper airway

obstruction, or fall in blood pressure, DETRUSITOL® SR should be discontinued and appropriate therapy promptly provided.

4.2 Urinary Retention

Administer DETRUSITOL® SR Capsules with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention *[see **CONTRAINDICATIONS** (3)]*.

4.3 Gastrointestinal Disorders

Administer DETRUSITOL ® SR with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention.

DETRUSITOL® SR, like other antimuscarinic drugs, may decrease gastrointestinal motility and should be used with caution in patients with conditions associated with decreased gastrointestinal motility (e.g., intestinal atony) *[see **CONTRAINDICATIONS** (3)]*.

4.4 Controlled Narrow-Angle Glaucoma

Administer DETRUSITOL® SR with caution in patients being treated for narrow-angle glaucoma *[see **CONTRAINDICATIONS** (3)]*.

4.5 Central Nervous System Effects

DETRUSITOL® SR is associated with anticholinergic central nervous system (CNS) effects [see Adverse Reactions (5.2)] including dizziness and somnolence [see Adverse Reactions (5.1)]. Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until the drug's effects have been determined. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

4.6 Hepatic Impairment

The clearance of orally administered tolterodine immediate release was substantially lower in cirrhotic patients than in the healthy volunteers. For patients with mild to moderate hepatic impairment (Child-Pugh Class A or B), the recommended dose for DETRUSITOL® SR is 2 mg once daily. DETRUSITOL® SR is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) *[see **DOSAGE AND ADMINISTRATION** (2.2) and **USE IN SPECIFIC POPULATIONS** (7.6)]*.

4.7 Renal Impairment

Renal impairment can significantly alter the disposition of tolterodine and its metabolites. The dose of DETRUSITOL® SR should be reduced to 2 mg once daily in patients with severe renal impairment (CCr: 10-30 mL/min). Patients with CCr<10 mL/min have not been studied and use of DETRUSITOL® SR in this population is not recommended *[see **DOSAGE AND ADMINISTRATION** (2) and **USE IN SPECIFIC POPULATIONS** (7.5)]*.

4.8 Myasthenia Gravis

Administer DETRUSITOL® SR with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

4.9 Use in Patients with Congenital or Acquired QT Prolongation

In a study of the effect of tolterodine immediate release tablets on the QT interval *[see **CLINICAL PHARMACOLOGY** (10.2)]*, 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). 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 DETRUSITOL ®SR to patients with a known history of QT prolongation or to patients who are taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications. There has been no association of Torsade de Pointes in the international post-marketing experience with DETRUSITOL® or DETRUSITOL® SR.

4.10 Important information regarding some of the ingredients of the medicine

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

5 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

5.1 Clinical Trials Experience

The efficacy and safety of DETRUSITOL® SR Capsules was evaluated in 1073 patients (537 assigned to DETRUSITOL® SR ; 536 assigned to placebo) who were treated with 2, 4, 6, or 8 mg/day for up to 15 months. These included a total of 1012 patients (505 randomized to DETRUSITOL® SR 4 mg once daily and 507 randomized to placebo) enrolled in a randomized, placebo-controlled, double-blind, 12-week clinical efficacy and safety study.

Adverse events were reported in 52% (n=263) of patients receiving DETRUSITOL® SR and in 49% (n=247) of patients receiving placebo. The most common adverse events reported by patients receiving DETRUSITOL® SR were dry mouth, headache, constipation, and abdominal pain. Dry mouth was the most frequently reported adverse event for patients treated with DETRUSITOL® SR, occurring in 23.4% of patients treated with DETRUSITOL® SR and 7.7% of placebo-treated patients. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and dry eyes are expected side effects of antimuscarinic agents. A serious adverse event was reported by 1.4% (n=7) of patients receiving SETRUSITOL® SR and by 3.6% (n=18) of patients receiving placebo.

Table 1 lists the adverse events, regardless of causality, that were reported in the randomized, double-blind, placebo-controlled 12-week study at an incidence greater than placebo and in greater than or equal to 1% of patients treated with DETRUSITOL® SR 4 mg once daily.

Table 1. Incidence* (%) of Adverse Events Exceeding Placebo Rate and Reported in ≥1% of Patients Treated with DETRUSITOL® SR (4 mg daily) in a 12-week, Phase 3 Clinical Trial

Body System	Adverse Event	% DETRUSITOL® SR n=505	% Placebo n=507
Autonomic Nervous	dry mouth	23	8
General	headache	6	5
	fatigue	2	1
Central/Peripheral Nervous	dizziness	2	1
Gastrointestinal	constipation	6	4
	abdominal pain	4	2
	dyspepsia	3	1
Vision	xerophthalmia	3	2
	vision abnormal	1	0
Psychiatric	somnolence	3	2
	anxiety	1	0
Respiratory	sinusitis	2	1
Urinary	dysuria	1	0

* in nearest integer.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Similar percentages of patients treated with DETRUSITOL® SR or placebo discontinued treatment due to adverse events. Dry mouth was the most common adverse event leading to treatment discontinuation among patients receiving DETRUSITOL® SR [n=12 (2.4%) vs. placebo n=6 (1.2%)].

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

5.2 Post-marketing Experience

The following events have been reported in association with tolterodine use in worldwide post-marketing experience:

General: anaphylaxis and angioedema; *Cardiovascular:* tachycardia, palpitations, peripheral edema; *Gastrointestinal:* diarrhea; *Central/Peripheral Nervous:* confusion, disorientation, memory impairment, hallucinations.

Reports 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.

Because these spontaneously reported events are from the worldwide post-marketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

6 DRUG INTERACTIONS

6.1 Potent CYP2D6 Inhibitors

Fluoxetine, a potent inhibitor of CYP2D6 activity, significantly inhibited the metabolism of tolterodine immediate release in CYP2D6 extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in C_{max} and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT), the pharmacologically active metabolite of tolterodine *[see **CLINICAL PHARMACOLOGY** (10.1)]*. The sums of unbound serum concentrations of tolterodine and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered *[see **CLINICAL PHARMACOLOGY** (10.3)]*.

6.2 Potent CYP3A4 Inhibitors

Ketoconazole (200 mg daily), a potent CYP3A4 inhibitor, increased the mean C_{max} and AUC of tolterodine by 2- and 2.5-fold, respectively, in CYP2D6 poor metabolizers.

For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as itraconazole, clarithromycin, or ritonavir, the recommended dose of DETRUSITOL® SR is 2 mg once daily *[see **DOSAGE AND ADMINISTRATION**(2) and **CLINICAL PHARMACOLOGY** (10.3)]*.

6.3 Other Interactions

No clinically relevant interactions have been observed when tolterodine was co-administered with warfarin, with a combined oral contraceptive drug containing ethinyl estradiol and levonorgestrel, or with diuretics *[see **CLINICAL PHARMACOLOGY** (10.3)]*.

6.4 Other Drugs Metabolized by Cytochrome P450 Isoenzymes

In vivo drug-interaction data show that tolterodine immediate release does not result in clinically relevant inhibition of CYP1A2, 2D6, 2C9, 2C19, or 3A4 as evidenced by lack of influence on the marker drugs caffeine, debrisoquine, S-warfarin, and omeprazole *[see **CLINICAL PHARMACOLOGY** (10.3)]*.

6.5 Drug-Laboratory-Test Interactions

Interactions between tolterodine and laboratory tests have not been studied.

6.6 Other Anticholinergics

The concomitant use DETRUSITOL® SR with other anticholinergic (antimuscarinic) agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision, somnolence, and other anticholinergic pharmacological effects.

7 USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Risk Summary

There are no available data with DETRUSITOL® SR use in pregnant women to inform drug-associated risks. In animal reproduction studies, oral administration of tolterodine and its 5-HMT metabolite to pregnant mice during organogenesis did not produce adverse developmental outcomes at doses approximately 9 to 12 times the clinical exposure at a dose of 20 mg/kg/day; however, higher doses produced adverse developmental outcomes *(see Data)*.

In the U.S. general population, the estimated background rate of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

No anomalies or malformations were observed after oral administration of tolterodine to pregnant mice during organogenesis at approximately 9-12 times the clinical exposure to the pharmacologically active components of DETRUSITOL® SR (based on the AUC of tolterodine and its 5-HMT metabolite at a dose of 20 mg/kg/day). At 14-18 times the clinical exposure (doses of 30 to 40 mg/kg/day) in mice, tolterodine was embryo-lethal, caused reduced fetal weight, and increased the incidence of fetal abnormalities (cleft palate, digital abnormalities, intra-abdominal hemorrhage, and various skeletal abnormalities, primarily reduced ossification). Pregnant rabbits administered tolterodine subcutaneously at about 0.3-2.5 times the clinical exposure (dose of 0.8 mg/kg/day) did not show any embryotoxicity or teratogenicity.

7.2 Lactation

Risk Summary

There is no information on the presence of tolterodine or its 5-HMT metabolite in human milk, the effects on the breastfed infant, or the effects on milk production. Based on limited data, tolterodine is excreted into the milk in mice in low amounts *(see Data)*. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for DETRUSITOL® SR and any potential adverse effects on the breastfed infant from DETRUSITOL® SR or from the underlying maternal condition.

Animal Data

The use of radiolabeled tolterodine in pregnant mice produced milk: plasma ratios that ranged between 0.0 and 0.7.

7.3 Pediatric Use

The effectiveness of DETRUSITOL® SR has not been established in pediatric patients.

Efficacy was not established in two randomized, placebo-controlled, double-blind, 12-week studies that enrolled 710 pediatric patients (486 on DETRUSITOL® SR, 224 on placebo) aged 5–10 years with urinary frequency and urge incontinence. The percentage of patients with urinary tract infections was higher in patients treated with DETRUSITOL® SR (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 DETRUSITOL ®SR compared to 0.9% of children treated with placebo.

7.4 Geriatric Use

No overall differences in safety were observed between the older and younger patients treated with tolterodine.

In multiple-dose studies in which tolterodine immediate release 4 mg (2 mg bid) was administered, serum concentrations of tolterodine and of 5-HMT were similar in healthy elderly volunteers (aged 64 through 80 years) and healthy young volunteers (aged less than 40 years). In another clinical study, elderly volunteers (aged

71 through 81 years) were given tolterodine immediate release 2 or 4 mg (1 or 2 mg bid). Mean serum concentrations of tolterodine and 5-HMT in these elderly volunteers were approximately 20% and 50% higher, respectively, than concentrations reported in young healthy volunteers. However, no overall differences were observed in safety between older and younger patients on tolterodine in the Phase 3, 12-week, controlled clinical studies; therefore, no tolterodine dosage adjustment for elderly patients is recommended.

7.5 Renal Impairment

Renal impairment can significantly alter the disposition of tolterodine immediate release and its metabolites. In a study conducted in patients with creatinine clearance between 10 and 30 mL/min, tolterodine and 5-HMT levels were approximately 2–3 fold higher in patients with renal impairment than in healthy volunteers. Exposure levels of other metabolites of tolterodine (e.g., tolterodine acid, *N*-dealkylated tolterodine acid, *N*-dealkylated tolterodine, and *N*-dealkylated hydroxy tolterodine) were significantly higher (10–30 fold) in renally impaired patients as compared to the healthy volunteers. The recommended dose for patients with severe renal impairment (CCr: 10-30 mL/min) is DETRUSITOL® SR 2 mg daily. Patients with CCr<10 mL/min have not been studied and use of DETRUSITOL® SR in this population is not recommended *[see **DOSAGE AND ADMINISTRATION** (2)* and ***WARNINGS AND PRECAUTIONS** (4.7)]*. DETRUSITOL® SR has not been studied in patients with mild to moderate renal impairment [CCr 30-80 mL/min].

7.6 Hepatic Impairment

Liver impairment can significantly alter the disposition of tolterodine immediate release. In a study of tolterodine immediate release conducted in cirrhotic patients (Child-Pugh Class A and B), the elimination half-life of tolterodine immediate release was longer in cirrhotic patients (mean, 7.8 hours) than in healthy, young, and elderly volunteers (mean, 2 to 4 hours). The clearance of orally administered tolterodine immediate release was substantially lower in cirrhotic patients (1.0 ± 1.7 L/h/kg) than in the healthy volunteers (5.7 ± 3.8 L/h/kg). The recommended dose for patients with mild to moderate hepatic impairment (Child-Pugh Class A or B) is DETRUSITOL® SR 2 mg once daily. DETRUSITOL® SR is not recommended for use in patients with severe hepatic impairment (Child-Pugh Class C) *[see **DOSAGE AND ADMINISTRATION** (2)* and ***WARNINGS AND PRECAUTIONS** (4.6)]*.

8 OVERDOSAGE

Overdosage with DETRUSITOL® Capsules can potentially result in severe central anticholinergic effects and should be treated accordingly.

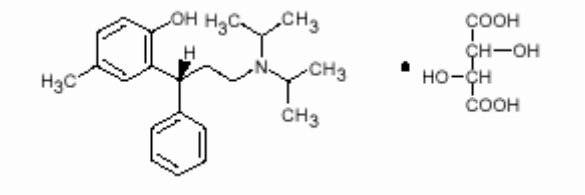
ECG monitoring is recommended in the event of overdosage. In dogs, changes in the QT interval (slight prolongation of 10% to 20%) were observed at a suprapharmacologic dose of 4.5 mg/kg, which is about 68 times higher than the recommended human dose. In clinical trials of normal volunteers and patients, QT interval prolongation was observed with tolterodine immediate release at doses up to 8 mg (4 mg bid) and higher doses were not evaluated *[see **WARNINGS AND PRECAUTIONS** (4.9) and **CLINICAL PHARMACOLOGY** (10.2)]*.

A 27-month-old child who ingested 5 to 7 tolterodine immediate release 2 mg tablets was treated with a suspension of activated charcoal and was hospitalized overnight with symptoms of dry mouth. The child fully recovered.

9 DESCRIPTION

DETRUSITOL® SR Capsules contain tolterodine tartrate. The active moiety, tolterodine, is a muscarinic

receptor antagonist. The chemical name of tolterodine tartrate is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate. The empirical formula of tolterodine tartrate is $C_{26}H_{37}NO_{7,}$. Its structure is:



Tolterodine tartrate is a white, crystalline powder with a molecular weight of 475.6. The pK_a value is 9.87 and the solubility in water is 12 mg/mL. It is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene. The partition coefficient (Log D) between n-octanol and water is 1.83 at pH 7.3.

DETRUSITOL® SR 4 mg capsule for oral administration contains 4 mg of tolterodine tartrate. Inactive ingredients are sugar spheres, ethylcellulose, medium chain triglycerides, oleic acid , ammonium hydroxide, purified water, hydroxypropyl methylcellulose, , , , gelatin, titanium dioxide and FD&C Blue #2.

DETRUSITOL® SR 2 mg capsule for oral administration contains 2 mg of tolterodine tartrate, and the following inactive ingredients: sugar spheres, ethylcellulose, medium chain triglycerides, oleic acid , ammonium hydroxide, purified water, hydroxypropyl methylcellulose, gelatin, yellow iron oxide, titanium dioxide and FD&C Blue #2.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Tolterodine acts as a competitive antagonist of acetylcholine at postganglionic muscarinic receptors. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors.

After oral administration, tolterodine is metabolized in the liver, resulting in the formation of 5-hydroxymethyl tolterodine (5-HMT), the major pharmacologically active metabolite. 5-HMT, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and 5-HMT exhibit a high specificity for muscarinic receptors, since both show negligible activity or affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels.

10.2 Pharmacodynamics

Tolterodine has a pronounced effect on bladder function. Effects on urodynamic parameters before and 1 and 5 hours after a single 6.4 mg dose of tolterodine immediate release were determined in healthy volunteers. The main effects of tolterodine at 1 and 5 hours were an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure. These findings are consistent with an antimuscarinic action on the lower urinary tract.

Cardiac Electrophysiology

The effect of 2 mg BID and 4 mg BID of DETRUSITOL® 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. Study subjects [approximately equal representation of CYP2D6 extensive metabolizers (EMs) and poor metabolizers (PMs)] completed sequential 4-day periods of dosing with moxifloxacin 400 mg QD, tolterodine 2 mg BID, tolterodine

4 mg BID, and placebo. 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 coadministration of tolterodine 2 mg BID with potent CYP3A4 inhibitors in patients who are CYP2D6 poor metabolizers *[see **DRUG INTERACTIONS** (6.2)]*. QT interval was measured over a 12-hour period following dosing, including the time of peak plasma concentration (T_{max}) of tolterodine and at steady state (Day 4 of dosing).

Table 2 summarizes the mean change from baseline to steady state in corrected QT interval (QT_c) relative to placebo at the time of peak tolterodine (1 hour) and moxifloxacin (2 hour) concentrations. Both Fridericia's (QT_cF) and a population-specific (QT_cP) method were used to correct QT interval for heart rate. No single QT correction method is known to be more valid than others. QT interval was measured manually and by machine, and data from both are presented. The mean increase of heart rate associated with a 4 mg/day dose of tolterodine in this study was 2.0 beats/minute and 6.3 beats/minute with 8 mg/day tolterodine. The change in heart rate with moxifloxacin was 0.5 beats/minute.

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

Drug/Dose	N	QT_cF (msec) (manual)	QT_cF (msec) (machine)	QT_cP (msec) (manual)	QT_cP (msec) (machine)
Tolterodine 2 mg BID*	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*	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 †	45	19.26‡ (15.49, 23.03)	8.90 (4.77, 13.03)	19.10‡ (15.32, 22.89)	9.29 (5.34, 13.24)

*At T_{max} of 1 hr; 95% Confidence Interval.
†At T_{max} of 2 hr; 90% Confidence Interval.
‡The effect on QT interval with 4 days of moxifloxacin dosing in this QT trial may be greater than typically observed in QT trials of other drugs.

The reason for the difference between machine and manual read of QT interval is unclear.

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. However, the confidence intervals overlapped.

Tolterodine's effect on QT interval was found to correlate with plasma concentration of tolterodine. There appeared to be a greater QT_c interval increase in CYP2D6 poor metabolizers than in CYP2D6 extensive metabolizers after tolterodine treatment in this study.

This study was not designed to make direct statistical comparisons between drugs or dose levels. There has been no association of Torsade de Pointes in the international post-marketing experience with DETRUSITOL® or DETRUSITOL® SR *[*see ***WARNINGS AND PRECAUTIONS** (4.9)]*.

10.3 Pharmacokinetics

Absorption: In a study with ^{14}C-tolterodine solution in healthy volunteers who received a 5 mg oral dose, at least 77% of the radiolabeled dose was absorbed. C_{max} and area under the concentration-time curve (AUC)

determined after dosage of tolterodine immediate release are dose-proportional over the range of 1 to 4 mg. Based on the sum of unbound serum concentrations of tolterodine and 5-HMT ("active moiety"), the AUC of tolterodine extended release 4 mg daily is equivalent to tolterodine immediate release 4 mg (2 mg bid). C_{max} and C_{min} levels of tolterodine extended release are about 75% and 150% of tolterodine immediate release, respectively. Maximum serum concentrations of tolterodine extended release are observed 2 to 6 hours after dose administration.

Effect of Food: There is no effect of food on the pharmacokinetics of tolterodine extended release.

Distribution: Tolterodine is highly bound to plasma proteins, primarily α_1-acid glycoprotein. Unbound concentrations of tolterodine average 3.7% ± 0.13% over the concentration range achieved in clinical studies. 5-HMT is not extensively protein bound, with unbound fraction concentrations averaging 36% ± 4.0%. The blood to serum ratio of tolterodine and 5-HMT averages 0.6 and 0.8, respectively, indicating that these compounds do not distribute extensively into erythrocytes. The volume of distribution of tolterodine following administration of a 1.28 mg intravenous dose is 113 ± 26.7 L.

Metabolism: Tolterodine is extensively metabolized by the liver following oral dosing. The primary metabolic route involves the oxidation of the 5-methyl group and is mediated by the cytochrome P450 2D6 (CYP2D6) and leads to the formation of a pharmacologically active metabolite, 5-HMT. Further metabolism leads to formation of the 5-carboxylic acid and *N*-dealkylated 5-carboxylic acid metabolites, which account for 51% ± 14% and 29% ± 6.3% of the metabolites recovered in the urine, respectively.

Variability in Metabolism: A subset of individuals (approximately 7% of Caucasians and approximately 2% of African Americans) are poor metabolizers for CYP2D6, the enzyme responsible for the formation of 5-HMT from tolterodine. The identified pathway of metabolism for these individuals ("poor metabolizers") is dealkylation via cytochrome P450 3A4 (CYP3A4) to *N*-dealkylated tolterodine. The remainder of the population is referred to as "extensive metabolizers." Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of 5-HMT.

Excretion: Following administration of a 5 mg oral dose of ^{14}C-tolterodine solution to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces in 7 days. Less than 1% (< 2.5% in poor metabolizers) of the dose was recovered as intact tolterodine, and 5% to 14% (<1% in poor metabolizers) was recovered as 5-HMT.

A summary of mean (± standard deviation) pharmacokinetic parameters of tolterodine extended release and 5-HMT in extensive (EM) and poor (PM) metabolizers is provided in Table 3. These data were obtained following single and multiple doses of tolterodine extended release administered daily to 17 healthy male volunteers (13 EM, 4 PM).

Table 3. Summary of Mean (±SD) Pharmacokinetic Parameters of Tolterodine Extended Release and its Active Metabolite (5-Hydroxymethyl Tolterodine) in Healthy Volunteers

	Tolterodine				5-Hydroxymethyl Tolterodine			
	t_{max}* (h)	C_{max} (µg/L)	C_{avg} (µg/L)	$t_{½}$ (h)	t_{max}* (h)	C_{max} (µg/L)	C_{avg} (µg/L)	$t_{½}$ (h)
Single dose 4 mg†								
EM	4(2–6)	1.3(0.8)	0.8(0.57)	8.4(3.2)	4(3–6)	1.6(0.5)	1.0(0.32)	8.8(5.9)
Multiple dose 4 mg								
EM	4(2–6)	3.4(4.9)	1.7(2.8)	6.9(3.5)	4(2–6)	2.7(0.90)	1.4(0.6)	9.9(4.0)
PM	4(3–6)	19(16)	13(11)	18(16)	‡	‡	‡	‡

C_{max} = Maximum serum concentration; t_{max} = Time of occurrence of C_{max};
C_{avg} = Average serum concentration; $t_{1/2}$ = Terminal elimination half-life.
*Data presented as median (range).
†Parameter dose-normalized from 8 to 4 mg for the single-dose data.
‡ = not applicable.

Drug Interactions:

Potent CYP2D6 inhibitors: Fluoxetine is a selective serotonin reuptake inhibitor and a potent inhibitor of CYP2D6 activity. In a study to assess the effect of fluoxetine on the pharmacokinetics of tolterodine immediate release and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine immediate release in extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. There was a 52% decrease in C_{max} and a 20% decrease in AUC of 5-hydroxymethyl tolterodine (5-HMT, the pharmacologically active metabolite of tolterodine). Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be CYP2D6 extensive metabolizers of tolterodine immediate release to resemble the pharmacokinetic profile in poor metabolizers. The sums of unbound serum concentrations of tolterodine immediate release and 5-HMT are only 25% higher during the interaction. No dose adjustment is required when tolterodine and fluoxetine are co-administered.

Potent CYP3A4 inhibitors: The effect of a 200 mg daily dose of ketoconazole on the pharmacokinetics of tolterodine immediate release was studied in 8 healthy volunteers, all of whom were CYP2D6 poor metabolizers. In the presence of ketoconazole, the mean C_{max} and AUC of tolterodine increased by 2- and 2.5-fold, respectively. Based on these findings, other potent CYP3A4 inhibitors may also lead to increases of tolterodine plasma concentrations.

For patients receiving ketoconazole or other potent CYP3A4 inhibitors such as itraconazole, miconazole, clarithromycin, ritonavir, the recommended dose of DETRUSITOL® SR is 2 mg daily *[see **DOSAGE AND ADMINISTRATION**(2)]*.

Warfarin: In healthy volunteers, coadministration of tolterodine immediate release 4 mg (2 mg bid) for 7 days and a single dose of warfarin 25 mg on day 4 had no effect on prothrombin time, Factor VII suppression, or on the pharmacokinetics of warfarin.

Oral Contraceptives**:** Tolterodine immediate release 4 mg (2 mg bid) had no effect on the pharmacokinetics of an oral contraceptive (ethinyl estradiol 30 µg/levo-norgestrel 150 µg) as evidenced by the monitoring of ethinyl estradiol and levo-norgestrel over a 2-month period in healthy female volunteers.

Diuretics: Coadministration of tolterodine immediate release up to 8 mg (4 mg bid) for up to 12 weeks with diuretic agents, such as indapamide, hydrochlorothiazide, triamterene, bendroflumethiazide, chlorothiazide, methylchlorothiazide, or furosemide, did not cause any adverse electrocardiographic (ECG) effects.

Effect of tolterodine on other drugs metabolized by Cytochrome P450 enzymes: Tolterodine immediate release does not cause clinically significant interactions with other drugs metabolized by the major drug-metabolizing CYP enzymes. *In vivo* drug-interaction data show that tolterodine immediate release does not result in clinically relevant inhibition of CYP1A2, 2D6, 2C9, 2C19, or 3A4 as evidenced by lack of influence on the marker drugs caffeine, debrisoquine, S-warfarin, and omeprazole. *In vitro* data show that tolterodine immediate release is a competitive inhibitor of CYP2D6 at high concentrations (K_i 1.05 µM), while tolterodine immediate release as well as the 5-HMT are devoid of any significant inhibitory potential regarding the other isoenzymes.

11 NONCLINICAL TOXICOLOGY

11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with tolterodine were conducted in mice and rats. At the maximum tolerated dose in mice (30 mg/kg/day), female rats (20 mg/kg/day), and male rats (30 mg/kg/day), exposure margins were approximately 6-9 times, 7 times, and 11 times the clinical exposure to the pharmacologically active components of DETRUSITOL® SR (based on AUC of tolterodine and its 5-HMT metabolite). At these exposure margins, no increase in tumors was found in either mice or rats.

No mutagenic or genotoxic effects of tolterodine were detected in a battery of *in vitro* tests, including bacterial mutation assays (Ames test) in 4 strains of *Salmonella typhimurium* and in 2 strains of *Escherichia coli,* a gene mutation assay in L5178Y mouse lymphoma cells, and chromosomal aberration tests in human lymphocytes. Tolterodine was also negative *in vivo* in the bone marrow micronucleus test in the mouse.

In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (about 9-12 times the clinical exposure via AUC), neither effects on reproductive performance or fertility were seen. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

12 CLINICAL STUDIES

DETRUSITOL® SR Capsules 2 mg were evaluated in 29 patients in a Phase 2 dose-effect study. DETRUSITOL® SR 4 mg was evaluated for the treatment of overactive bladder with symptoms of urge urinary incontinence and frequency in a randomized, placebo-controlled, multicenter, double-blind, Phase 3, 12-week study. A total of 507 patients received DETROL LA 4 mg once daily in the morning and 508 received placebo. The majority of patients were Caucasian (95%) and female (81%), with a mean age of 61 years (range, 20 to 93 years). In the study, 642 patients (42%) were 65 to 93 years of age. The study included patients known to be responsive to tolterodine immediate release and other anticholinergic medications, however, 47% of patients never received prior pharmacotherapy for overactive bladder. At study entry, 97% of patients had at least 5 urge incontinence episodes per week and 91% of patients had 8 or more micturitions per day.

The primary efficacy assessment was change in mean number of incontinence episodes per week at week 12 from baseline. Secondary efficacy measures included change in mean number of micturitions per day and mean volume voided per micturition at week 12 from baseline.

Patients treated with DETRUSITOL ®SR experienced a statistically significant decrease in number of urinary incontinence per week from baseline to last assessment (week 12) compared with placebo as well as a decrease in the average daily urinary frequency and an increase in the average urine volume per void.

Mean change from baseline in weekly incontinence episodes, urinary frequency, and volume voided between placebo and DETRUSITOL® SR are summarized in Table 4.

Table 4. 95% Confidence Intervals (CI) for the Difference between DETRUSITOL® SR (4 mg daily) and Placebo for Mean Change at Week 12 from Baseline*

	DETRUSITOL® SR (n=507)	Placebo (n=508)†	Treatment Difference, vs. Placebo (95% CI)
Number of incontinence episodes/ week Mean Baseline Mean Change from Baseline	22.1 –11.8 (SD 17.8)	23.3 –6.9 (SD 15.4)	-4.8‡ (–6.9, –2.8)
Number of micturitions/day Mean Baseline Mean Change from Baseline	10.9 –1.8 (SD 3.4)	11.3 –1.2 (SD 2.9)	-0.6‡ (–1.0, –0.2)
Volume voided per micturition (mL) Mean Baseline Mean Change from Baseline	141 34 (SD 51)	136 14 (SD 41)	20‡ (14, 26)

SD = Standard Deviation.

* Intent-to-treat analysis.

† 1 to 2 patients missing in placebo group for each efficacy parameter.

‡ The difference between DETRUSITOL® SR and placebo was statistically significant.

13. HOW SUPPLIED/STORAGE AND HANDLING

DETRUSITOL® SR Capsules are supplied as follows:

Carton with PVC-/PVDC/-Aluminum foil blisters containing 28 tablets.

DETRUSITOL® Capsules 2 mg are blue-green with symbol printed in white ink.

DETRUSITOL® Capsules 4 mg are blue with symbol printed in white ink.

Store below 25°C.

The expiry date of the product is indicated on the packaging materials.

14. MANUFACTURER:

Pfizer Italia S.R.L, Ascoli Piceno, Italy.

15 . LICENSE MARKETING HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd. 9 Shenkar St., Herzliya Pituach, 46725 Israel

16.LICENSE NUMBER

Detrusitol ®SR 2mg: 125-56-30466
Detrusitol ®SR 4mg: 125-55-30467

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