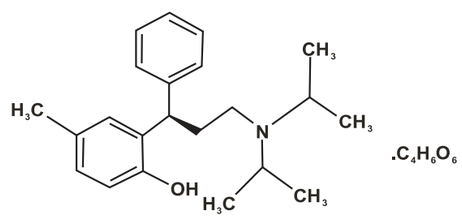
806-2021-05

Tolterodine Tartrate
Tablets
2100931

2D
Code

Tolterodine Tartrate Tablets

DESCRIPTION
Tolterodine tartrate tablets contain tolterodine tartrate. The active moiety, tolterodine, is a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is 2-[(1R)-3-[Bis (1-methylethyl) amino]-1-phenylpropyl] - 4- Methyl phenol tartrate. The empirical formula of tolterodine tartrate is $C_{22}H_{31}NO.C_4H_6O_6$, and its molecular weight is 475.57. The structural formula of tolterodine tartrate is represented below:



Tolterodine tartrate USP is a white or almost white crystalline powder. The pKa value is 9.87. Sparingly soluble in water, slightly soluble in anhydrous ethanol, practically insoluble in heptane.

Tolterodine tartrate tablets for oral administration contain 1 or 2 mg of tolterodine tartrate USP. The inactive ingredients are colloidal silicon dioxide, dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, microcrystalline cellulose, purified stearic acid, sodium starch glycolate and titanium dioxide. Additionally 1 mg tablet contains iron oxide yellow and iron oxide red.

CLINICAL PHARMACOLOGY

Tolterodine is a competitive muscarinic receptor antagonist. 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 the 5-hydroxymethyl derivative, a major pharmacologically active metabolite. The 5-hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and the 5-hydroxymethyl metabolite 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.

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.

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. Tolterodine immediate release is rapidly absorbed, and maximum serum concentrations (C_{max}) typically occur within 1 to 2 hours after dose administration. 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.

Effect of Food: Food intake increases the bioavailability of tolterodine (average increase 53%), but does not affect the levels of the 5-hydroxymethyl metabolite in extensive metabolizers. This change is not expected to be a safety concern and adjustment of dose is not needed.

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. The 5-hydroxymethyl metabolite is not extensively protein bound, with unbound fraction concentrations averaging 36% ± 4.0 %. The blood to serum ratio of tolterodine and the 5-hydroxymethyl metabolite 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 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% of the metabolites recovered in the urine, respectively.

Variability in Metabolism: A subset (about 7%) of the population is devoid of CYP2D6, the enzyme responsible for the formation of the 5-hydroxymethyl metabolite of 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 the 5-hydroxymethyl metabolite.

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 the active 5-hydroxymethyl metabolite.

A summary of mean (± standard deviation) pharmacokinetic parameters of tolterodine immediate release and the 5-hydroxymethyl metabolite in extensive (EM) and poor (PM) metabolizers is provided in Table 1. These data were obtained following single and multiple doses of tolterodine 4 mg administered twice daily to 16 healthy male volunteers (8 EM, 8 PM).

Table 1. Summary of Mean (±SD) Pharmacokinetic Parameters of Tolterodine and its Active Metabolite (5-hydroxymethyl metabolite) in Healthy Volunteers

	Tolterodine					5-Hydroxymethyl Metabolite			
Phenotype (CYP2D6)	**t_{max} (h)**	**C_{max}* (mcg/L)**	**C_{avg}* (mcg/L)**	**$t_{1/2}$ (h)**	**CL/F (L/h)**	**t_{max} (h)**	**C_{max}* (mcg/L)**	**C_{avg}* (mcg/L)**	**$t_{1/2}$ (h)**
Single-dose									
EM	1.6±1.5	1.6±1.2	0.50±0.35	2.0±0.7	534±697	1.8±1.4	1.8±0.7	0.62±0.26	3.1±0.7
PM	1.4±0.5	10±4.9	8.3±4.3	6.5±1.6	17±7.3	†	†	†	†
Multiple-dose									
EM	1.2±0.5	2.6±2.8	0.58±0.54	2.2±0.4	415±377	1.2±0.5	2.4±1.3	0.92±0.46	2.9±0.4
PM	1.9±1.0	19±7.5	12±5.1	9.6±1.5	11±4.2	†	†	†	†

* Parameter was dose-normalized from 4 mg to 2 mg.

C_{max} = Maximum plasma concentration; t_{max} = Time of occurrence of C_{max};

C_{avg} = Average plasma concentration; $t_{1/2}$ = Terminal elimination half-life; CL/F = Apparent oral clearance.

EM = Extensive metabolizers; PM = Poor metabolizers.

† = not applicable.

Pharmacokinetics in Special Populations

Age: In Phase 1, multiple-dose studies in which tolterodine immediate release 4 mg (2 mg bid) was administered, serum concentrations of tolterodine and of the 5-hydroxymethyl metabolite were similar in healthy elderly volunteers (aged 64 through 80 years) and healthy young volunteers (aged less than 40 years). In another Phase 1 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 the 5-hydroxymethyl metabolite 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 on tolterodine in Phase 3, 12-week, controlled clinical studies; therefore, no tolterodine dosage adjustment for elderly patients is recommended (see **PRECAUTIONS, Geriatric Use**).

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

Gender: The pharmacokinetics of tolterodine immediate release and the 5-hydroxymethyl metabolite are not influenced by gender. Mean C_{max} of tolterodine (1.6 mcg/L in males versus 2.2 mcg/L in females) and the active 5-hydroxymethyl metabolite (2.2 mcg/L in males versus 2.5 mcg/L in females) are similar in males and females who were administered tolterodine immediate release 2 mg. Mean AUC values of tolterodine (6.7 mcg•h/L in males versus 7.8 mcg•h/L in females) and the 5-hydroxymethyl metabolite (10 mcg•h/L in males versus 11 mcg•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 the 5-hydroxymethyl metabolite is 3 hours in females and 3.3 hours in males.

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

Renal Insufficiency: 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 immediate release and the 5-hydroxymethyl metabolite levels were approximately 2 to 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 hydroxylated tolterodine) were significantly higher (10 to 30 fold) in renally impaired patients as compared to the healthy volunteers. The recommended dosage for patients with significantly reduced renal function is tolterodine tartrate tablets 1 mg twice daily (see **PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION**).

Hepatic Insufficiency: Liver impairment can significantly alter the disposition of tolterodine immediate release. In a study conducted in cirrhotic patients, 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 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 significantly reduced hepatic function is tolterodine tartrate tablets 1 mg twice daily (see **PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions

Fluoxetine: 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 the 5-hydroxymethyl metabolite. Fluoxetine thus alters the pharmacokinetics in patients who would otherwise be 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 the 5-hydroxymethyl metabolite are only 25% higher during the interaction. No dose adjustment is required when tolterodine tartrate tablets and fluoxetine are coadministered.

Other Drugs Metabolized by Cytochrome P450 Isoenzymes: 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 (Ki 1.05 µM), while tolterodine immediate release as well as the 5-hydroxymethyl metabolite are devoid of any significant inhibitory potential regarding the other isoenzymes.

CYP3A4 Inhibitors: The effect of 200 mg daily dose of ketoconazole on the pharmacokinetics of tolterodine immediate release was studied in 8 healthy volunteers, all of whom were poor metabolizers (see **Pharmacokinetics**, Variability in Metabolism for discussion of 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 CYP3A inhibitors such as other azole antifungals (e.g., itraconazole, miconazole) or macrolide antibiotics (e.g., erythromycin, clarithromycin) or cyclosporine or vinblastine may also lead to increases of tolterodine plasma concentrations (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

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 mcg /levonorgestrel 150 mcg) as evidenced by the monitoring of ethinyl estradiol and levonorgestrel over a 2-month cycle 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.

Cardiac Electrophysiology

The effect of 2 mg BID and 4 mg BID of tolterodine immediate release (IR) 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 to 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 **PRECAUTIONS, Drug Interactions**). 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 (QTc) relative to placebo at the time of peak tolterodine (1 hour) and moxifloxacin (2 hour) concentrations. Both Fridericia's (QTcF) and a population-specific (QTcP) 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 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 QTc from baseline to steady state (Day 4 of dosing) at T_{max} (relative to placebo)

Drug/Dose	**N**	**QTcF(msec) (manual)**	**QTcF (msec) (machine)**	**QTcP (msec) (manual)**	**QTcP (msec) (machine)**
Tolterodine 2 mg BID[1]	48	5.01 (0.28, 9.74)	1.16 (-2.99, 5.30)	4.45 (-0.37, 9.26)	2.0 (-1.81, 5.81)
Tolterodine 4 mg BID[1]	48	11.84 (7.11, 16.58)	5.63 (1.48, 9.77)	10.31(5.49, 15.12)	8.34 (4.53, 12.15)
Moxifloxacin 400 mg QD[2]	45	19.26[3] (15.49, 23.03)	8.90 (4.77, 13.03)	19.10[3] (15.32, 22.89)	9.29 (5.34, 13.24)

[1] At T_{max} of 1 hr; 95% Confidence Interval

[2] At T_{max} of 2 hr; 90% Confidence Interval

[3] The effect on QT interval with 4 days of moxifloxacin dosing in this QT trial may be greater than typically observed in QT trials 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 QTc 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 tolterodine tartrate tablets or tolterodine extended-release capsules (see **PRECAUTIONS, Patients with Congenital or Acquired QT Prolongation**).

CLINICAL STUDIES

Tolterodine tartrate tablets were evaluated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in four randomized, double-blind, placebo-controlled, 12-week studies. A total of 853 patients received tolterodine tartrate tablets 2 mg twice daily and 685 patients received placebo. The majority of patients were Caucasian (95%) and female (78%), with a mean age of 60 years (range, 19 to 93 years). At study entry, nearly all patients perceived they had urgency and most patients had increased frequency of micturitions and urge incontinence. These characteristics were well balanced across treatment groups for the studies.

The efficacy endpoints for study 007 (see Table 3) included the change from baseline for:

- Number of incontinence episodes per week
- Number of micturitions per 24 hours (averaged over 7 days)
- Volume of urine voided per micturition (averaged over 2 days)

The efficacy endpoints for studies 008, 009, and 010 (see Table 4) were identical to the above endpoints with the exception that the number of incontinence episodes was per 24 hours (averaged over 7 days).

Table 3. 95% Confidence Intervals (CI) for the Difference between Tolterodine Tartrate Tablets (2 mg bid) and Placebo for the Mean Change at Week 12 from Baseline in Study 007

	Tolterodine tartrate tablets (SD) N=514	**Placebo (SD) N=508**	**Difference (95% CI)**
Number of Incontinence Episodes per Week			
Mean baseline	23.2	23.3	
Mean change from baseline	-10.6 (17)	-6.9 (15)	-3.7 (-5.7, -1.6)
Number of Micturitions per 24 Hours			
Mean baseline	11.1	11.3	
Mean change from baseline	-1.7 (3.3)	-1.2 (2.9)	-0.5* (-0.9, -0.1)
Volume Voided per Micturition (mL)			
Mean baseline	137	136	
Mean change from baseline	29 (47)	14 (41)	15* (9, 21)

SD = Standard Deviation.

*The difference between tolterodine tartrate tablets and placebo was statistically significant.

Table 4. 95% Confidence Intervals (CI) for the Difference between Tolterodine Tartrate Tablets (2 mg bid) and Placebo for the Mean Change at Week 12 from Baseline in Studies 008, 009, 010

Study		**Tolterodine Tartrate Tablets (SD)**	**Placebo (SD)**	**Difference (95% CI)**
Number of Incontinence Episodes per 24 Hours				
008	Number of patients	93	40	
	Mean baseline	2.9	3.3	
	Mean change from baseline	-1.3 (3.2)	-0.9 (1.5)	0.5 (-1.3, 0.3)
009	Number of patients	116	55	
	Mean baseline	3.6	3.5	
	Mean change from baseline	-1.7 (2.5)	-1.3 (2.5)	-0.4 (-1.0, 0.2)
010	Number of patients	90	50	
	Mean baseline	3.7	3.5	
	Mean change from baseline	-1.6 (2.4)	-1.1 (2.1)	-0.5 (-1.1,0.1)
Number of Micturitions per 24 Hours				
008	Number of patients	118	56	
	Mean baseline	11.5	11.7	
	Mean change from baseline	-2.7 (3.8)	-1.6 (3.6)	-1.2* (-2.0,-0.4)
009	Number of patients	128	64	
	Mean baseline	11.2	11.3	
	Mean change from baseline	-2.3 (2.1)	-1.4 (2.8)	-0.9* (-1.5,-0.3)
010	Number of patients	108	56	
	Mean baseline	11.6	11.6	
	Mean change from baseline	-1.7 (2.3)	-1.4 (2.8)	-0.38 (-1.1,0.3)

PATIENT INFORMATION
Tolterodine Tartrate
(tol-TER-oh-deen TAR-trate)
Tablets

Read the Patient Information that comes with tolterodine tartrate tablets before you start using them and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or your treatment. Only your doctor can determine if treatment with tolterodine tartrate tablets are right for you.

What are tolterodine tartrate tablets?
Tolterodine tartrate tablets are a prescription medicine for **adults** used to treat the following symptoms due to a condition called **overactive bladder**:

- Urge urinary incontinence: a strong need to urinate with leaking or wetting accidents
- Urgency: a strong need to urinate right away
- Frequency: urinating often

Tolterodine tartrate extended release capsules did not help the symptoms of overactive bladder when studied in children.

What is overactive bladder?
Overactive bladder happens when you cannot control your bladder muscle. When the muscle contracts too often or cannot be controlled, you get symptoms of overactive bladder, which are leakage of urine (urge urinary incontinence), needing to urinate right away (urgency), and needing to urinate often (frequency).

Who should not take tolterodine tartrate tablets?
Do not take tolterodine tartrate tablets if you:

- Are not able to empty your bladder (urinary retention)
- Have delayed or slow emptying of your stomach (gastric retention)
- Have an eye problem called "uncontrolled narrow-angle glaucoma"
- Are allergic to tolterodine tartrate tablets or to any of its ingredients. See the end of this leaflet for a complete list of ingredients of tolterodine.
- Are allergic to TOVIAZ which contains fesoterodine.

What should I tell my doctor before starting tolterodine tartrate tablets?
Before starting tolterodine tartrate tablets, tell your doctor about all of your medical and other conditions that may affect the use of tolterodine tartrate tablets, including:

- Stomach or intestinal problems or problems with constipation
- Problems emptying your bladder or if you have a weak urine stream
- Treatment for an eye problem called narrow-angle glaucoma
- Liver problems
- Kidney problems
- A condition called myasthenia gravis
- If you or any family members have a rare heart condition called QT prolongation (long QT syndrome)
- If you are pregnant or trying to become pregnant. It is not known if tolterodine tartrate tablets could harm your unborn baby.
- If you are breastfeeding. It is not known if tolterodine tartrate passes into your breast milk or if it can harm your baby. Talk to your doctor about the best way to feed your baby if you take tolterodine tartrate tablets.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Other medicines can affect how your body handles tolterodine tartrate tablets. Your doctor may use a lower dose of tolterodine tartrate tablets if you are taking:

- Certain medicines for fungus or yeast infections
- Certain medicines for bacterial infections
- Sandimmune® (cyclosporine) or Velban® (vinblastine)

Ask your doctor or pharmacist for a list of these medicines, if you are not sure.

Know the medicines you take. Keep a list of them with you to show your doctor or pharmacist each time you get a new medicine.

How should I take tolterodine tartrate tablets?

- Take tolterodine tartrate tablets exactly as your doctor tells you to take them.
- Your doctor will tell you how many tolterodine tartrate tablets to take and when to take them.
- Do not change your dose unless told to do so by your doctor.
- You can take tolterodine tartrate tablets with or without food.
- Take tolterodine tartrate tablets at the same times each day.

Size: 300 x 400 mm
Pharma Code: Front-59 & Back-60
Spec.: Printed on 40 GSM Bible paper, front & back side printing
Pharma code position and Orientation are tentative, will be changed based on folding size.
No of Colours: 01 - Black

Study		Tolterodine Tartrate Tablets (SD)	Placebo (SD)	Difference (95% CI)
Volume Voided per Micturition (mL)				
008	Number of patients	118	56	
	Mean baseline	166	157	
	Mean change from baseline	38 (54)	6 (42)	32* (18,46)
009	Number of patients	129	64	
	Mean baseline	155	158	
	Mean change from baseline	36 (50)	10 (47)	26* (14,38)
010	Number of patients	108	56	
	Mean baseline	155	160	
	Mean change from baseline	31 (45)	13 (52)	18* (4,32)

SD = Standard Deviation.

*The difference between tolterodine tartrate tablets and placebo was statistically significant.

INDICATIONS AND USAGE

Tolterodine tartrate tablets are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

Tolterodine tartrate tablets are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Tolterodine tartrate tablets is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients, or to fesoterodine fumarate extended-release tablets which, like tolterodine tartrate tablets, are metabolized to 5-hydroxymethyl tolterodine.

WARNINGS

Anaphylaxis and angioedema requiring hospitalization and emergency medical treatment have occurred with the first or subsequent doses of tolterodine tartrate tablets. In the event of difficulty in breathing, upper airway obstruction, or fall in blood pressure, tolterodine tartrate tablets should be discontinued and appropriate therapy promptly provided.

PRECAUTIONS

General

Risk of Urinary Retention and Gastric Retention: Tolterodine tartrate tablets should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention and to patients with gastrointestinal obstructive disorders, such as pyloric stenosis, because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Decreased Gastrointestinal Motility: Tolterodine tartrate tablets, like other antimuscarinic drugs, should be used with caution in patients with decreased gastrointestinal motility.

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

Central Nervous System (CNS) Effects: Tolterodine tartrate tablet is associated with anticholinergic central nervous system (CNS) effects including dizziness and somnolence (see Adverse Reactions). 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.

Reduced Hepatic and Renal Function: For patients with significantly reduced hepatic function or renal function, the recommended dose of tolterodine tartrate tablets is 1 mg twice daily (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations**).

Myasthenia Gravis: Tolterodine tartrate tablets should be used with caution in patients with myasthenia gravis, a disease characterized by decreased cholinergic activity at the neuromuscular junction.

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, Cardiac Electrophysiology**), 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 tolterodine tartrate tablets for patients with a known history of QT prolongation or patients who are taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications (see **PRECAUTIONS, Drug Interactions**). There has been no association of Torsade de Pointes in the international post-marketing experience with tolterodine tartrate tablets.

Information for Patients

Patients should be informed that antimuscarinic agents such as tolterodine tartrate tablets may produce the following effects: blurred vision, dizziness, or drowsiness. Patients should be advised to exercise caution in decisions to engage in potentially dangerous activities until the drug's effects have been determined.

Drug Interactions

CYP3A4 Inhibitors: Ketoconazole, an inhibitor of the drug metabolizing enzyme CYP3A4, significantly increased plasma concentrations of tolterodine when coadministered to subjects who were poor metabolizers (see **CLINICAL PHARMACOLOGY**, Variability in Metabolism and **Drug-Drug Interactions**). For patients receiving 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, the recommended dose of tolterodine tartrate tablets is 1 mg twice daily (see **DOSAGE AND ADMINISTRATION**).

Drug-Laboratory-Test Interactions

Interactions between tolterodine and laboratory tests have not been studied.

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), AUC values obtained for tolterodine were 355, 291, and 462 mcg•h/L, respectively. In comparison, the human AUC value for a 2 mg dose administered twice daily is estimated at 34 mcg•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.

No mutagenic 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 (corresponding to AUC value of about 500 mcg•h/L), neither effects on reproductive performance or fertility were seen. Based on AUC values, the systemic exposure was about 15-fold higher in animals than in humans. In male mice, a dose of 30 mg/kg/day did not induce any adverse effects on fertility.

Pregnancy: *Teratogenic Effects*

Pregnancy Category C. At oral doses of 20 mg/kg/day (approximately 14 times the human exposure), no anomalies or malformations were observed in mice. When given at doses of 30 to 40 mg/kg/day, tolterodine has been shown to be embryolethal, reduce fetal weight, and increase the incidence of fetal abnormalities (cleft palate, digital abnormalities, intra-abdominal hemorrhage, and various skeletal abnormalities, primarily reduced ossification) in mice. At these doses, the AUC values were about 20- to 25-fold higher than in humans. Rabbits treated subcutaneously at a dose of 0.8 mg/kg/day achieved an AUC of 100 mcg•h/L, which is about 3-fold higher than that resulting from the human dose. This dose did not result in any embryotoxicity or teratogenicity. There are no studies of tolterodine in pregnant women. Therefore, tolterodine tartrate tablets should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus.

Nursing Mothers

Tolterodine is excreted into the milk in mice. Offspring of female mice treated with tolterodine 20 mg/kg/day during the lactation period had slightly reduced body weight gain. The offspring regained the weight during the maturation phase. It is not known whether tolterodine is excreted in human milk; therefore, tolterodine tartrate tablets should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue tolterodine tartrate tablets in nursing mothers.

Pediatric Use

Efficacy in the pediatric population has not been demonstrated.

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

Geriatric Use

Of the 1120 patients who were treated in the four Phase 3, 12-week clinical studies of tolterodine tartrate tablets, 474 (42%) were 65 to 91 years of age. No overall differences in safety were observed between the older and younger patients (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations**).

ADVERSE REACTIONS

The Phase 2 and 3 clinical trial program for tolterodine tartrate tablets included 3071 patients who were treated with tolterodine tartrate tablets (N=2133) or placebo (N=938). The patients were treated with 1, 2, 4, or 8 mg/day for up to 12 months. No differences in the safety profile of tolterodine were identified based on age, gender, race, or metabolism.

The data described below reflect exposure to tolterodine tartrate tablets 2 mg bid in 986 patients and to placebo in 683 patients exposed for 12 weeks in five Phase 3, controlled clinical studies. 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. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and approximating rates.

Sixty-six percent of patients receiving tolterodine tartrate tablets 2 mg bid reported adverse events versus 56% of placebo patients. The most common adverse events reported by patients receiving tolterodine tartrate tablets were dry mouth, headache, constipation, vertigo/dizziness, and abdominal pain. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and xerophthalmia are expected side effects of antimuscarinic agents.

Dry mouth was the most frequently reported adverse event for patients treated with tolterodine tartrate tablets 2 mg bid in the Phase 3 clinical studies, occurring in 34.8% of patients treated with tolterodine tartrate tablets and 9.8% of placebo-treated patients. One percent of patients treated with tolterodine tartrate tablets discontinued treatment due to dry mouth.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Seven percent of patients treated with tolterodine tartrate tablets 2 mg bid discontinued treatment due to adverse events versus 6% of placebo patients. The most common adverse events leading to discontinuation of tolterodine tartrate tablets were dizziness and headache.

Three percent of patients treated with tolterodine tartrate tablets 2 mg bid reported a serious adverse event versus 4% of placebo patients. Significant ECG changes in QT and QTc have not been demonstrated in clinical-study patients treated with tolterodine tartrate tablets 2 mg bid. Table 5 lists the adverse events reported in 1% or more of the patients treated with tolterodine tartrate tablets 2 mg bid in the 12-week studies. The adverse events are reported regardless of causality.

Table 5. Incidence* (%) of Adverse Events Exceeding Placebo Rate and Reported in >1% of Patients Treated with Tolterodine Tartrate Tablets (2 mg bid) in 12-week, Phase 3 Clinical Studies

Body System	Adverse Event	% Tolterodine Tartrate Tablets N=986	% Placebo N=683
Autonomic Nervous	accommodation abnormal	2	1
	dry mouth	35	10
General	chest pain	2	1
	fatigue	4	3
	headache	7	5
	influenza-like symptoms	3	2
Central/Peripheral Nervous	vertigo/dizziness	5	3
Gastrointestinal	abdominal pain	5	3
	constipation	7	4
	diarrhea	4	3
	dyspepsia	4	1
Urinary	dysuria	2	1
Skin/Appendages	dry skin	1	0
Musculoskeletal	arthralgia	2	1
Vision	xerophthalmia	3	2
Psychiatric	somnolence	3	2
Metabolic/Nutritional	weight gain	1	0
Resistance Mechanism	infection	1	0

*in nearest integer.

Post-marketing Surveillance

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; *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.

OVERDOSAGE

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

Management of Overdosage

Overdosage with tolterodine tartrate tablets 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 supratherapeutic 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 **PRECAUTIONS, Patients with Congenital or Acquired QT Prolongation**).

DOSAGE AND ADMINISTRATION

The initial recommended dose of tolterodine tartrate tablets is 2 mg twice daily. The dose may be lowered to 1 mg twice daily based on individual response and tolerability. 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 tolterodine tartrate tablets is 1 mg twice daily (see **PRECAUTIONS, General, PRECAUTIONS, Reduced Hepatic and Renal Function, and PRECAUTIONS, Drug Interactions**).

HOW SUPPLIED

Tolterodine Tartrate Tablets 1 mg are pale yellow, round, biconvex, film-coated tablets debossed with 'J' on one side and '157' on the other side.

They are supplied as follows:

Bottle of 60 tablets	NDC 31722-805-60
Bottle of 500 tablets	NDC 31722-805-05
Blister card of 10 unit dose tablets (ALU-ALU)	NDC 31722-805-31
Blister pack of 100 (10x10) unit dose tablets (ALU-ALU)	NDC 31722-805-01
Blister card of 10 unit dose tablets (PVC-PVDC)	NDC 31722-805-32
Blister pack of 100 (10x10) unit dose tablets (PVC-PVDC)	NDC 31722-805-02

Tolterodine Tartrate Tablets 2 mg are white, round, biconvex, film-coated tablets debossed with 'J' on one side and '158' on the other side.

They are supplied as follows:

Bottle of 60 tablets	NDC 31722-806-60
Bottle of 500 tablets	NDC 31722-806-05
Blister card of 10 unit dose tablets (ALU-ALU)	NDC 31722-806-31
Blister pack of 100 (10x10) unit dose tablets (ALU-ALU)	NDC 31722-806-01
Blister card of 10 unit dose tablets (PVC-PVDC)	NDC 31722-806-32
Blister pack of 100 (10x10) unit dose tablets (PVC-PVDC)	NDC 31722-806-02

Store at 20°C to 25°C (68° F to 77°F) [see USP Controlled Room Temperature].

CAMBER® PHARMACEUTICALS, INC.

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

By: Annora Pharma Pvt. Ltd.
Sangareddy - 502313, Telangana, India.

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- If you miss a dose of tolterodine tartrate tablets, just take your next regular dose at your next regular time. Do not try to make up for your missed dose.
- If you take too much tolterodine tartrate tablets, call your doctor, or go to the hospital emergency room right away.

What should I avoid while taking tolterodine tartrate tablets?

Medicines like tolterodine tartrate tablets can cause blurred vision, dizziness, and drowsiness. Do not drive, operate machinery, or do other dangerous activities until you know how tolterodine tartrate tablets affects you.

What are possible side effects of tolterodine tartrate tablets?

Tolterodine tartrate tablets may cause allergic reactions that may be serious. Symptoms of a serious allergic reaction may include swelling of the face, lips, throat or tongue. If you experience these symptoms, you should stop taking tolterodine tartrate tablets and get emergency medical help right away.

The most common side effects with tolterodine tartrate tablets are:

- Dry mouth
- Dizziness
- Headache
- Stomach pain
- Constipation

Tell your doctor if you have any side effects that bother you or that do not go away.

These are not all the side effects with tolterodine tartrate tablets. For a complete list, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How do I store tolterodine tartrate tablets?

- Store tolterodine tartrate tablets at room temperature 20°C to 25°C (68°F to 77°F).
- Keep them in a dry place.

Keep tolterodine tartrate tablets and all medicines out of the reach of children.

General Information about tolterodine tartrate tablets

Medicines are sometimes prescribed for conditions that are not mentioned in the patient information leaflet. Only use tolterodine tartrate tablets the way your doctor tells you. Do not give tolterodine tartrate tablets to other people even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about tolterodine tartrate tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about tolterodine tartrate tablets that is written for health professionals.

For more information, call 1-866-495-1995.

What are the ingredients in tolterodine tartrate tablets?

Active ingredients: tolterodine tartrate USP

Inactive ingredients: colloidal silicon dioxide, dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, microcrystalline cellulose, purified stearic acid, sodium starch glycolate and titanium dioxide. Additionally 1 mg tablet contains iron oxide yellow and iron oxide red.

Patient Information available at http://camberpharma.com/medication-guides

CAMBER® PHARMACEUTICALS, INC.

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

By: Annora Pharma Pvt. Ltd.
Sangareddy - 502313, Telangana, India.

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