PRODUCT MONOGRAPH

[Pr]TEVA-TOLTERODINE

(tolterodine L-tartrate)

1 mg and 2 mg Tablets

Anticholinergic - Antispasmodic Agent

Teva Canada Limited
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Toronto, Ontario
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[Pr]TEVA-TOLTERODINE

(tolterodine L-tartrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablets / 1 mg, 2 mg	Calcium Phosphate Dibasic Dihydrate, Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polyvinyl Alcohol-Partially Hydrolyzed, Sodium Starch Glycolate, Talc and Titanium Dioxide

INDICATIONS AND CLINICAL USE

TEVA-TOLTERODINE (tolterodine L-tartrate) is indicated for:

- the symptomatic management of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms (see **WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY, Electrophysiology**).

Geriatrics (≥ 65 years of age): No overall differences were observed in safety between older (patients ≥ 65 years) and younger patients (patients < 65 years) on tolterodine immediate release tablets; and therefore, no dosage adjustment for elderly patients is recommended (see **WARNINGS AND PRECAUTIONS, Special Populations, DETAILED PHARMACOLOGY and CLINICAL TRIALS**).

CONTRAINDICATIONS

TEVA-TOLTERODINE (tolterodine L-tartrate) is contraindicated in patients with:

- urinary retention,
- gastric retention,
- uncontrolled narrow angle glaucoma,
- a known hypersensitivity to this drug or to any ingredient in the formulation or component of the container (see **PHARMACEUTICAL INFORMATION**).

WARNINGS AND PRECAUTIONS

Gastrointestinal and Genitourinary

Patients at Risk of Urinary Retention and Gastric Retention
TEVA-TOLTERODINE (tolterodine L-tartrate) should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention, to patients at risk of decreased gastrointestinal motility, and to patients with gastrointestinal obstructive disorders, such as pyloric stenosis, because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Cardiovascular

Patients with Congenital or Acquired QT Prolongation:
In a clinical QT study, the QT prolonging effect of two times the highest labeled dose of tolterodine (8 mg/per day in divided doses, given as tolterodine L-tartrate immediate release tablets) was 50% to 60% less than that of the active control moxifloxacin (400 mg) at its labeled dose. At the recommended therapeutic dose (4 mg daily) of tolterodine L-tartrate, the effect was lower.

The clinical relevance of these findings will depend on individual patient risk factors and susceptibilities present. Particular care should be exercised in patients who are at an increased risk of experiencing torsade de pointes during treatment with QT/QTc-prolonging drugs. This especially holds true in patients with abnormally long baseline QT/QTc intervals or when taking potent CYP3A4 inhibitors (see **DRUG INTERACTIONS, Drug-Drug Interactions, DOSAGE AND ADMINISTRATION, DETAILED PHARMACOLOGY, Electrophysiology**).

In the general population, the risk factors for torsade de pointes include, but are not limited to, the following:

- female;
- elderly (65 years);
- genetic variants affecting cardiac ion channels or regulatory proteins, especially congenital long QT syndrome;
- family history of sudden cardiac death at <50 years;
- cardiac disease (e.g., myocardial ischemia or infarction, congestive heart failure, left ventricular hypertrophy, cardiomyopathy);
- demonstrated history of arrhythmias (especially ventricular arrhythmias, atrial fibrillation, or recent conversion from atrial fibrillation);
- bradycardia (<50 beats per minute);
- acute neurological events (e.g., intracranial or subarachnoid haemorrhage, stroke, intracranial trauma;
- electrolyte disturbances (e.g., hypokalemia, hypomagnesemia, hypocalcemia);
- nutritional deficits (e.g., eating disorders, extreme diets);

- diabetes mellitus;
- autonomic neuropathy;
- hepatic or renal dysfunction if relevant to the elimination of the drug.

Approximately 7% of Caucasians are poor metabolizers of CYP2D6 substrates. A pharmacokinetic/pharmacodynamic model estimated that QTc interval increases in poor metabolizers treated with tolterodine 2 mg BID are comparable to those observed in extensive metabolizers receiving 4 mg BID.

Discontinuation of the drug should be considered if symptoms suggestive of arrhythmia occur.

Aggravation with Pre-existing Cardiac Conditions
Although there are no clinical trial or post-marketing data to confirm the potential for tolterodine L-tartrate to aggravate certain pre-existing cardiac conditions, this product is in the class anticholinergic medications which are known to have cardiac effects. Prescribers should therefore use caution when prescribing TEVA-TOLTERODINE to patients with ischemic heart disease, congestive heart failure, cardiac arrhythmias, or tachycardia.

Neurologic
TEVA-TOLTERODINE should be used with caution in patients with myasthenia gravis.

Ophthalmologic

Controlled Narrow Angle Glaucoma:
TEVA-TOLTERODINE should be used with caution in patients being treated for narrow angle glaucoma.

Hepatic/Biliary/Pancreatic/Renal

Patients with impaired hepatic function and patients with renal impairment should not receive doses of TEVA-TOLTERODINE greater than 1 mg, twice daily (see **DETAILED PHARMACOLOGY, Pharmacokinetics in Special Populations).**

Special Populations

Pregnant Women: Studies in mice have shown that at doses of 30 to 40 mg/kg/day, tolterodine caused embryolethality, reduced fetal weight, and increased incidence of fetal abnormalities (cleft palate, digital abnormalities, intraabdominal hemorrhage, various skeletal abnormalities, primarily reduced ossification in mice). At these doses, AUC values were about 20- to 25-fold higher than in humans. At doses of 20 mg/kg/day (AUC value was about 15-fold higher than in humans), no anomalies or malformations were seen in mice. There are no studies of tolterodine in pregnant women. Therefore, TEVA-TOLTERODINE (tolterodine L-tartrate) should be used during pregnancy only if the potential benefit for the mother justifies the potential risk for the fetus. Women of childbearing potential should be considered for treatment only if using adequate contraception (see **TOXICOLOGY**).

Nursing Women: Tolterodine is excreted into the milk in mice. It is not known whether tolterodine is excreted in human milk. Because many drugs are excreted into human milk, administration of TEVA-TOLTERODINE should be avoided during nursing.

Pediatrics: The safety and effectiveness of tolterodine L-tartrate in pediatric patients have not been established.

Geriatrics (65 - 91 years of age): Of the 1120 patients who were treated in the four, phase III, 12-week clinical studies of tolterodine L-tartrate, 474 (42%) were 65 to 91 years of age. No overall differences in safety were observed between the older and younger patients (see **DETAILED PHARMACOLOGY, Pharmacokinetics in Special Populations**).

Monitoring and Laboratory Tests

Monitoring of the QT/QTc interval and/or serum electrolyte levels may be appropriate in high risk patients who are being treated with TEVA-TOLTERODINE, such as:

- patients with known congenital or acquired QT/QTc prolongation or electrolyte disturbances;
- patients with impaired hepatic or renal function or other comorbid conditions that may increase tolterodine exposure or cause QT/QTc prolongation;
- patients who are taking drugs that have been associated with QT/QTc prolongation and/or torsade de pointes such as Class IA (e.g. quinidine, procainamide or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or those taking potent CYP3A4 inhibitors.

(see **WARNINGS AND PRECAUTIONS, Cardiovascular, DRUG INTERACTIONS, Drug-Drug Interactions, DOSAGE AND ADMINISTRATION, DETAILED PHARMACOLOGY, Electrophysiology**).

Discontinuation of the drug should be considered if symptoms suggestive of arrhythmia occur or if the QT/QTc interval becomes markedly prolonged.

Information for Patients

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The clinical trial program for tolterodine L-tartrate comprised 2398 patients who were treated with either tolterodine L-tartrate (N= 1619), oxybutynin (N=349), or placebo (N=430). No differences in the safety profile of tolterodine were identified based on age, gender, race, or metabolism.

A total of 1120 patients were treated in four, phase III, 12-week, controlled clinical studies with either tolterodine L-tartrate, 2 mg twice daily (N=474), tolterodine L-tartrate 1 mg twice daily (N=121), oxybutynin 5 mg three times daily (N=349), or placebo (N=176). The percentage of patients reporting any adverse event in the 12-week studies was similar for tolterodine L-tartrate 2 mg twice daily (75.5%), tolterodine L-tartrate 1 mg twice daily (74.4%), and placebo (77.8%). The overall incidence rates for these treatment groups were lower than that reported for oxybutynin 5 mg three times daily (93.1%); these rates were significantly less for tolterodine L-tartrate 2 mg and placebo compared with oxybutynin (P<0.0001). The incidence of serious adverse events was similar among treatment groups (tolterodine L-tartrate 1 and 2 mg twice daily, 3.7%; oxybutynin 5 mg three times daily, 3.7%; placebo, 3.4%).

Dry mouth was the most frequently reported adverse event across all treatment groups. However, the incidence was significantly less for patients treated with either dose of tolterodine L-tartrate or placebo compared with oxybutynin 5 mg three times daily (P=0.001). Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and xerophthalmia are all expected side effects of antimuscarinic agents.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The following table lists all adverse events that occurred in ≥5% of patients in either of the tolterodine treatment groups in the 12-week studies.

Incidence of Adverse Events that Occurred in ≥5% Tolterodine-Treated Patients (1 or 2 mg b.i.d.) In the 12-Week Controlled Clinical Studies

		Placebo		**Tolterodine 1 mg b.i.d.**		**Tolterodine 2 mg b.i.d.**		**Oxybutynin 5 mg t.i.d.**	
	Number treated	176		121		474		349	
	Reported AE n(%)	137	(77.8)	90	(74.4)	358	(75.5)	325	(93.1)
Body System	Adverse Event	n	%	n	%	n	%	n	%
Autonomic	Mouth dry	28	(15.9)	29	(24.0)	187	(39.5)	273	(78.2)
Nerv	Palpitation	5	(2.8)	8	(6.6)	2	(0.4)	8	(2.3)
General	Headache	13	(7.4)	8	(6.6)	52	(11.0)	24	(6.9)
	Fatigue	13	(7.4)	9	(7.4)	32	(6.8)	16	(4.6)
Cent/peri nerv	Vertigo/dizziness	16	(9.1)	11	(9.1)	42	(8.9)	30	(8.6)
Gastro-intestin	Abdominal pain	11	(6.3)	7	(5.8)	36	(7.6)	22	(6.3)
	Constipation	8	(4.5)	7	(5.8)	31	(6.5)	33	(9.5)
	Dyspepsia	3	(1.7)	2	(1.7)	28	(5.9)	39	(11.2)
	Diarrhea	11	(6.3)	7	(5.8)	19	(4.0)	18	(5.2)
Respiratory	Upper resp tract infect	16	(9.1)	3	(2.5)	28	(5.9)	11	(3.2)
	Sinusitis	10	(5.7)	7	(5.8)	5	(1.1)	8	(2.3)
Urinary	Urinary tract infect	13	(7.4)	6	(5.0)	26	(5.5)	27	(7.7)

Other adverse events observed in patients during the 12-week clinical trials were chest pain (3.4%), somnolence (3.0%), dysuria (2.5%), bronchitis (2.1%), dry skin (1.7%), increased weight (1.3%), and flatulence (1.3%).

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Central and Peripheral Nervous System: confusion
Gastrointestinal: gastroesophageal reflux
Skin/Appendages: flushed skin, and allergic reactions

Post-Market Adverse Drug Reactions

The following events have been reported in association with tolterodine use in clinical practice: anaphylactoid reactions (including angioedema), tachycardia, palpitations, peripheral edema, hallucinations, disorientation, memory impairment, and diarrhea.

Cholinesterase Inhibitors: Worsening 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.

DRUG INTERACTIONS

Overview

Concomitant medication with other drugs that possess antimuscarinic properties may result in more pronounced therapeutic and/or adverse effects. Conversely, the therapeutic effect of tolterodine may be reduced by concomitant administration of muscarinic receptor agonists.

Drug-Drug Interactions

Effects of Other Drugs on TEVA-TOLTERODINE

Drugs Which Prolong the QT/QTc Interval:
Drugs that have been associated with QT/QTc interval prolongation and/or torsade de pointes include, but are not limited to, the examples in the following list. Chemical/pharmacological classes are listed if some, although not necessarily all, class members have been implicated in QT/QTc prolongation and/or torsade de pointes:

- Antiarrhythmics (Class IA, e.g., quinidine, procainamide, disopyramide; Class III, e.g., amiodarone, sotalol, ibutilide; Class IC, e.g., flecainide, propafenone);
- Antipsychotics (e.g., thioridazine, chlorpromazine, pimozide, haloperidol, droperidol);
- Antidepressants (e.g., amitriptyline, imipramine, maprotiline, fluoxetine, venlafaxine);
- Opioids (e.g., methadone);
- Antibacterials (eg., erythromycin, clarithromycin, telithromycin, moxifloxacin, gatifloxacin);

- Antimalarials (e.g., quinine);
- Pentamidine
- Azole antifungals (e.g., ketoconazole, fluconazole, voriconazole);
- Gastrointestinal drugs (e.g., domperidone, dolasetron, ondasetron);
- B_2-adrenoreceptor agonist (salmeterol, formoterol);
- Tacrolimus

This list of potentially interacting drugs is not comprehensive. Prior to initiating drug treatment in the presence of concomitant medications, physicians should consult current scientific literature for information on the ability of newly approved drugs to prolong the QT/QTc interval, inhibit the metabolizing enzyme or transporter, or cause electrolyte disturbances, as well for older drugs for which these effects have recently been established (see **WARNINGS AND PRECAUTIONS**).

Cytochrome P450 3A4 inhibitors: Patients treated with ketoconazole or other potent CYP3A4 inhibitors such as other azole antifungals (e.g., itraconazole, miconazole) or macrolide antibiotics (e.g., erythromycin, clarithromycin) or cyclosporine or vinblastine, should not receive doses of tolterodine L-tartrate greater than 1 mg twice daily (see **DETAILED PHARMACOLOGY, Drug Interactions**).

Fluoxetine: Fluoxetine, a potent inhibitor of P450 2D6, inhibits significantly the metabolism of tolterodine in extensive metabolizers. The sum of unbound serum concentrations of tolterodine and the 5-hydroxymethyl derivative (DD 01) is 25% higher when the two drugs are administered concomitantly. No dose adjustment is required (see **DETAILED PHARMACOLOGY, Drug Interactions**).

Effects of TEVA-TOLTERODINE on Other Drugs

Other Drugs Metabolized by P450 2D6: The potential effect of tolterodine on the pharmacokinetics of drugs that are metabolized by P450 2D6 (such as flecainide, vinblastine, carbamazepine, tricyclic antidepressants) has not been formally evaluated (see **DETAILED PHARMACOLOGY, Drug Interactions**).

Diuretics: Coadministration of diuretics (such as indapamide, hydrochlorothiazide, triamterene, bendroflumethiazide, chlorothiazide, methylchlorothiazide, or furosemide) with tolterodine L-tartrate (2 mg, twice daily) did not cause any adverse ECG effects, however, in the presence of diuretics causing hypokalemia, and, concomitant medications known or suspected to cause adverse ECG effects (such as QT/QTC prolongation), the physician is advised to exercise caution and advise the patient about the signs and symptoms of cardiac arrhythmia (see **DETAILED PHARMACOLOGY, Drug Interactions**).

Oral Contraceptives: Clinical drug interaction studies have shown that there are no known interactions between tolterodine and oral contraceptives (ethinyl estradiol/levonorgestrel) (see **DETAILED PHARMACOLOGY, Drug interactions**).

Warfarin: Clinical drug interaction studies have shown that there are no known interactions between tolterodine and warfarin (see **DETAILED PHARMACOLOGY, Drug Interactions**).

Drug-Food Interactions

Food intake does not result in clinically relevant changes in the pharmacokinetic profile (see **DETAILED PHARMACOLOGY**).

Drug-Herb Interactions

Interaction with herbal products has not been established.

Drug Laboratory Interactions

Interactions between tolterodine and laboratory tests have not been studied.

Patient Counseling
Patients should be informed that antimuscarinic agents such as TEVA-TOLTERODINE (tolterodine L-tartrate) may produce blurred vision or dizziness.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosing of TEVA-TOLTERODINE (tolterodine L-tartrate) may be affected by the following:
- individual response and tolerability
- impaired hepatic function and renal impairment
- potent CYP3A4 inhibitors

(see **WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).

Recommended Dose and Dosage Adjustment

The initial recommended dose of TEVA-TOLTERODINE (tolterodine L-tartrate) is 2 mg twice daily. The dose may be reduced to 1 mg twice daily based on individual response and tolerability. For patients with impaired hepatic function and patients with renal impairment, the recommended dose is 1 mg twice daily (see **WARNINGS AND PRECAUTIONS**). No dosage adjustment for elderly patients (≥ 65 years of age) is recommended (see **WARNINGS AND PRECAUTIONS, Special Populations and DETAILED PHARMACOLOGY**).

Patients treated with potent CYP3A4 inhibitors should **NOT** receive doses of TEVA-TOLTERODINE greater than 1 mg twice daily (see **WARNINGS AND PRECAUTIONS**).

The maximum recommended daily dose of 4 mg should not be exceeded.

Administration

Administration of TEVA-TOLTERODINE (tolterodine L-tartrate) at the recommended dosage, for a minimum of two weeks may be required before relief of overactive bladder can be expected/detected. Further improvement is seen after 8 weeks. TEVA-TOLTERODINE can be taken with food.

OVERDOSAGE

The highest dose of 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. One case of overdose has been reported prior to the marketing of tolterodine L-tartrate that involved a 27-month-old child who ingested 5 to 7 tablets of tolterodine L-tartrate 2 mg. He was hospitalized overnight with symptoms of dry mouth and was treated with a suspension of activated charcoal. The child recovered fully.

Management of Overdosage
Treatment of overdosage with TEVA-TOLTERODINE should consist of gastric lavage and activated charcoal. Treatments for symptoms are recommended as follows. For severe central anticholinergic effects (hallucinations, severe excitation), an anticholinesterase agent, such as physostigmine, may be used. If excitation and convulsions occur, administer an anticonvulsant, such as diazepam. Patients with respiratory insufficiency should be given respiratory assistance. If respiratory arrest occurs, patients should be given artificial respiration. Patients with tachycardia may be treated with a beta-blocker, and those with urinary retention may be catheterized. Patients with troublesome mydriasis may be placed in a dark room or treated with pilocarpine eye drops, or both. ECG should be monitored. In clinical trials of normal volunteers, QT interval prolongation was observed with tolterodine immediate release at doses of 8 mg (4 mg BID). The risk of torsade de pointes with a QT/QTc-prolonging drug is usually dose-dependent. It is recommended that continuous ECG monitoring may be appropriate in cases of overdose with TEVA-TOLTERODINE. Concomitant therapy should be immediately reviewed and stopped if potential for drug-drug interaction and exacerbation of the QT prolongation effect is possible (see **WARNINGS AND PRECAUTIONS, DRUG INTERACTIONS, Drug-Drug Interactions, DETAILED PHARMACOLOGY, Electrophysiology**).

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Tolterodine L-tartrate, is a competitive muscarinic receptor antagonist, which has been shown to inhibit carbachol-induced contraction of isolated bladder preparations from rats, guinea pigs, and man. Tolterodine L-tartrate (henceforth referred to as tolterodine) inhibits contractions of the detrusor muscle from the guinea pig, and electrically induced contractions of human detrusor muscle from stable and overactive bladders *ex vivo*. Tolterodine is significantly more active in

inhibiting acetylcholine-induced urinary bladder contractions than electrically induced salivation in the anesthetized cat.

Pharmacodynamics

Tolterodine has a pronounced effect on bladder function in healthy volunteers. The main effects following a 6.4 mg single dose of tolterodine were an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure. These findings are consistent with antimuscarinic action on the lower urinary tract.

In patients with an overactive bladder who received recommended therapeutic doses of tolterodine, urodynamic measurements have shown that tolterodine increased the volume at first contraction and maximum cystometric capacity.

Tolterodine is converted to a pharmacologically active 5-hydroxymethyl metabolite (DD 01) by the isozyme cytochrome P450 2D6 (debrisoquine hydroxylase). This metabolite exhibits an antimuscarinic profile similar to that of tolterodine, both *in vitro* and *in vivo*. In view of the antimuscarinic activity of DD 01 and pharmacokinetic data from both humans and animals, it has been concluded that this metabolite contributes significantly to the therapeutic effect in extensive metabolizers (see **Metabolism below, and DETAILED PHARMACOLOGY**).

Pharmacokinetics

Absorption: In a study of ^{14}C-tolterodine in healthy volunteers who received a 5 mg oral dose, at least 77% of the radiolabeled dose was absorbed. Tolterodine is rapidly absorbed, and maximum serum concentrations (C_{max}) typically occur within 1 to 2 hours after dose administration. The pharmacokinetics of tolterodine, based on C_{max} and area under the concentration-time curve (AUC) determinations, are dose-proportional over the range of 1 to 4 mg. Food intake does not result in clinically relevant changes in the pharmacokinetic profile (see **DETAILED PHARMACOLOGY**).

Metabolism: Tolterodine is extensively metabolized by the liver following oral dosing, and is converted to DD 01 by the isozyme cytochrome P450 2D6. 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 (see **DETAILED PHARMACOLOGY**).

The potential effect of tolterodine on the phannacokinetics of other drugs also metabolized by P450 2D6, such as tricyclic antidepressants, some antiarrhythmics and selective serotonin reuptake inhibitors, and neuroleptics has not been formally evaluated.

Variability in Metabolism: A subset (about 7%) of the population is devoid of the drug-metabolizing isoenzyme cytochrome P450 2D6, the enzyme responsible for the formation of DD 01. The identified pathway of metabolism for these individuals, referred to as “poor metabolizers” (PMs), is dealkylation via cytochrome P450 3A4 to N-dealkylated tolterodine.

The remainder of the population is referred to as "extensive metabolizers" (EMs). Since tolterodine and DD 01 have similar antimuscarinic effects, the net activity of tolterodine L-tartrate is expected to be similar in EMs and PMs (see **DETAILED PHARMACOLOGY).**

Distribution: Tolterodine is highly bound to plasma proteins, primarily α1-acid glycoprotein. Unbound concentrations of tolterodine average 3.7% ± 0.13% over the concentration range achieved in clinical studies. The 5-hydroxymethyl metabolite (DD 01) is not extensively protein bound, with unbound fraction concentrations averaging 36% ± 4.0%. The blood to serum ratio of tolterodine and DD 01 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.

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 in urine and feces as intact tolterodine; 5% to 14% (<1% in poor metabolizers) was recovered as DD 01 within the first 24 hours. This is consistent with the apparent half-life of tolterodine: 1.9 to 3.7 hours (see **DETAILED PHARMACOLOGY**).

Special Populations and Conditions

Age: No overall differences were observed in safety between older and younger patients on tolterodine in Phase III, 12 week, controlled clinical studies; and therefore, no dosage adjustment for elderly patients is recommended (see **DETAILED PHARMACOLOGY, Drug Interactions**).

Gender: There are no sex dependent differences in the pharmacokinetic profile of tolterodine or DD 01.

Race: Pharmacokinetic differences due to race have not been identified.

Hepatic Insufficiency: Subjects with hepatic cirrhosis exhibit higher serum concentrations and longer half-lives of tolterodine and DD 01 compared to young healthy subjects given the same dose (see **DETAILED PHARMACOLOGY, Drug Interactions**).

Renal Insufficiency: Potential pharmacologic effects and also the toxicological significance of metabolite levels should be taken into account if exposing subjects with renal impairment (GFR <30 mL/min) to repeated doses of tolterodine (see **DETAILED PHARMACOLOGY, Drug Interactions**).

STORAGE AND STABILITY

Store at controlled room temperature 15°C to 30°C. Keep the product in the original packaging.

SPECIAL HANDLING INSTRUCTIONS

Not applicable.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-TOLTERODINE (tolterodine L-tartrate) is available as:

1 mg tablet:	White, round, film-coated tablet, - engraved with "**93**" on one side and "**10**" on the other side. Blister packages of 30 tablets and bottles of 100 tablets.
2 mg tablet:	White, round, film-coated tablet, - engraved with "**93**" on one side and "**18**" on the other side. Blister packages of 30 tablets (3 sheets of 10 tablets) and bottles of 100 tablets.

Composition: TEVA-TOLTERODINE tablets contain 1 mg or 2 mg tolterodine L-tartrate and the following non-medicinal ingredients: Calcium Phosphate Dibasic Dihydrate, Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polyvinyl Alcohol-Partially Hydrolyzed, Sodium Starch Glycolate, Talc and Titanium Dioxide.

PART II SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

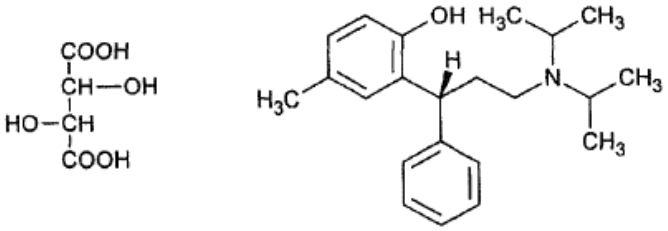
Drug substance

Common name: Tolterodine L-Tartrate

Chemical name(s): (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine-L-hydrogen tartrate

Molecular formula: $C_{22}H_{31}NOC_4H_6O_6$

Structural formula:



Molecular weight: 475.59 (anhydrous)

Physical form: White to creamy powder

Solubility: Tolterodine Tartrate dissolves in ethanol and water

pH: At 25°C in water:
3.48 at concentration of 12 mg/ml
3.69 at concentration of 1 mg/mL

pKa: 9.87

Melting point: 211 - 212°C

CLINICAL TRIALS

Study demographics and trial design

Tolterodine L-tartrate was evaluated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms in four, 12-week controlled studies. Two studies compared tolterodine L-tartrate 2 mg twice daily (N=227) with oxybutynin 5 mg three times daily (N=230) and placebo (N=113). A third study compared tolterodine L-tartrate 1 mg (N=123) and 2 mg (N=129) twice daily and placebo (N=64). The fourth study compared tolterodine L-tartrate 2 mg twice daily (N=120) and oxybutynin 5 mg three times daily (N=120). The primary efficacy end point in these studies was the mean number of micturitions per 24 hours; secondary end points were the mean number of incontinence episodes per 24 hours and the mean volume of urine voided per micturition.

Study results

After 12 weeks of treatment, tolterodine L-tartrate was shown to be significantly more effective than placebo in two (008, 009) of the three placebo-controlled studies in reducing the mean number of micturitions per 24 hours, and in all three placebo-controlled studies in increasing the mean volume voided per micturition. Patients treated with tolterodine L-tartrate tended to have a lower mean number of incontinence episodes per 24 hours than patients treated with placebo in all three placebo-controlled studies. Results of pooled analyses for these three studies also showed this. In the three active comparator studies, tolterodine L-tartrate and oxybutynin were equivalent in the reduction of mean number of micturitions per 24 hours and mean number of incontinence episodes per 24 hours. Significant improvement was seen after 2 weeks of treatment with tolterodine L-tartrate, with further improvement up to 8 weeks of treatment; this therapeutic effect was sustained for up to 12 months of treatment.

The following table presents the results of the four 12-week Phase III studies (-008, -009, -010 and -015).

	Placebo	**Tolterodine 2 mg b.i.d.**	**Oxybutynin 5 mg t.i.d.**	**Equivalence**
Efficacy Results in Study B008				
Micturitions/24 hrs				
n	56	118	117	
Baseline (SD)	11.7 (4.9)	11.5 (4.4)	10.7 (3.3)	
Change from baseline (SD)	-1.6 (3.6)	-2.7 (3.8)	-2.3 (2.7)	
pv. placebo	-	0.0022	NS	YES
*Incontinence/24 hr				
n	40	93	88	
Baseline (SD)	3.3 (3.9)	2.9 (3.1)	2.6 (3.3)	
Change from baseline (SD)	-0.9 (1.5)	-1.3 (3.2)	-1.7 (3.1)	
pv. placebo	-	NS	0.023	YES
Volume voided/Micturition				
n	56	118	116	
Baseline (SD)	157 (63)	166 (61)	176 (62)	-
Change from baseline (SD)	6 (42)	38 (54)	47 (58)	

	Placebo	Tolterodine 2 mg b.i.d.	Oxybutynin 5 mg t.i.d.	Equivalence
pv. placebo	-	<0.0001	<0.0001	
Efficacy Results in Study B010				
Micturitions/24 hrs				
n	56	109	112	
Baseline (SD)	11.6 (3.1)	11.6 (2.9)	11.5 (3.5)	
Change from baseline (SD)	-1.4 (2.8)	-1.7 (2.3)	-1.7 (3.0)	
pv. placebo	-	NS	NS	YES
*Incontinence/24 hr				
n	50	91	103	
Baseline (SD)	3.5 (3.3)	3.7 (3.3)	3.4 (3.1)	
Change from baseline (SD)	-1.1 (2.1)	-1.6 (2.4)	-1.9 (2.3)	
pv. placebo	-	NS	0.012	YES
Volume voided/Micturition				
n	56	109	112	
Baseline (SD)	160 (73)	155 (57)	149 (56)	--
Change from baseline (SD)	13 (52)	31 (45)	46 (49)	
pv. placebo	-	0.015	<0.0001	
Efficacy Results in Study B009				
Micturitions/24 hrs				
n	64	123	129	
Baseline (SD)	11.3 (3.4)	11.5 (3.7)	11.2 (3.1)	--
Change from baseline (SD)	-1.4 (2.3)	-2.3 (3.0)	-2.3 (2.1)	
pv. placebo	-	0.0029	0.0045	
*Incontinence/24 hr				
n	55	109	117	
Baseline (SD)	3.5 (3.2)	3.9 (4.0)	3.6 (4.0)	--
Change from baseline (SD)	-1.3 (2.5)	-1.7 (2.8)	-1.7 (2.5)	
pv. placebo	-	NS	NS	
Volume voided/Micturition				
n	64	123	129	
Baseline (SD)	158 (53)	151 (56)	155 (52)	--
Change from baseline (SD)	10 (47)	27 (41)	36 (50)	
pv. placebo	--	0.0059	<0.0001	
Efficacy Results in Study B015				
Micturitions/24 hrs				
n	--	119	119	
Baseline (SD)		12 (4.8)	12.0 (4.7)	
Change from baseline (SD)		-2.1 (2.3)	-2.7 (5.3)	YES
*Incontinence/24 hr				
n		93	95	
Baseline (SD)	--	4.8 (5.5)	4.3 (5.2)	
Change from baseline (SD)		-1.7 (2.5)	-2.1 (3.2)	YES
Volume voided/Micturition				
n		119	119	
Baseline (SD)	--	153 (67)	142 (61)	--
Change from baseline (SD)		35 (53)	54 (64)	
p vs oxybutynin		0.0032		

* Excludes patients with no incontinence at baseline

NS = Not Significant; SD = Standard Deviation; pv = p value

A comparative bioavailability study was conducted to determine the relative bioavailability of one Tolterodine Tartrate Tablet 2 mg (Teva Pharmaceutical Industries, Ltd) versus one DETROL Tablet 2 mg (Pharmacia & Upjohn, US) in 35 healthy, non-smoking, adult subjects. The study design was a single-dose, randomized, two-period, two-treatment, two sequence crossover conducted under fasting conditions. Results are summarised in the following table.

Summary Table of the Comparative Bioavailability Data for
Single-Dose Studies Tolterodine (N=35)
(Amount of product administered: TEVA-TOLTERODINE 1x 2 mg tablets and
Detrol* 1 x 2 mg tablets, under fasting conditions.)

Tolterodine (1 x 2 mg Tablets) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means*	90% Confidence Interval*
AUC_T (ng.hr/mL)	8.22609 13.928 (128%)	8.47286 14.379 (122%)	97.1	90.7 – 104
AUC_I (ng.hr/mL)	8.53265 14.454 (131%)	8.77145 14.879 (125%)	97.3	91.0 – 104
C_{max} (ng/mL)	2.56267 3.415 (76.7%)	2.71474 3.598 (73.6%)	94.4	86.6 – 103
T_{max}§ (hrs)	1.131 (40.2%)	1.114 (43.6%)		
$T_{½}$§ (hrs)	3.013 (63.6%)	2.950 (60.1%)		

* Tolterodine Tartrate 2 mg Tablets (Teva Pharmaceutical Industries, Ltd.)
† DETROL 2 mg (tolterodine tartrate) Tablets (Pharmacia & Upjohn, US), purchased in US.
* Calculation based on least squares estimate
§ Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

Preclinical Pharmacology

Tolterodine is a competitive muscarinic receptor antagonist, which has been shown to inhibit carbachol-induced contraction of isolated bladder preparations from rats, guinea pigs and man. Tolterodine is significantly more active in inhibiting acetylcholine-induced urinary bladder contractions (ID_{50}=101 nmol/kg) than electrically induced salivation (ID_{50} = 257 nmol/kg) in the anesthetized cat; whereas oxybutynin exhibits the opposite selectivity profile (urinary bladder contraction ID_{50} = 200 nmol/kg; salivation ID_{50}= 104 nmol/kg). At unbound serum concentrations relevant to those observed clinically, tolterodine has no effects on central nervous system (CNS) or intestinal motility in mice. Tolterodine has high affinity for muscarinic receptors and has a very weak affinity for α-adrenoreceptors, histamine receptors, the neuromuscular junction, and calcium channels.

Preclinical studies have shown that tolterodine is as active as oxybutynin in inhibiting contractions of the detrusor muscle from the guinea pig. Tolterodine also has similar activity to oxybutynin in inhibiting electrically induced contractions of human detrusor muscle from stable and overactive bladders *ex vivo*. These electrically induced contractions are completely blocked by tolterodine.

Effects on the cardiovascular system in conscious dogs, treated orally with tolterodine for 10 days, have been investigated using telemetry technique. Heart rate and diastolic blood pressure were increased at 1 mg/kg (tolterodine 103 μg/L, 5-hydroxymethyl metabolite (DD 01) 25 μg/L). Except for a prolongation of the QT-interval (10-20%) observed at 4.5 mg/kg (tolterodine >600 μg/L, DD 01 100 μg/L), there were no abnormalities of the ECG pattern and no signs of arrhythmias were observed.

In anaesthetised dogs, tolterodine had little or no effect on the cardiovascular and respiratory systems when administered as a continuous i.v. infusion. Marked effects (20-40% prolongation of the QT-interval and T-wave duration) occurred only at tolterodine concentrations 500 μg/L. Heart rate, blood pressure and respiration remained virtually unaffected (1000 μg/L).

Effects of tolterodine (p.o.) on the central nervous system, gastrointestinal tract and renal function have been evaluated in the mouse. The strict no observed effect level for these effects is 1.5 mg/kg (tolterodine 2.1 μg/L, DD 01 2.4 μg/L). However, the dose at which effects were observed (15 mg/kg) was in some other studies a no effect dose. The true no observed effect level may therefore be closer to 15 mg/kg than to 1.5 mg/kg. A dose of 15 mg/kg can be expected to result in high serum levels of both tolterodine (83 μg/L) and DD 01 (63 μg/L).

Most of the effects observed at high doses in the mouse (≥5 mg/kg) and dog (≥1 mg/kg) were antimuscarinic in nature. Increased locomotor activity, mydriasis, decreased intestinal motility, increased residual urine and increased heart rate can all be attributed to the primary action of tolterodine and DD 01 on muscarinic receptors. Preclinical studies have shown that DD 01 exhibits a similar antimuscarinic profile to that of tolterodine, and a greater antimuscarinic activity on the bladder relative to the salivary gland *in vivo*.

The degree of serum protein binding differs between species and this must be taken into account when comparisons to humans are made. Thus, the unbound concentrations of tolterodine (2.2 μg/L) and DD 01 (8 μg/L) at which an increased heart rate was observed in the dog, are 17 and 8 times higher than the unbound serum concentrations achieved in most patients treated with tolterodine 2 mg bid (tolterodine: 0.13 μg/L; DD 01: 1.04 μg/L). The unbound concentrations at which effects on the central nervous system, intestinal motility and renal function were observed in the mouse (tolterodine: 13 μg/L; DD 01: 45 μg/L) are approximately 100 and 40 times, respectively, higher than those expected to be achieved in patients. Almost the same factors (100 and 30 times) were calculated for the unbound concentrations at which a slight QT-prolongation was recorded in the conscious dog (tolterodine 13 μg/L; DD 01: 32 μg/L).

Clinical Pharmacology

Pharmacodynamics

After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The 5-hydroxymethyl metabolite (DD 01), which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and DD 01 exhibit a high affinity for muscarinic receptors and have a very weak affinity for α-adrenoreceptors, histamine receptors, neuromuscular junction, and calcium channels.

Preclinical studies have shown that tolterodine is as active as oxybutynin in inhibiting contractions of the detrusor muscle from the guinea pig; it has a potency similar to that of oxybutynin in inhibiting electrically induced contractions of human detrusor muscle from stable and overactive bladders *ex vivo.*

Bioavailability

The absolute bioavailability of tolterodine was determined using a 1.28 mg intravenous dose as reference. Reported values in the oral dose interval 3.2 – 12.8 mg were 29-39%. In selected extensive metabolizers (EMs) and poor metabolizers (PMs) the bioavailability was 17±9% and 65±26%. This difference is explained by a higher degree of first-pass metabolism in EMs. The bioavailability estimate as such is, however, not an informative parameter with respect to clinical effect, since DD 01 is found in pharmacologically active concentrations in the majority of the population (EMs) (see **Metabolism**).

Pharmacokinetics

Absorption: In a study of ^{14}C-tolterodine in healthy volunteers who received a 5 mg oral dose, at least 77% of the radiolabeled dose was absorbed. Tolterodine is rapidly absorbed, and maximum serum concentrations (C_{max}) typically occur within 1 to 2 hours after dose administration. The pharmacokinetics of tolterodine, based on C_{max} and area under the concentration-time curve (AUC) determinations, are dose-proportional over the range of 1 to 4 mg. Food intake does not result in clinically relevant changes in the pharmacokinetic profile.

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 isoenzyme cytochrome P450 2D6 and leads to the formation, of a major pharmacologically active 5-hydroxymethyl metabolite. 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%, respectively, of the metabolites recovered in the urine.

Variability in Metabolism: A subset (about 7%) of the population is devoid of the drug-metabolizing isoenzyme cytochrome P450 2D6, the enzyme responsible for the formation of DD 01. The identified pathway of metabolism for these individuals, referred to as "poor metabolizers" (PMs), is dealkylation via cytochrome P450 3A4 to N-dealkylated tolterodine. The remainder of the population is referred to as "extensive metabolizers" (EMs). Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in PMs than in EMs. This results in significantly higher serum concentrations of tolterodine and in negligible concentrations of DD 01. Because of differences in the protein-binding characteristics of tolterodine and DD 01, the sum of unbound serum concentrations of tolterodine and DD 01 is similar in EMs and PMs at steady state. Since tolterodine and DD 01 have similar antimuscarinic effects, the net activity of tolterodine L-tartrate is expected to be similar in EMs and PMs.

Excretion: Following administration of a 5 mg oral dose of ^{14}C-tolterodine to healthy volunteers, about 77% of radioactivity was recovered in urine and 17% was recovered in feces. Less than 1% (<2.5% in PMs) of the dose was recovered as intact tolterodine, and 5% to 14% was recovered as the active DD 01 metabolite. Most of the radioactivity was recovered within the first 24 hours, which is consistent with the apparent half-life of tolterodine: 1.9 to 3.7 hours in pharmacokinetic studies.

Pharmacokinetics in Special Populations

Age: In phase I multiple-dose studies in which tolterodine 2 mg was administered twice daily, serum concentrations of tolterodine and of DD 01 were similar in healthy elderly volunteers (aged 64 through 80 years) and healthy young volunteers (aged less than 40 years). In another phase I study, elderly volunteers (aged 71 through 81 years) were given tolterodine 1 or 2 mg twice daily. Mean serum concentrations of tolterodine and DD 01 in these elderly volunteers were approximately 20% and 50% higher, respectively, than reported in young healthy volunteers. However, no overall differences were observed in safety between older and younger patients in phase III, 12-week, controlled clinical studies; and therefore, no dosage adjustment is recommended (see **WARNINGS AND PRECAUTIONS, Geriatric Use**).

Pediatric: The pharmacokinetics of tolterodine have not been established in pediatric patients.

Gender: Pharmacokinetic data from three Phase I clinical studies (Studies 022, 024, and 028) in which a tolterodine dose of 2 mg was administered in the fasting state were analyzed with respect to gender. The pharmacokinetics of tolterodine and DD 01 are not influenced by gender. Mean C_{max} of tolterodine (1.6 µg/L in males versus 2.2 µg/L in females) and DD 01 (2.2 µg/L in males versus 2.5 µg/L in females) are similar in males and females who were administered tolterodine 2 mg. Mean AUC values of tolterodine (6.7 µg/h/L in males versus 7.8 µg/h/L in females) and DD

01(10 µg/h/L in males versus 11 µg/h/L in females) are also similar. The elimination half-life of tolterodine for both males and females is 2.4 hours, and the half-life of DD 01 is 3.3 hours in males and 3.0 hours in females.

Race: Differences among races regarding metabolic capacity can be assumed to be of quantitative nature and are probably less than the thoroughly documented difference between extensive and poor metabolizers. The few non-Caucasians included do not show a different pharmacokinetic profile of tolterodine or DD 01.

Renal Impairment: A study was conducted to evaluate the pharmacokinetics of tolterodine in 12 subjects with renal impairment compared to 12 healthy volunteers. The exposure to unbound tolterodine and DD 01 was on average 2-3 fold higher in patients with renal impairment compared with healthy volunteers. AUC of N-dealkylated tolterodine was in an extreme case, about 60-fold higher in a poor metabolizer (PM) in the renal impairment group than in the only healthy extensive metabolizer (EM) with quantifiable AUC. However, the corresponding ratio for what is generally observed in healthy PMs is about 10. Tolterodine acid levels and N-dealkylated tolterodine acid were on average 5 times and 11 times higher, respectively, in the renal impairment group with respect to AUC (extreme case 9-fold and 31-fold higher than most exposed healthy subjects). Potential pharmacologic effects and also the toxicological significance of metabolite levels should be taken into account if exposing subjects with renal impairment (GFR <30 mL/min to repeated doses of tolterodine (see **WARNINGS AND PRECAUTIONS**).

Hepatic Insufficiency: As might be predicted from a drug in which hepatic metabolism is the primary route of elimination, liver impairment can significantly alter the disposition of tolterodine. In a study of cirrhotic patients, elimination half-life of tolterodine was longer in cirrhotic patients (mean, 8.7 hours) than in healthy, young and elderly volunteers (mean, 2 to 4 hours). The clearance of orally administered tolterodine was substantially lower in cirrhotic patients (1.1 ± 1.7 L/h/kg) than in the healthy volunteers (5.7 ± 3.8 L/h/kg). Patients with significantly reduced hepatic function should not receive doses of tolterodine L-tartrate greater than 1 mg twice daily (see **WARNINGS AND PRECAUTIONS**).

Drug Interactions

Fluoxetine: Fluoxetine is a selective serotonin reuptake inhibitor and a potent inhibitor of cytochrome P450 2D6 activity. In a study to assess the effect of fluoxetine on the pharmacokinetics of tolterodine and its metabolites, it was observed that fluoxetine significantly inhibited the metabolism of tolterodine in extensive metabolizers, resulting in a 4.8-fold increase in tolterodine AUC. However, DD 01 showed a 52% decrease in C_{max} and a 20% decrease in AUC. Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be extensive metabolizers of tolterodine to resemble the pharmacokinetic profile in poor metabolizers. The sums of unbound serum concentrations of tolterodine and DD 01 are 25% higher during the interaction. However, no dose adjustment is required when tolterodine L-tartrate and fluoxetine are coadministered (see **DRUG INTERACTIONS**).

Other Drugs Metabolized by P450 2D6: The potential effect of tolterodine on the pharmacokinetics of drugs that are metabolized by P450 2D6 (such as flecainide, vinblastine,

carbamazepine, tricyclic antidepressants) has not been formally evaluated (see **DRUG INTERACTIONS**).

Warfarin: In healthy volunteers, coadministration of tolterodine 2 mg twice daily 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 2 mg twice daily has no effect on the pharmacokinetics of an oral contraceptive (ethinyl estradiol 30 μg; levonorgestrel 150 μg) as evidenced by the monitoring of ethinyl estradiol and levonorgestrel over a 2-month cycle in healthy female volunteers.

Diuretics: Coadministration of tolterodine up to 4 mg twice daily 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 in patients with overactive bladder.

Cytochrome P450 3A4 inhibitors: The use of tolterodine in combination with ketoconazole, a potent CYP3A4 inhibitor, was studied in 8 healthy subjects, all of whom were poor metabolizers of CYP2D6. Concomitant treatment with ketoconazole resulted in a 2.2 fold increase in tolterodine AUC at steady state. Based on these findings, potent CYP3A4 inhibitors such as macrolide antibiotics (erythromycin and clarithromycin) or azole antifungal agents (ketoconazole, itraconazole and miconazole), or cyclosporin or vinblastine may also lead to increases of tolterodine plasma concentrations (see **DRUG INTERACTIONS**).

A clinical explorative study with marker drugs for the major P450 isoenzymes suggests that metabolic activity of CYP2D6, 2C19, 3A4 or 1A2 is unlikely to be inhibited by tolterodine L-tartrate.

Electrophysiology

The QT effect of 2 mg BID and 4 mg BID doses of tolterodine L-tartrate immediate release tablets was evaluated in a steady-state, 4-way crossover, double-blind, placebo- and active-controlled (moxifloxacin 400 mg QD) study in 48 healthy volunteers (18-55 yrs age, with approximately equal representations of males and females and of CYP2D6 poor and extensive metabolizers). The QT interval was measured over a 12-hour period including peak times at steady state. This evaluation was done at up to two times the highest dose of tolterodine L-tartrate immediate release tablets.

The following table summarizes the largest time-matched, placebo and baseline-adjusted mean effects on Fridericia-corrected QTc (QTcF) at steady-state. 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.

Largest Time-Matched, Placebo and Baseline-Adjusted Mean Effects on Fridericia-corrected QTc (QTcF) at Steady-State

Treatment Dose	Multiple of Maximum Recommend Dose	Machine-Read QTcF (msec)**			Manually-Read QTcF (msec)**		
		Time of Max Increase	Point Estimate*	90% Confidence Interval	Time of Max Increase	Point Estimate*	90% Confidence Interval
Tolterodine 2 mg BID	1X	3	1.4	-2.8, 5.6	1	5.0	1.0, 9.0
Tolterodine 4 mg BID	2X	1	5.6	2.2, 9.1	1	11.8	7.9, 15.8
Moxifloxacin 400 mg QD	1X	4	13.5	9.9, 17.1	4	22.4***	19.3, 27.1

* The point estimate is the difference between arithmetic means for pair-wise comparisons of the drug versus placebo treatments. QTc values are corrected for heart rate using Fridericia's formula (QTc =QT/RR^0.33)
** The machine-read methodology is based on earliest Q onset to latest T offset in 12 simultaneous recorded leads, while the manual over-read method is based on lead II only. The reason for the difference between machine and manual read of QT interval is unclear.
*** The effect on QTc interval with 4 days of moxifloxacin dosing in this QT trial may be greater than typically observed in QT trials of other drugs.

The QT effect appeared greater for 8 mg/day compared with 4 mg/day tolterodine immediate release tablets. The effect of the highest tolterodine dose (two times the therapeutic dose) was 50-60% less than that of the active control moxifloxacin (400 mg) at its therapeutic dose. Tolterodine's effect on QT interval was found to correlate with plasma concentration of tolterodine. The effect on QTc interval appeared to be greater in CYP2D6 poor metabolizers than in CYP2D6 extensive metabolizers. In this study, the point estimates of manual-read QTc interval increase were 2.1 msec in extensive metabolizers and 8.7 msec in poor metabolizers receiving tolterodine 2 mg BID treatment. However, this study was not designed to make direct statistical comparisons by CYP2D6 metabolizer status nor between drugs or dose levels. At both doses of tolterodine, no subject, irrespective of their metabolic profile (i.e. poor/extensive metabolizers), exceeded 500 msec for absolute QTcF or 60 msec for change from baseline. The clinical relevance of these findings will depend on individual patient risk factors and susceptibilities present (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).

TOXICOLOGY

Acute toxicity

The single oral dose administration studies in mice, rats and dogs showed species differences. At 300 mg/kg in mice, a 10-60% mortality was recorded, whereas 375 mg/kg was non-lethal in rats. In mice, a dose of 200 mg/kg caused no lethality. In the dog, at 40 mg/kg (the highest dose tested) no mortality occurred, but pronounced clinical signs were seen such as decreased locomotor activity, clouding of consciousness and stupor. Following a single intravenous dose, 8 mg/kg was a no observed effect level in both rats and mice. At 24 mg/kg, 30% mortality was recorded in rats, and 80% mortality in mice.

Long-term toxicity
The metabolic profiles in urine from the mouse, rat, dog and man given an oral dose of radioactively labeled tolterodine show that the mouse, dog and man have a similar metabolic pattern including the formation of the pharmacologically active 5-hydroxymethyl metabolite, DD 01. In contrast, the metabolism of tolterodine in the rat is more extensive and occurs also via other pathways involving mono and dihydroxylation of the unsubstituted benzene ring. The mouse is considered to be a more appropriate species than the rat for the safety evaluation of tolterodine in man.

Mouse: In the 2 week study, dose levels of 4, 12, 40 or 80 mg/kg/day were used, and in the 13 week study, the dose levels were 4, 12 or 40 mg/kg/day. In the 26 week study dose levels of 3, 10 or 30 mg/kg/day were used. In the 2 week study, no toxicity was found after doses up to 80 mg/kg/day, During the 13 week study, 7 males and 8 females receiving 40 mg/kg/day died shortly after dosing. Treatment related deaths also occurred in the 26 week study, where 12 males and 15 females treated at 30 mg/kg/day died within one hour of dosing. In both studies, the deaths were distributed throughout the treatment period starting from the second week of treatment. Although the mechanism of the unexpected deaths is unknown, it is most likely related to exaggerated pharmacological effects (circulatory and/or respiratory failure) occurring at serum peak levels.

Rat: In the 13 week repeated dose study in rats, doses of 4, 12 or 40 mg/kg/day were given. In females given 40 mg/kg/day depressed body weight gain and reduced food consumption were recorded. Also, ten female rats died approximately 20 hours after dosing. The deaths occurred from week 3. Cause of death could not be established, but is most likely related to exaggerated pharmacologic effects (circulatory and/or respiratory failure) following the accumulation of tolterodine with time.

Dog: The clinical signs that were associated with tolterodine treatment in the 13 week, 26 week and 52 week (0.5, 1.5 or 4.5 mg/kg/day) studies were characterized mainly by dose related peripheral antimuscarinic effects, i.e. dry mouth, mydriasis and dryness of the eye. In some dogs receiving 1.5 or 4.5 mg/kg/day, diminished lacrimation caused conjunctivitis and/or corneal changes especially at the high dose level.

Central antimuscarinic effects, i.e. locomotor disturbances and drowsiness, were seen in all three studies on day 1, in a few dogs receiving 4.5 or 8 mg/kg/day. These symptoms occurred in dogs with high serum concentrations of tolterodine (C_{max} 800-1250 µg/L), and DD 01. Ataxia and tremor were also observed occasionally in high dose animals during the 26 week study.

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).

Carcinogenicity

Carcinogenicity studies with tolterodine were conducted in mice and rats. At the maximum-tolerated dose in mice (30 mg/kg/day [123 mg/m^2/day]) female rats (20 mg/kg/day), and male rats (30 mg/kg/day), AUC values obtained for tolterodine were 355, 291, and 462 μg•h/L, respectively. In comparison, the human AUC value for a 2-mg dose administered twice daily is estimated at 34 μg•h/L. Thus, tolterodine exposure in the carcinogenicity studies was 9- to 14- fold higher than expected in humans. No increase in tumors was found in either mice or rats.

Mutagenicity
No mutagenic effects of tolterodine were detected in a battery of *in vitro* tests, including bacterial mutation assays (Ames test) in four strains of *Salmonella typhimurium* and in two 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.

Reproduction and Teratology
In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (corresponding to AUC value of about 500 μg•h/L), neither effects on reproductive performance or fertility nor any anomalies or malformations were seen. Based on AUC values, the systemic exposure was about 15-fold higher in animals than in humans. At doses of 30 to 40 mg/kg/day, tolterodine caused a dose-related increase in embryolethality, reduced fetal weight, and increased incidence of fetal abnormalities. At these doses, AUC values were about 20- to 25-fold higher than in humans. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

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PART III: CONSUMER INFORMATION

[Pr]TEVA-TOLTERODINE
(Tolterodine L-tartrate)

This leaflet is part III of a three part "Product Monograph" published when TEVA-TOLTERODINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-TOLTERODINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

The name of this medication is TEVA-TOLTERODINE. It is used for the treatment of the symptoms of overactive bladder which include frequency, urgency, and urge incontinence.

REMEMBER: This medication is for YOU. Never give it to others. It may harm them even if their symptoms are the same as yours.

What it does:

Tolterodine prevents abnormal bladder contractions. This results in more bladder capacity and less frequency, urgency and involuntary loss of urine.

When it should not be used:

You should **not take** TEVA-TOLTERODINE if you have:
- Urinary retention,
- gastric retention
- uncontrolled narrow angle glaucoma,
- known hypersensitivity to the drug or any of the other ingredients.

What the medicinal ingredient is:

Each tablet contains 1 mg or 2 mg of the active ingredient tolterodine L-tartrate.

What the important nonmedicinal ingredients are:

Calcium Phosphate Dibasic Dihydrate, Colloidal Silicon Dioxide, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Polyvinyl Alcohol-Partially Hydrolyzed, Sodium Starch Glycolate, Talc and Titanium Dioxide.

What dosage forms it comes in:

Tablets, 1 mg and 2 mg

WARNINGS AND PRECAUTIONS

TEVA-TOLTERODINE may have an effect on the electrical activity of the heart. This effect can be measured as a change in the electrocardiogram (ECG). It is important to follow the instructions of your doctor with regard to dosing or any special tests. In very rare cases, drugs with an effect on the ECG can lead to disturbances in heart rhythm (arrhythmias/dysrhythmias). These heart rhythm disturbances are more likely in patients with risk factors, such as heart disease, or in the presence of certain interacting drugs. If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensation of rapid, pounding, or irregular heart beat), fainting, or seizures, you should stop taking TEVA-TOLTERODINE and seek immediate medical attention.

BEFORE you use TEVA-TOLTERODINE talk to your doctor or pharmacist if:

- you are pregnant, or trying to become pregnant
- you are breastfeeding your child
- you have myasthenia gravis (a chronic autoimmune neuromuscular disease which cause muscle weakness)
- you have stomach problems affecting passage and digestion of food
- you have liver problems
- you have kidney problems
- you are taking medication bought without a prescription. They may affect your condition, or how TEVA-TOLTERODINE works for you.
- you are a female or are over 65 years of age; you have a disorder known as Long QT Syndrome; a heart disease; a history of stroke or brain hemorrhage; a personal history of fainting spells; a family history of sudden cardiac death at <50 years; electrolyte disturbances (e.g., low blood potassium levels); an eating disorder or are following an extreme diet; diabetes, especially with associated nerve disorders

INTERACTIONS WITH THIS MEDICATION

The following list includes some, but not all, of the drugs that may increase the risk of side effects while receiving TEVA-TOLTERODINE. You should check with your doctor or pharmacist before taking any other medication with TEVA-TOLTERODINE.

Drugs that may interact with TEVA-TOLTERODINE INCLUDE:
- other drugs that possess antimuscarinic/anticholinergic properties (drugs that cause blurred vision, constipation, dry mouth, etc.)

- antifungals (drugs to treat fungal infections, such as, fluconazole, ketoconazole, or itraconazole)
- antibiotics (i.e. erythromycin, clarithromycin)
- cyclosporine (a drug to prevent rejection of organ transplants)
- vinblastine (a drug to treat some types of cancer)
- antiarrhythmics (drugs that stabilize the heart rhythm function, such as procainamide, quinidine amiodarone, sotalol, etc.)
- antidepressants (mood disorder drugs)
- antipsychotics (drugs to stabilize thinking and behavior)
- anti-asthmatic (salmeterol)

PROPER USE 0F THIS MEDICATION

Take TEVA-TOLTERODINE as instructed by your doctor. Do not increase, decrease or stop taking TEVA-TOLTERODINE without first talking to your doctor.

Usual dose
Adults and Elderly:
The usual starting dose is 2 mg twice daily, but may be decreased to 1 mg twice daily.

Overdose
Do not take more tablets than your doctor has told you to. If you take too many tablets by accident, call your doctor or pharmacist or a poison control centre immediately.

Missed Dose
If you should forget to take your tablet at the usual time, take it as soon as you remember unless it is time to take the next one. Continue with the remaining doses as before. Do not take more than one dose at a time.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with most drugs, TEVA-TOLTERODINE can cause some side effects.

Tell your doctor or pharmacist right away if you suffer from any of the following side effects while taking this medication:
- dry mouth
- decreased tear production (dry irritable eye)
- heartburn
- blurred vision
- dizziness
- palpitations (sensation of rapid, pounding, or irregular heart beat)
- fainting
- difficulty in urination (passing water)

The most common side effects are dry mouth and headache. Less commonly reported side effects are dizziness, fatigue, abdominal pain, constipation and heartburn.

If you experience any symptoms of a possible heart rhythm disturbance, such as dizziness, palpitations (sensations of rapid, pounding, or irregular heart beat), fainting, or seizures, you should stop taking TEVA-TOLTERODINE and seek immediate medical attention.

Check with your doctor or pharmacist right away if you have ***any*** bothersome or unusual effects while taking TEVA-TOLTERODINE.

Use caution while driving or using machinery until you know how TEVA-TOLTERODINE affects you.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek emergency medical assistance
		Only if severe	**In all cases**	
Uncommon	Allergic reaction			✓

This is not a complete list of side effects. For any unexpected effects while taking TEVA-TOLTERODINE, stop taking the drug and contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature 15°C to 30°C. Keep the product in the original packaging.

You should not use your medication after the expiration date printed on the carton and label.

Keep all medications out of the reach of children. This medication could harm them.

REPORTING SIDE EFFECTS

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph prepared for health professionals can be found by contacting Teva Canada Limited at:
1-800-268-4127 ext. 1255005 (**English**)
1-877-777-9117 (**French**)
or druginfo@tevacanada.com

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