PRODUCT MONOGRAPH

DETROL*

(tolterodine L-tartrate)

1 mg and 2 mg Tablets

Anticholinergic - Antispasmodic Agent

Pfizer Canada Inc
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Kirkland, Quebec H9J 2M5

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PRODUCT MONOGRAPH

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(tolterodine L-tartrate tablets)

Anticholinergic- Antispasmodic Agent

ACTION AND CLINICAL PHARMACOLOGY

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. 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*.

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}) 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 PHARMACOLOGY).

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% $\pm$ 14% and 29% $\pm$ 6.3% of the metabolites recovered in the urine respectively. 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* (see PHARMACOLOGY).

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.

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

Pharmacokinetics in Special Populations

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 PHARMACOLOGY).

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 PHARMACOLOGY).

Renal Impairment: 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 PHARMACOLOGY).

INDICATIONS AND CLINICAL USE

DETROL (tolterodine L-tartrate tablets) 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.

CONTRAINDICATIONS

DETROL (tolterodine L-tartrate tablets) is contraindicated in patients with:

- urinary retention,
- gastric retention,
- uncontrolled narrow angle glaucoma,
- known hypersensitivity to the drug or its ingredients.

WARNINGS

Patients at Risk of Urinary Retention and Gastric Retention

DETROL (tolterodine L-tartrate tablets) 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).

Controlled Narrow Angle Glaucoma

DETROL should be used with caution in patients being treated for narrow angle glaucoma.

Use in Pregnancy

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, DETROL 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.

Use in 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 DETROL should be avoided during nursing.

Use in Children

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

PRECAUTIONS

Impaired Hepatic and Renal Function

Patients with impaired hepatic function and patients with renal impairment should not receive doses of DETROL (tolterodine L-tartrate tablets) greater than 1 mg, twice daily. (see CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations).

Use in Geriatrics

Of the 1120 patients who were treated in the four, phase III, 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).

Drug Interactions

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.

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 CLINICAL PHARMACOLOGY, Drug Interactions).

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 CLINICAL PHARMACOLOGY, Drug Interactions).

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 DETROL greater than 1 mg twice daily (see CLINICAL PHARMACOLOGY, Drug Interactions).

Coadministration of diuretics (such as indapamide, hydrochlorothiazide, triamterene, bendroflumethiazide, chlorothiazide, methylchlorothiazide, or furosemide) with DETROL (2 mg, twice daily) did not cause any adverse ECG effects.

Clinical drug interaction studies have shown that there are no known interactions between tolterodine and warfarin or oral contraceptives (ethinyl estradiol/levonorgestrel).

Drug-Laboratory Test Interactions

Interactions between tolterodine and laboratory tests have not been studied.

Patient Counselling

Patients should be informed that antimuscarinic agents such as DETROL may produce blurred vision or dizziness.

ADVERSE REACTIONS

The clinical trial program for DETROL (tolterodine L-tartrate tablets) comprised 2398 patients who were treated with either DETROL (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 DETROL, 2 mg twice daily (N=474), DETROL 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 DETROL 2 mg twice daily (75.5%), DETROL 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 DETROL 2 mg and placebo compared with oxybutynin ($P<0.0001$). The incidence of serious adverse events was similar among treatment groups (DETROL 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 DETROL 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.

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 nerv	Mouth dry	28	(15.9)	29	(24.0)	187	(39.5)	273	(78.2)
	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%). Adverse events observed in <1% of patients were confusion, gastroesophageal reflux, flushed skin, and allergic reactions.

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

SYMPTOMS AND TREATMENT OF 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 DETROL (tolterodine L- tartrate tablets) that involved a 27-month-old child who ingested 5 to 7 tablets of DETROL 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 DETROL 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.

DOSAGE AND ADMINISTRATION

The initial recommended dose of DETROL (tolterodine L- tartrate tablets) 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 PRECAUTIONS).

Patients treated with potent CYP3A4 inhibitors should **NOT** receive doses of DETROL greater than 1 mg twice daily (see PRECAUTIONS).

Administration of DETROL 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.

DETROL can be taken with food.

PHARMACEUTICAL INFORMATION

Drug substance

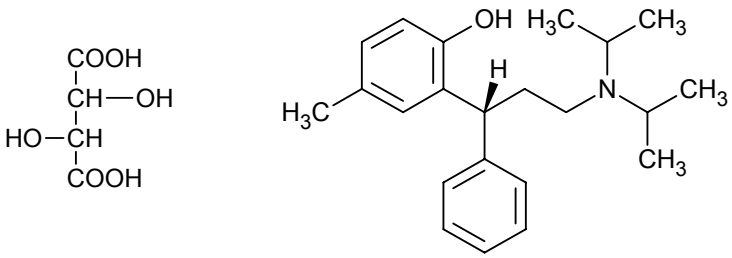
Proper name: tolterodine L-tartrate

Chemical name(s): (1) (R)-2-[3[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methylphenol [R-(R*,R*)]-2,3-dihydroxybutanedioate (1:1) (salt)

(2) (+)-(R)-2-[α-[2-(diisopropylamino)ethyl]benzyl]-p-cresol L-tartrate (1:1) (salt)

Molecular formula: $C_{26}H_{37}NO_7$

Structural formula:



Molecular weight: 475.6

Physical form: Crystalline, white powder

Solubility: soluble at 12 mg/mL in water at room temperature, soluble in methanol, slightly soluble in ethanol and practically insoluble in toluene.

pH: 3.0 - 4.5 in water (1%, m/V)

pKa: 9.9

Melting point: 206˚C – 212˚C

Tablet Composition

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

Stability and storage recommendations

Store at room temperature 15˚C to 30˚C.

AVAILABILITY OF DOSAGE FORMS

DETROL (tolterodine L-tartrate tablets) is available as **1 mg tablets** (white, round, biconvex, film-coated tablets engraved with arcs above and below the letters "TO"), and **2 mg tablets** (white, round, biconvex, film-coated tablets engraved with arcs above and below the letters "DT") and are supplied as follows:

Bottles of 60: 1 mg and 2 mg.

Bottles of 500: 1 mg and 2 mg.

INFORMATION FOR THE PATIENT

Please read this leaflet carefully before you use this medication. This leaflet provides some useful information for you on DETROL (tolterodine L-tartrate tablets). If you have any questions about this medication or your condition, please ask your doctor or pharmacist.

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 is DETROL?

The name of this medication is DETROL. Each tablet contains 1 mg or 2 mg of the active ingredient tolterodine L-tartrate.

The tablets also contain the following inactive ingredients:

colloidal anhydrous silica, calcium hydrogen phosphate dihydrate, hypromellose, magnesium stearate, cellulose microcrystalline, sodium starch glycolate, stearic acid, and titanium dioxide.

DETROL 1 mg tablets are white and marked with curved lines above and below the lettering “TO”.

DETROL 2 mg tablets are white and marked with curved lines above and below the lettering “DT”.

What is DETROL used for?

It is used for the treatment of the symptoms of overactive bladder which include frequency, urgency, and urge incontinence.

How does DETROL work?

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

Before taking DETROL

You should tell your doctor if:

- You are pregnant, or trying to become pregnant.
- You are breastfeeding your child.
- You have ever had a reaction to tolterodine or any of the other ingredients before.
- You suffer with glaucoma (high pressure and pain in the eyes)
- You have difficulty voiding
- You have stomach problems affecting passage and digestion of food.
- You have liver problems.
- You have kidney problems.
- About any other medication you are taking or have taken recently, including medication bought without a prescription. They may affect your condition, or how DETROL works for you.

How should you take DETROL?

Adults and Elderly:

The usual starting dose is 2 mg twice daily, but may be decreased to 1 mg twice daily. Your doctor will advise you of how many tablets to take and how often. Do not take more or less tablets than have been prescribed for you.

How long should you take DETROL?

Do not stop taking DETROL without first talking to your doctor. Your doctor will advise you of the length of treatment.

What should you do if you forget to take your tablets?

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.

What if you take too many tablets?

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 immediately.

Are there any side effects with DETROL?

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
- difficulty in urination (passing water)

Check with your doctor or pharmacist right away if you have ***any*** bothersome or unusual effects while

taking DETROL.

How to store DETROL

Store at room temperature 15˚C to 30˚C.

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.

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 (≥15 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.

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

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).

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).

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.

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 (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.

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.

The potential effect of tolterodine on the pharmacokinetics 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). 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 DETROL 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 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 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 DETROL greater than 1 mg twice daily (see 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 DETROL and fluoxetine are coadministered. (see PRECAUTIONS, 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 PRECAUTIONS, 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 PRECAUTIONS, 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 DETROL.

Clinical Trials

DETROL (tolterodine L- tartrate tablets) 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 DETROL 2 mg twice daily (N=227) with oxybutynin 5 mg three times daily (N=230) and placebo (N=113). A third study compared DETROL 1 mg (N=123) and 2 mg (N=129) twice daily and placebo (N=64). The fourth study compared

DETROL 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.

After 12 weeks of treatment, DETROL 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 DETROL 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, DETROL 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 DETROL, 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).

Efficacy Results in Study –008

	Placebo	**Tolterodine 2 mg b.i.d.**	**Oxybutynin 5 mg t.i.d.**	**Equivalence**
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)	
pv. placebo	-	<0.0001	<0.0001	

Efficacy Results in Study –010

	Placebo	**Tolterodine 2 mg b.i.d.**	**Oxybutynin 5 mg t.i.d**	**Equivalence**
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 –009

	Placebo	Tolterodine 1 mg b.i.d.	Tolterodine 2 mg b.i.d.	Equivalence
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 –015

	Placebo	Tolterodine 2 mg b.i.d.	Oxybutynin 5 mg t.i.d	Equivalence
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

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.

In the 26 and 52 week studies, ECG recordings revealed increased tachycardia which was most pronounced at one hour after dosing on day 1. However, the dogs adapted and on later occasions, no effect on heart rate was found. In the 26 week study, ECG measurements showed a slight QT-prolongation, although within normal range, and an increased T-wave duration, occasionally in some dogs from the high dose group.

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.

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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