Detrol™

tolterodine tartrate tablets

Pharmacia &Upjohn

Detrol tolterodine tartrate tablets

0817413000

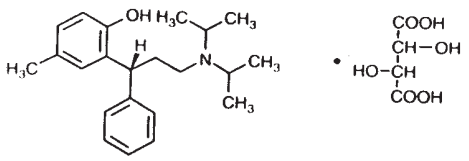
Detrol tolterodine tartrate tablets

0817413000

DESCRIPTION

DETROL Tablets contain tolterodine tartrate. The active moiety, tolterodine, is a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate. The empirical formula of tolterodine tartrate is $C_{26}H_{37}NO_7$, and its molecular weight is

475.6. The structural formula of tolterodine tartrate is represented below:



Tolterodine tartrate is a white, crystalline powder. It is soluble at 12 mg/mL in water at room temperature and is soluble in methanol, slightly soluble in ethanol, and practically insoluble in toluene.

DETROL Tablets for oral administration contain 1 or 2 mg of tolterodine tartrate. The inactive ingredients are colloidal anhydrous silica, calcium hydrogen phosphate dihydrate, cellulose microcrystalline, hydroxypropyl methylcellulose, magnesium stearate, sodium starch glycolate (pH 3.0 to 5.0), stearic acid, and titanium dioxide.

CLINICAL PHARMACOLOGY

Tolterodine is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors. In the anesthetized cat, tolterodine shows a selectivity for the urinary bladder over salivary glands; however, the clinical relevance of this finding has not been established.

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 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 a potent antimuscarinic action on the lower urinary tract.

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.

Effect of Food: Food intake increases the bioavailability of tolterodine (average increase 53%) and 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.

Detrol
brand of tolterodine tartrate tablets

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 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 cytochrome P450 2D6, the enzyme responsible for the formation of the 5-hydroxymethyl metabolite of tolterodine. The identified pathway of metabolism for these individuals, referred to as "poor metabolizers," is dealkylation via cytochrome P450 3A4 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. Because of differences in the protein-binding characteristics of tolterodine and the 5-hydroxymethyl metabolite, the sum of unbound serum concentrations of tolterodine and the 5-hydroxymethyl metabolite is similar in extensive and poor metabolizers at steady state. Since tolterodine and the 5-hydroxymethyl metabolite have similar antimuscarinic effects, the net activity of DETROL Tablets is expected to be similar in extensive and poor metabolizers.

Excretion: Following administration of a 5-mg oral dose of ^{14}C-tolterodine to healthy volunteers, 77% of radioactivity was recovered in urine and 17% was recovered in feces. 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. 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.

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

Detrol
brand of tolterodine tartrate tablets

Phenotype (CYP2D6)	Tolterodine					5-Hydroxymethyl Metabolite			
	t_{max} (h)	C_{max}* (µg/L)	C_{avg}* (µg/L)	$t_{1/2}$ (h)	CL/F (L/h)	t_{max} (h)	C_{max}* (µg/L)	C_{avg}* (µg/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.
† – = not applicable.

Pharmacokinetics in Special Populations

Age: In Phase 1, multiple-dose studies in which tolterodine 2 mg was administered twice daily, 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 1 or 2 mg twice daily. 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 in Phase 3, 12-week, controlled clinical studies; therefore, no dosage adjustment is recommended (see PRECAUTIONS, Geriatric Use).

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

Gender: The pharmacokinetics of tolterodine and the 5-hydroxymethyl metabolite are not influenced by gender. Mean C_{max} of tolterodine (1.6 µg/L in males versus 2.2 µg/L in females) and the active 5-hydroxymethyl metabolite (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/L in males versus 7.8 µg/L in females) and the 5-hydroxymethyl metabolite (10 µg/L in males versus 11 µg/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 3.0 hours in females and 3.3 hours in males.

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

Renal Insufficiency: The pharmacokinetics of tolterodine in patients with renal insufficiency have not been evaluated. The renal excretion of tolterodine and the 5-hydroxymethyl metabolite are negligible, and a decrease in total body clearance is not expected in patients with renal insufficiency. However, patients with renal impairment should be treated with caution.

Hepatic Insufficiency: Liver impairment can significantly alter the disposition of tolterodine. In a study conducted in cirrhotic patients, the 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 DETROL greater than 1 mg twice daily (see PRECAUTIONS, General).

Drug-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. 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 to resemble the pharmacokinetic profile in poor metabolizers. The sums of unbound serum concentrations of tolterodine and the 5-hydroxymethyl metabolite are only 25% higher during the interaction. No dose adjustment is required when DETROL and fluoxetine are coadministered.

Other Drugs Metabolized by Cytochrome P450 2D6: Tolterodine is not expected to influence the pharmacokinetics of drugs that are metabolized by cytochrome P450 2D6, such as flecainide, vinblastine, carbamazepine, and tricyclic antidepressants; however, the potential effect of tolterodine on the pharmacokinetics of these drugs has not been formally evaluated.

Warfarin: In healthy volunteers, coadministration of tolterodine 2 mg twice daily for 7 days and a single 25-mg dose of warfarin 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 had 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.

CLINICAL STUDIES

DETROL Tablets were evaluated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence in three placebo-controlled, 12-week studies. A total of 339 patients received DETROL 2 mg twice daily and 177 patients received placebo. The majority of patients were Caucasian (95%) and female (75%), with a mean age of 60 years (range,

Detrol
brand of tolterodine tartrate tablets

19 to 91 years). At study entry, nearly all patients perceived they had urgency (98%) and most patients had increased frequency of micturitions (89%) and urge incontinence (83%). These characteristics were well balanced across treatment groups for the three studies.

The efficacy endpoints included the change from baseline for:

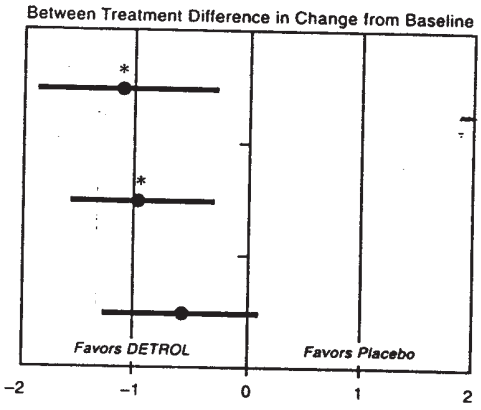
- number of micturitions per 24 hours (averaged over 7 days)
- number of incontinence episodes per 24 hours (averaged over 7 days)
- volume of urine voided per micturition (averaged over 2 days)

Efficacy results for the three placebo-controlled, 12-week studies are presented in the following figures:

95% Confidence Intervals for the Difference between DETROL (2 mg bid) and Placebo for the Median Change at Week 12 from Baseline

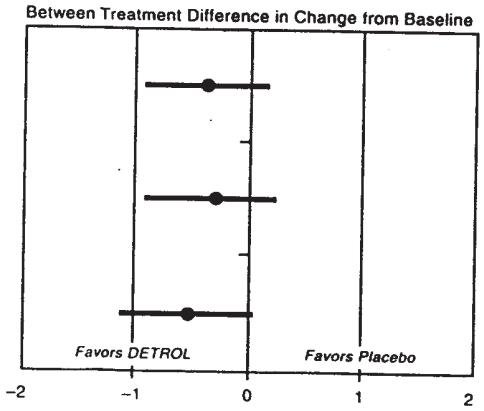
Number of Micturitions per 24 Hours

Study		DETROL	Placebo
008	number of patients	118	56
	median baseline	10.5	10.6
	median (SD) change from baseline	-2.2 (3.8)	-1.1 (3.6)
009	number of patients	128	64
	median baseline	10.4	10.4
	median (SD) change from baseline	-2.2 (2.1)	-1.2 (2.3)
010	number of patients	108	56
	median baseline	11.0	10.9
	median (SD) change from baseline	-1.6 (2.3)	-1.1 (2.8)



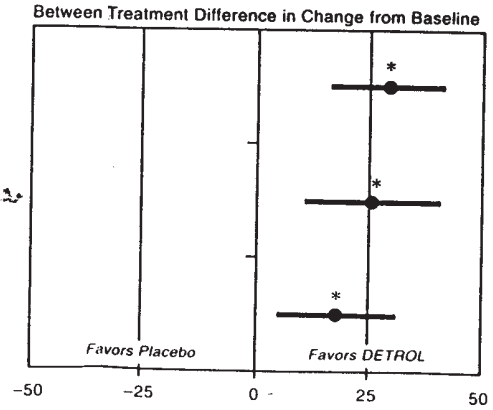
Number of Incontinence Episodes per 24 Hours

Study		DETROL	Placebo
008	number of patients	93	40
	median baseline	2.4	2.5
	median (SD) change from baseline	-1.2 (3.2)	-0.8 (1.5)
009	number of patients	116	55
	median baseline	2.5	3.2
	median (SD) change from baseline	-1.4 (2.5)	-1.1 (2.5)
010	number of patients	90	50
	median baseline	2.7	2.2
	median (SD) change from baseline	-1.5 (2.4)	-0.9 (2.1)



Volume Voided per Micturition (mL)

Study		DETROL	Placebo
008	number of patients	118	56
	median baseline	156	155
	median (SD) change from baseline	34 (54)	5 (42)
009	number of patients	128	64
	median baseline	149	157
	median (SD) change from baseline	34 (50)	8 (47)
010	number of patients	108	56
	median baseline	148	164
	median (SD) change from baseline	27 (45)	10 (52)



*The difference between DETROL and placebo was statistically significant

Detrol
brand of tolterodine tartrate tablets

INDICATIONS AND USAGE
DETROL Tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

CONTRAINDICATIONS
DETROL Tablets are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. DETROL is also contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

PRECAUTIONS
General
Risk of Urinary Retention and Gastric Retention: DETROL 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).

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

Reduced Hepatic and Renal Function: Patients with significantly reduced hepatic function should not receive doses of DETROL greater than 1 mg twice daily. Patients with renal impairment should be treated with caution (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

Information for Patients
Patients should be informed that antimuscarinic agents such as tolterodine may produce blurred vision.

Drug Interactions
Cytochrome P450 3A4 Inhibitors: Pharmacokinetic studies with patients concomitantly receiving cytochrome P450 3A4 inhibitors, such as macrolide antibiotics (erythromycin and clarithromycin) or antifungal agents (ketoconazole, itraconazole, and miconazole), have not been performed. Patients receiving cytochrome P450 3A4 inhibitors should not receive doses of DETROL greater than 1 mg twice daily.

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 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.

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.

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 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
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 cause embryolethality, 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 µg•h/L, which is about three-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, DETROL should be used during pregnancy only if the potential benefit for the mother justifies the potential risk for 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, administration of DETROL should be discontinued during nursing.

Pediatric Use
The safety and effectiveness of DETROL in pediatric patients have not been established.

Geriatric Use
Of the 1120 patients who were treated in the four, Phase 3, 12-week clinical studies of DETROL, 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 DETROL included 2049 patients who were treated with DETROL (N=1619) or placebo (N=430). No differences in the safety profile of tolterodine were identified based on age, gender, race, or metabolism. Four Phase 3, 12-week, controlled clinical studies form the basis for the main evaluation of safety, and the results are summarized below.

Adverse events considered to be treatment-related were dry mouth, dyspepsia, headache, constipation, and xerophthalmia. Dry mouth, constipation, abnormal vision (accommodation

Detrol
brand of tolterodine tartrate tablets

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.