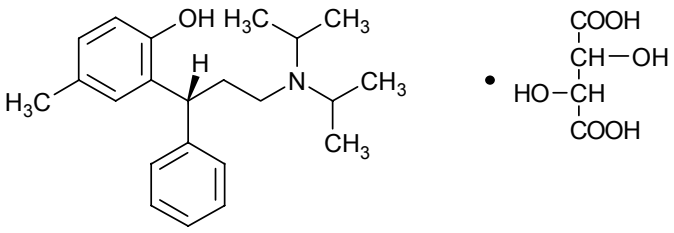
Detrol® LA

tolterodine tartrate

extended release capsules

DESCRIPTION

DETROL LA Capsules contain tolterodine tartrate. The active moiety, tolterodine, is a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is (R)-N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate. The empirical formula of tolterodine tartrate is $C_{26}H_{37}NO_7$, and its molecular weight is 475.6. The structural formula of tolterodine tartrate is represented below.



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

DETROL LA for oral administration contains 2 mg or 4 mg of tolterodine tartrate. Inactive ingredients are sucrose, starch, hypromellose, ethylcellulose, medium chain triglycerides, oleic acid, gelatin, and FD&C Blue #2. The 2-mg capsules also contain yellow iron oxide. Both capsule strengths are imprinted with a pharmaceutical grade printing ink that contains shellac glaze, titanium dioxide, propylene glycol, and simethicone.

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

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

Distribution: Tolterodine is highly bound to plasma proteins, primarily α_1-acid glycoprotein. Unbound concentrations of tolterodine average 3.7% ± 0.13% over the concentration range achieved in clinical studies. 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 Caucasian 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 extended 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 extended release administered daily to 17 healthy male volunteers (13 EM, 4 PM).

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

	Tolterodine				5-hydroxymethyl metabolite			
	t_{max}† (h)	C_{max} (µg/L)	C_{avg} (µg/L)	t½ (h)	t_{max}† (h)	C_{max} (µg/L)	C_{avg} (µg/L)	t½ (h)
Single dose 4 mg*								
EM	4 (2 - 6)	1.3 (0.8)	0.8 (0.57)	8.4 (3.2)	4 (3 - 6)	1.6 (0.5)	1.0 (0.32)	8.8 (5.9)
Multiple dose 4 mg								
EM	4 (2 - 6)	3.4 (4.9)	1.7 (2.8)	6.9 (3.5)	4 (2 - 6)	2.7 (0.90)	1.4 (0.6)	9.9 (4.0)
PM	4 (3 - 6)	19 (16)	13 (11)	18 (16)	--‡	--	--	--

*Parameter dose-normalized from 8 to 4 mg for the single-dose data.
C_{max} = Maximum serum concentration; t_{max} = Time of occurrence of C_{max};
C_{avg} = Average serum concentration; t½ = Terminal elimination half-life.
†Data presented as median (range).
‡ = 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 the Phase 3, 12-week, controlled clinical studies; therefore, no tolterodine dosage adjustment for elderly patients is recommended (see **PRECAUTIONS, Geriatric Use**).

Pediatric:
Efficacy in the pediatric population has not been demonstrated.

The pharmacokinetics of tolterodine extended release capsules have been evaluated in pediatric patients ranging in age from 11-15 years. The dose-plasma concentration relationship was linear over the range of doses assessed. Parent/metabolite ratios differed according to CYP2D6 metabolizer status: EMs had low serum concentrations of tolterodine and high concentrations of the active 5-hydroxymethyl metabolite, while PMs had high concentrations of tolterodine and negligible active metabolite concentrations.

Gender: The pharmacokinetics of tolterodine immediate release and the 5-hydroxymethyl metabolite are not influenced by gender. Mean C_{max} of tolterodine immediate release (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 immediate release 2 mg. Mean AUC values of tolterodine (6.7 µg·h/L in males versus 7.8 µg·h/L in females) and the 5-hydroxymethyl metabolite (10 µg·h/L in males versus 11 µg·h/L in females) are also similar. The elimination half-life of tolterodine immediate release 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: Renal impairment can significantly alter the disposition of tolterodine immediate release and its metabolites. In a study conducted in patients with

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