CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-228 S006

APPROVED LABELING

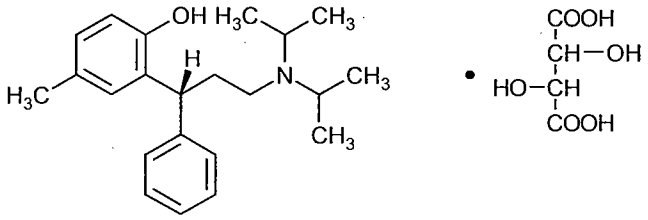
Detrol® LA

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

creatinine clearance between 10 and 30 mL/min, tolterodine immediate release and the 5-hydroxymethyl metabolite levels were approximately 2-3 fold higher in patients with renal impairment than in healthy volunteers. Exposure levels of other metabolites of tolterodine (eg, tolterodine acid, *N*-dealkylated tolterodine acid, *N*-dealkylated tolterodine and *N*-dealkylated hydroxy tolterodine) were significantly higher (10-30 fold) in renally impaired patients as compared to the healthy volunteers. The recommended dose for patients with significantly reduced renal function is tolterodine 2 mg daily (see **PRECAUTIONS, General**).

Hepatic Insufficiency: Liver impairment can significantly alter the disposition of tolterodine immediate release. In a study of tolterodine immediate release 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 immediate release 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 2 mg daily (see **PRECAUTIONS, General**).

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 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 a 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 CYP3A4 inhibitors such as other azole antifungals (eg, itraconazole, miconazole) or macrolide antibiotics (eg, 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 μg/levonorgestrel 150 μg) as evidenced by the monitoring of ethinyl estradiol and levonorgestrel over a 2-month period 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.

CLINICAL STUDIES

DETROL LA Capsules 2 mg were evaluated in 29 patients in a Phase 2 dose-effect study. DETROL LA 4 mg was evaluated for the treatment of overactive bladder with symptoms of urge urinary incontinence and frequency in a randomized, placebo-controlled, multicenter, double-blind, Phase 3, 12-week study. A total of 507 patients received DETROL LA 4 mg once daily in the morning and 508 received placebo. The majority of patients were Caucasian (95%) and female (81%), with a mean age of 61 years (range, 20 to 93 years). In the study, 642 patients (42%) were 65 to 93 years of age. The study included patients known to be responsive to tolterodine immediate release and other anticholinergic medications, however, 47% of patients never received prior pharmacotherapy for overactive bladder. At study entry, 97% of patients had at least 5 urge incontinence episodes per week and 91% of patients had 8 or more micturitions per day. The primary efficacy endpoint was change in mean number of incontinence episodes per week at week 12 from baseline. Secondary efficacy endpoints included change in mean number of micturitions per day and mean volume voided per micturition at week 12 from baseline.

Table 2. 95% Confidence Intervals (CI) for the Difference between DETROL LA (4 mg daily) and Placebo for Mean Change at Week 12 from Baseline*

	DETROL LA (n=507)	Placebo (n=508)†	Treatment Difference, vs Placebo (95% CI)
Number of incontinence episodes/week			
Mean Baseline	22.1	23.3	-4.8‡
Mean Change from Baseline	-11.8 (SD 17.8)	-6.9 (SD 15.4)	(-6.9, -2.8)
Number of micturitions/day			
Mean Baseline	10.9	11.3	
Mean Change from Baseline	-1.8 (SD 3.4)	-1.2 (SD 2.9)	-0.6‡ (-1.0, -0.2)
Volume Voided per micturition (mL)			
Mean Baseline	141	136	
Mean Change from Baseline	34 (SD 51)	14 (SD 41)	20‡ (14, 26)

SD = Standard Deviation.
* Intent-to-treat analysis.
† 1 to 2 patients missing in placebo group for each efficacy parameter.
‡ The difference between DETROL LA and placebo was statistically significant.

INDICATIONS AND USAGE

DETROL LA Capsules are once daily extended release capsules indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

CONTRAINDICATIONS

DETROL LA Capsules are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. DETROL LA 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 LA Capsules 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 LA should be used with caution in patients being treated for narrow-angle glaucoma.

Reduced Hepatic and Renal Function: For patients with significantly reduced hepatic function or renal function, the recommended dose for DETROL LA is 2 mg daily (see **CLINICAL PHARMACOLOGY**, **Pharmacokinetics in Special Populations**).

Information for Patients

Patients should be informed that antimuscarinic agents such as DETROL LA may produce the following effects: blurred vision, dizziness, or drowsiness.

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 (eg, itraconazole, miconazole) or macrolide antibiotics (eg, erythromycin, clarithromycin) or cyclosporine or vinblastine, the recommended dose of DETROL LA is 2 mg daily.

Drug-Laboratory-Test Interactions

Interactions between tolterodine and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with tolterodine immediate release 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 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 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 be embryolethal and 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 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, DETROL LA should be used during pregnancy only if the potential benefit for the mother justifies the potential risk to the fetus.

Nursing Mothers

Tolterodine immediate release 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, DETROL LA should not be administered during nursing. A decision should be made whether to discontinue nursing or to discontinue DETROL LA in nursing mothers.

Pediatric Use

Efficacy in the pediatric population has not been demonstrated.

A total of 710 pediatric patients (486 on DETROL LA, 224 on placebo) aged 5-10 with urinary frequency and urge incontinence were studied in two phase 3 randomized, placebo-controlled, double blind, 12 week studies. The percentage of patients with

urinary tract infections was higher in patients treated with DETROL LA (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 DETROL LA compared to 0.9% of children treated with placebo.

Geriatric Use

No overall differences in safety were observed between the older and younger patients treated with tolterodine (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations**).

ADVERSE REACTIONS

The Phase 2 and 3 clinical trial program for DETROL LA Capsules included 1073 patients who were treated with DETROL LA (n=537) or placebo (n=536). The patients were treated with 2, 4, 6, or 8 mg/day for up to 15 months. 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 for approximating rates. The data described below reflect exposure to DETROL LA 4 mg once daily every morning in 505 patients and to placebo in 507 patients exposed for 12 weeks in the Phase 3, controlled clinical study.

Adverse events were reported in 52% (n=263) of patients receiving DETROL LA and in 49% (n=247) of patients receiving placebo. The most common adverse events reported by patients receiving DETROL LA were dry mouth, headache, constipation, and abdominal pain. Dry mouth was the most frequently reported adverse event for patients treated with DETROL LA occurring in 23.4% of patients treated with DETROL LA and 7.7% of placebo-treated patients. Dry mouth, constipation, abnormal vision (accommodation abnormalities), urinary retention, and dry eyes are expected side effects

of antimuscarinic agents. A serious adverse event was reported by 1.4% (n=7) of patients receiving DETROL LA and by 3.6% (n=18) of patients receiving placebo.

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Similar percentages of patients treated with DETROL LA or placebo discontinued treatment due to adverse events. Treatment was discontinued due to adverse events and dry mouth was reported as an adverse event in 2.4% (n=12) of patients treated with DETROL LA and in 1.2% (n=6) of patients treated with placebo.

Table 3 lists the adverse events reported in 1% or more of patients treated with DETROL LA 4 mg once daily in the 12-week study. The adverse events were reported regardless of causality.

Table 3. Incidence* (%) of Adverse Events Exceeding Placebo Rate and Reported in ≥1% of Patients Treated with DETROL LA (4 mg daily) in a 12-week, Phase 3 Clinical Trial

Body System	Adverse Event	% DETROL LA n=505	% Placebo n=507
Autonomic Nervous	dry mouth	23	8
General	headache	6	4
	fatigue	2	1
Central/Peripheral Nervous	dizziness	2	1
Gastrointestinal	constipation	6	4
	abdominal pain	4	2
	dyspepsia	3	1
Vision	xerophthalmia	3	2
	vision abnormal	1	0
Psychiatric	somnolence	3	2
	anxiety	1	0
Respiratory	sinusitis	2	1
Urinary	dysuria	1	0

* in nearest integer.

Postmarketing Surveillance

The following events have been reported in association with tolterodine use in clinical practice: anaphylactoid reactions, including angioedema; tachycardia; palpitations; peripheral edema; and hallucinations. Because these spontaneously reported events are from the worldwide postmarketing 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 immediate release 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 DETROL LA Capsules 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 suprapharmacologic 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 not observed with tolterodine immediate release at doses up to 8 mg (4 mg bid) and higher doses were not evaluated.

DOSAGE AND ADMINISTRATION

The recommended dose of DETROL LA Capsules are 4 mg daily. DETROL LA should be taken once daily with liquids and swallowed whole. The dose may be lowered to 2 mg daily based on individual response and tolerability, however, limited efficacy data is available for DETROL LA 2 mg (see **CLINICAL STUDIES**).

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 DETROL LA is 2 mg daily (see **CLINICAL PHARMACOLOGY** and **PRECAUTIONS, Drug Interactions**).

HOW SUPPLIED

DETROL LA Capsules 2 mg are blue-green with symbol and 2 printed in white ink. DETROL LA Capsules 4 mg are blue with symbol and 4 printed in white ink. DETROL LA Capsules are supplied as follows:

Bottles of 30		Bottles of 500	
2 mg Capsules	NDC 0009-5190-01	2 mg Capsules	NDC 0009-5190-03
4 mg Capsules	NDC 0009-5191-01	4 mg Capsules	NDC 0009-5191-03
		Unit Dose	
Bottles of 90		Blisters	
2 mg Capsules	NDC 0009-5190-02	2 mg Capsules	NDC 0009-5190-04
4 mg Capsules	NDC 0009-5191-02	4 mg Capsules	NDC 0009-5191-04

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from light.

Rx only

US Patent No. 5,382,600

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Pharmacia & Upjohn Company

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By

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