

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-771/S-011

Trade Name: Detrol 1 and 2 mg

Generic Name: tolterodine tartrate tablets

Sponsor: Pharmacia & Upjohn Company

Approval Date: 01/05/2004

Indications: For the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

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**APPLICATION NUMBER:
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APPLICATION NUMBER:

20-771/S-011

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-771/S-011

Pharmacia & Upjohn Company
Attention: Tara Feehan
Manager, US Regulatory Affairs
235 East 42nd Street
New York, New York 10017

Dear Ms. Feehan:

Please refer to your supplemental new drug application dated August 20, 2002 received August 21, 2002 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Detrol[®] (tolterodine tartrate) 1 mg and 2 mg tablets.

We are also in receipt of your submission dated September 25, 2003 received on September 26, 2003, wherein the "Changes Being Effected" Labeling Supplement provides for the addition of angioedema, palpitations, and minor editorial changes to the "Postmarketing Surveillance" section of the package insert (PI).

We have completed our review of this supplemental application and it is approved, effective on the date of this letter. Other than the approved revisions identified in this letter, the final printed label (FPL) must be identical to the labeling submission dated July 30, 2003.

Please submit the updated final printed labeling (FPL), with the aforementioned approved revisions, electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-771/S-011." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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Detrol (tolterodine tartrate)
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We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call, Jean Makie, R.D., MS, Regulatory Project Manager, at (301) 872-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Drug
Products (HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Daniel A. Shames
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APPLICATION NUMBER:

20-771/S-011

LABELING

Detrol[®]

tolterodine tartrate tablets

PHARMACIA

Detrol
tolterodine tartrate
tablets



0817413008

Detrol
tolterodine tartrate
tablets



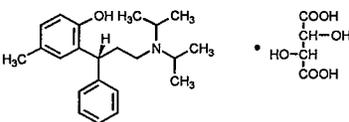
0817413008

Detrol

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DESCRIPTION

DETROL Tablets contain tolterodine tartrate. The active moiety, tolterodine, is a muscarinic receptor antagonist. The chemical name of tolterodine tartrate is (R)-2-[3-(1-methylethyl-amino)-1-phenylpropyl]-4-methylphenol [(R-(R*,R*))]-2,3-dihydroxybutanedioate (1:1) (salt). The empirical formula of tolterodine tartrate is C₂₆H₃₇NO₇, 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 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, hypromellose, 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.

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 ¹⁴C-tolterodine solution in healthy volunteers who received a 5-mg oral dose, at least 77% of the radiolabeled dose was absorbed. Tolterodine immediate

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release is rapidly absorbed, and maximum serum concentrations (C_{max}) typically occur within 1 to 2 hours after dose administration. C_{max} and area under the concentration-time curve (AUC) determined after dosage of tolterodine immediate release are dose-proportional over the range of 1 to 4 mg.

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

Distribution: Tolterodine is highly bound to plasma proteins, primarily α_1 -acid glycoprotein. Unbound concentrations of tolterodine average 3.7% \pm 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% \pm 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 \pm 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% \pm 14% and 29% \pm 6.3% of the metabolites recovered in the urine, respectively.

Variability in Metabolism: A subset (about 7%) of the population is devoid of CYP2D6, the enzyme responsible for the formation of the 5-hydroxymethyl metabolite of tolterodine. The identified pathway of metabolism for these individuals ("poor metabolizers") is dealkylation via cytochrome P450 3A4 (CYP3A4) to N-dealkylated tolterodine. The remainder of the population is referred to as "extensive metabolizers." Pharmacokinetic studies revealed that tolterodine is metabolized at a slower rate in poor metabolizers than in extensive metabolizers; this results in significantly higher serum concentrations of tolterodine and in negligible concentrations of the 5-hydroxymethyl metabolite.

Excretion: Following administration of a 5-mg oral dose of ¹⁴C-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 (\pm standard deviation) pharmacokinetic parameters of tolterodine immediate release and the 5-hydroxymethyl metabolite in extensive (EM) and poor (PM) metabolizers is provided in Table 1. These data were obtained following single- and multiple-doses of tolterodine 4 mg administered twice daily to 16 healthy male volunteers (8 EM, 8 PM).

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

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.
 EM = Extensive metabolizers; PM = Poor metabolizers.
 † - = not applicable.

Pharmacokinetics in Special Populations

Age: In Phase 1, multiple-dose studies in which tolterodine immediate release 4 mg (2 mg bid) was administered, serum concentrations of tolterodine and of the 5-hydroxymethyl metabolite were similar in healthy elderly volunteers (aged 64 through 80 years) and healthy young volunteers (aged less than 40 years). In another Phase 1 study, elderly volunteers (aged 71 through 81 years) were given tolterodine immediate release 2 or 4 mg (1 or 2 mg bid). Mean serum concentrations of tolterodine and the 5-hydroxymethyl metabolite in these elderly volunteers were approximately 20% and 50% higher, respectively, than reported in young healthy volunteers. However, no overall differences were observed in safety between older and younger patients on tolterodine in Phase 3, 12-week, controlled clinical studies; therefore, no tolterodine dosage adjustment for elderly patients is recommended (see **PRECAUTIONS, Geriatric Use**).

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

Gender: The pharmacokinetics of tolterodine immediate release and the 5-hydroxymethyl metabolite are not influenced by gender. Mean C_{max} of tolterodine (1.6 mg/L in males versus 2.2 mg/L in females) and the active 5-hydroxymethyl metabolite (2.2 mg/L in males versus 2.5 mg/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 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 hydroxylated tolterodine) were significantly higher (10-30 fold) in renally impaired patients as compared to the healthy volunteers. The recommended dosage for patients with significantly reduced renal function is DETROL 1 mg twice daily (see **PRECAUTIONS, General**).

Hepatic Insufficiency: Liver impairment can significantly alter the disposition of tolterodine immediate release. In a study conducted in cirrhotic patients, the elimination half-life of tolterodine immediate release was longer in cirrhotic patients (mean, 7.8 hours) than in healthy, young, and elderly volunteers (mean, 2 to 4 hours). The clearance of orally administered tolterodine was substantially lower in cirrhotic patients (1.0 ± 1.7 L/h/kg) than in the healthy volunteers (5.7 ± 3.8 L/h/kg). The recommended dose for patients with significantly reduced hepatic function is DETROL 1 mg twice 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-hydroxy-

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methyl 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 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 (K_i 1.05 μM), while tolterodine immediate release as well as the 5-hydroxymethyl metabolite are devoid of any significant inhibitory potential regarding the other isoenzymes.

CYP3A4 Inhibitors: The effect of 200 mg daily dose of ketoconazole on the pharmacokinetics of tolterodine immediate release was studied in 8 healthy volunteers, all of whom were poor metabolizers (see **Pharmacokinetics, Variability in Metabolism** for discussion of poor metabolizers). In the presence of ketoconazole, the mean C_{max} and AUC of tolterodine increased by 2 and 2.5 fold, respectively. Based on these findings, other potent CYP3A inhibitors such as other azole antifungals (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.

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Oral Contraceptives: Tolterodine immediate release 4 mg (2 mg bid) had no effect on the pharmacokinetics of an oral contraceptive (ethinyl estradiol 30 mg/levonorgestrel 150 mg) as evidenced by the monitoring of ethinyl estradiol and levonorgestrel over a 2-month cycle in healthy female volunteers.

Diuretics: Coadministration of tolterodine immediate release up to 8 mg (4 mg bid) for up to 12 weeks with diuretic agents, such as indapamide, hydrochlorothiazide, triamterene, bendroflumethiazide, chlorothiazide, methyldichlorothiazide, or furosemide, did not cause any adverse electrocardiographic (ECG) effects.

CLINICAL STUDIES

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

The efficacy endpoints for study 007 (see Table 2) included the change from baseline for:

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

The efficacy endpoints for studies 008, 009, and 010 (see Table 3) were identical to the above endpoints with the exception that the number of incontinence episodes was per 24 hours (averaged over 7 days).

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

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

SD = Standard Deviation.

*The difference between DETROL and placebo was statistically significant.

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Table 3. 95% Confidence Intervals (CI) for the Difference between DETROL (2 mg bid) and Placebo for the Mean Change at Week 12 from Baseline in Studies 008, 009, 010

Study		DETROL (SD)	Placebo (SD)	Difference (95% CI)
Number of Incontinence Episodes per 24 Hours				
008	Number of patients	93	40	
	Mean baseline	2.9	3.3	
	Mean change from baseline	-1.3 (3.2)	-0.9 (1.5)	0.5 (-1.3,0.3)
009	Number of patients	116	55	
	Mean baseline	3.6	3.5	
	Mean change from baseline	-1.7 (2.5)	-1.3 (2.5)	-0.4 (-1.0,0.2)
010	Number of patients	90	50	
	Mean baseline	3.7	3.5	
	Mean change from baseline	-1.6 (2.4)	-1.1 (2.1)	-0.5 (-1.1,0.1)
Number of Micturitions per 24 Hours				
008	Number of patients	118	56	
	Mean baseline	11.5	11.7	
	Mean change from baseline	-2.7 (3.8)	-1.6 (3.6)	-1.2* (-2.0,-0.4)
009	Number of patients	128	64	
	Mean baseline	11.2	11.3	
	Mean change from baseline	-2.3 (2.1)	-1.4 (2.8)	-0.9* (-1.5,-0.3)
010	Number of patients	108	56	
	Mean baseline	11.6	11.6	
	Mean change from baseline	-1.7 (2.3)	-1.4 (2.8)	-0.38 (-1.1,0.3)
Volume Voided per Micturition (mL)				
008	Number of patients	118	56	
	Mean baseline	166	157	
	Mean change from baseline	38 (54)	6 (42)	32* (18,46)
009	Number of patients	129	64	
	Mean baseline	155	158	
	Mean change from baseline	36 (50)	10 (47)	26* (14,38)
010	Number of patients	108	56	
	Mean baseline	155	160	
	Mean change from baseline	31 (45)	13 (52)	18* (4,32)

SD = Standard Deviation.

*The difference between DETROL and placebo was statistically significant.

INDICATIONS AND USAGE

DETROL Tablets are indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

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 Tablets should be administered with caution to patients with clinically significant bladder outflow obstruction because of

the risk of urinary retention and to patients with gastrointestinal obstructive disorders, such as pyloric stenosis, because of the risk of gastric retention (see **CONTRAINDICATIONS**).

Controlled Narrow-Angle Glaucoma: DETROL 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 of DETROL is 1 mg twice daily (see **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations**).

Information for Patients

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

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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 is 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 mg·h/L, respectively. In comparison, the human AUC value for a 2-mg dose administered twice daily is estimated at 34 mg·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 mg·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, 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 mg·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 should be used during pregnancy only if the potential bene-

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fit for the mother justifies the potential risk to the fetus.

Nursing Mothers

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

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

The data described below reflect exposure to DETROL 2 mg bid in 986 patients and to placebo in 683 patients exposed for 12 weeks in five Phase 3, controlled clinical studies. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and approximating rates.

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

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

The frequency of discontinuation due to adverse events was highest during the first 4 weeks of treatment. Seven percent of patients treated with DETROL 2 mg bid discontinued treatment due to adverse events versus 6% of placebo patients. The most common adverse events

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Table 4. Incidence* (%) of Adverse Events Exceeding Placebo Rate and Reported in >1% of Patients Treated with DETROL Tablets (2 mg bid) in 12-week, Phase 3 Clinical Studies

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

*In nearest integer.

leading to discontinuation of DETROL were dizziness and headache.

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

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 DETROL 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 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 4 mg twice daily (higher doses were not evaluated).

DOSAGE AND ADMINISTRATION

The initial recommended dose of DETROL Tablets is 2 mg twice daily. The dose may be lowered to 1 mg twice daily based on individual response and tolerability. For patients with significantly reduced hepatic or renal function or who are currently taking drugs that are potent inhibitors of CYP3A4, the recommended dose of DETROL is 1 mg twice daily (see **PRECAUTIONS, General** and **PRECAUTIONS, Drug Interactions**).

HOW SUPPLIED

DETROL Tablets 1 mg (white, round, biconvex, film-coated tablets engraved with arcs above and below the letters "10") and **DETROL Tablets 2 mg** (white, round, biconvex, film-coated tablets engraved with arcs above and below the letters "DT") are supplied as follows:

Bottles of 60	
1 mg	NDC 0009-4541-02
2 mg	NDC 0009-4544-02

Bottles of 500	
1 mg	NDC 0009-4541-03
2 mg	NDC 0009-4544-03

Unit Dose Pack of 140	
1 mg	NDC 0009-4541-01
2 mg	NDC 0009-4544-01

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

℞ only

US Patent No. 5,382,600
Pharmacia & Upjohn Company
A subsidiary of Pharmacia Corporation
Kalamazoo, MI 49001, USA

Revised July 2003

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692167

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-771/S-011

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 20-771

Pfizer Global Pharmaceuticals
Attention: Naumann Chaudry, Pharm.D.
Senior Manager, U.S. Regulatory Affairs
235 East 42nd Street
New York, NY 10017

Dear Dr. Chaudry:

Please refer to your new drug application (NDA) for Detrol® (tolterodine tartrate) tablets.

Since the approval on January 5, 2004, of your revised package insert (PI) submitted in supplement 011 (S-011), we have reviewed additional materials pertaining to the use of tolterodine in pediatric patients. Our review of this additional information has identified the need for labeling changes to reflect this information. We have also identified errors in the presentation of clinical pharmacology data in the Detrol® label's Clinical Pharmacology section. Your package insert (PI) should be revised as follows:

1. Revise Precautions; Pediatric Use section as follows:

- Delete the current sentence: "The safety and effectiveness of Detrol in pediatric patients have not been established."
- Add two new paragraphs:

Efficacy in the pediatric population has not been demonstrated.

Two pediatric phase 3 randomized, placebo-controlled, double blind, 12 week studies were conducted using tolterodine extended release (DETROL LA) tablets. A total of 710 pediatric patients (486 on DETROL LA and 224 on placebo) aged 5-10 years with urinary frequency and urge urinary incontinence were studied. The percentage of patients with urinary tract infections was higher in patients treated with 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.

2. Clarify units in the following sections:

- **Clinical Pharmacology; Pharmacokinetics in Special Populations; Gender:** In the second sentence, all C_{max} references should be expressed in $\mu\text{g/L}$ rather than mg/L .

- **Clinical Pharmacology; Drug-Drug Interactions; Oral Contraceptives:** The units should be changed from mg to μg (ethinyl estradiol 30 μg /levonorgestrel 150 μg).
- **Precautions; Carcinogenesis, Mutagenesis, Impairment of Fertility:** All AUC values in first and third paragraph should be expressed in $\mu\text{g}\cdot\text{h}/\text{L}$ rather than $\text{mg}\cdot\text{h}/\text{L}$.
- **Precautions; Pregnancy:** AUC values in the fourth sentence should be expressed in $\mu\text{g}\cdot\text{h}/\text{L}$ rather than $\text{mg}\cdot\text{h}/\text{L}$.

Submit draft labeling as a prior approval supplement to this application. Incorporate all previous revisions as reflected in the most recently approved package insert. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes that are being made. This change is not appropriate for reporting in an annual report.

If you have any questions, call Jean Makie, M.S., R.D., Sr. Project Manager, at 301-827-4260.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel
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**Division of Reproductive and Urologic Drug Products
Project Manager Labeling Review**

Application Number: NDA 20-771/ S-011
Detrol (tolterodine tartrate) 1 mg and 2 mg tablets

Sponsor: Pharmacia & Upjohn Company

Material Reviewed: NDA 20-711: Changes Being Effected Labeling Supplement, revision of "Postmarketing Surveillance" section of the package insert (PI).

Background and Summary:

This product was approved for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

Pharmacia & Upjohn Company submitted revisions to the "Postmarketing Surveillance" section of the package insert in accordance with 21 CFR 314.70(c).

Review:

The labeling submitted in NDA 20-771/SLR-011 was compared to the last approved PI dated August 20, 2002 and the final printed labeling submitted July 30, 2003. The "Postmarketing Surveillance" section of the last approved PI with the additional language of SLR-010 reads, "The following events have been reported in association with tolterodine use in clinical practice: anaphylactoid reactions, tachycardia, peripheral edema, and hallucinations."

Pharmacia & Upjohn has added angioedema and palpitations as additional reported events to the "Postmarketing Surveillance" section of the PI in SLR-011, a CBE-0, dated September 25, 2003. The sponsor has also replaced the commas after each reported event with semicolons. This portion of the "Postmarketing Surveillance" section now reads, "The following events have been reported in association with tolterodine use in clinical practice: anaphylactoid reactions, including angioedema; tachycardia; palpitations; peripheral edema; and hallucinations."

NDA 20-711/SLR-011
Detrol (tolterodine tartrate)
PM Review

Conclusion:

An Approval letter should be sent to the sponsor.

Albert Perrine, RN, BSN
PM, HFD-580

Drafted: AP 10/07/03
Revised: AP 12/03/03

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/s/

Albert Perrine
12/11/03 07:43:21 AM
CSO

Margaret Kober
12/15/03 02:58:37 PM
CSO
Chief, Project Management Staff



NDA 20-771/S-011

CBE-0 SUPPLEMENT

Pharmacia & Upjohn Company
Attention: Tara Feehan
Manager, US Regulatory Affairs
235 East 42nd Street
New York, New York 10017

Dear Ms. Feehan:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Detrol (tolterodine tartrate) 1 mg and 2 mg tablets
NDA Number: 20-771
Supplement number: S-011
Date of supplement: September 25, 2003
Date of receipt: September 26, 2003

This supplemental application, submitted as "Supplement – Changes Being Effected" proposes the revision of the "Post Marketing Surveillance" section of the package insert to include angioedema and palpitations as reported events.

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call Albert Perrine, RN, BSN, Regulatory Project Manager, at (301) 827-7511.

Sincerely,

{See appended electronic signature page}

Kassandra Sherrod, R.Ph.
Regulatory Project Manager
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Kassandra C. Sherrod
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