

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**20-771/S-004**

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Rec.  
4/10/01  
8:48AM

## NDA 20-771/S-004 – Action Package

**Drug Product:** Detrol (tolterodine tartrate) tablets

**Sponsor:** Pharmacia & Upjohn

**Indication:** Treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency or urge incontinence.

**Goal date:** October 23, 2000

**Review team:** Brenda Gierhart, M.D. – Clinical  
Alexander Jordan, Ph.D. – Toxicology  
D. J. Chatterjee, Ph.D. – Clinical Pharmacology and  
Biopharmaceutics  
David Lin, Ph.D. – Chemistry  
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager

**Division:** Reproductive and Urologic Drug Products (HFD-580)  
Susan Allen, M.D., M.P.H.  
Director

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-771/S-004**

**APPROVAL LETTER**

NDA 20-771/S-004

Pharmacia & Upjohn Company  
Attention: Gregory Shawaryn  
Regulatory Manager, Regulatory Affairs  
7000 Portage Road  
Kalamazoo, MI 49001

06 APR 2001

Dear Mr. Shawaryn:

Please refer to your supplemental new drug application dated December 22, 1999, received December 23, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Detrol (tolterodine tartrate) tablets.

We acknowledge receipt of your submissions dated February 27, March 15 (facsimile), March 20 (facsimile), and April 3, 2001 (facsimile). Your submission of October 26, 2000 constituted a complete response to our October 23, 2000 Approvable action letter.

This supplemental new drug application provides for the use of Detrol (tolterodine tartrate) tablets for the treatment of overactive bladder with symptoms of urgency, frequency and urge urinary incontinence.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 20, 2001).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten 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-004." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and

the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D.  
Director  
Division of Reproductive and Urologic Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-771/S-004**

**APPROVABLE LETTER**

NDA 20-771/S-004

OCT 23 2000

Pharmacia & Upjohn Company  
Attention: Gregory Shawaryn  
Regulatory Manager, Regulatory Affairs  
7000 Portage Road  
Kalamazoo, MI 49001

Dear Mr. Shawaryn:

Please refer to your supplemental new drug application dated December 22, 1999, received December 23, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Detrol (tolterodine tartrate) tablets.

We acknowledge receipt of your submissions dated May 5, July 14, August 28, and September 21, 2000.

This supplemental new drug application proposes the use of Detrol (tolterodine tartrate) tablets for treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency and urge incontinence.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit draft labeling revised in accordance with the enclosed labeling. Approval of this application is also dependent on satisfactory completion of the Division of Scientific Investigations' inspection of all study sites.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.
4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

151  
Susan Allen, M.D., M.P.H.  
Director  
Division of Reproductive and Urologic Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Enclosure

cc:

Archival NDA 20-771

HFD-580/Div. Files

HFD-580/E.Farinas

HFD-580/Allen/Shames/Hirsch/Gierhart/Parekh/Chatterjee/Jordan/Lin/Rhee/Kammerman/  
Hoberman/Rumble

HFD-002/ORM

HFD-103/ADRA

HFD-42/DDMAC (with labeling)

DISTRICT OFFICE

Drafted by: erf/October 23, 2000

Initialed by:

Allen/Shames/Hirsch/Gierhart/Jordan/Parekh/Chatterjee/Lin/Rhee/Kammerman/Hoberman/  
Rumble

final: erf/ 10.23.00

filename: NDA 20771 S004 approvable letter October.doc

APPROVABLE (AE)

Concurrence		
Name/Title	Signature	Date
Evelyn R. Farinas, R. Ph., M.G.A. Regulatory Project Manager	/s/	10-23-00
Terri Rumble, B.S.N. Chief, Project Management Staff		10/23/00
Brenda Gierhart, M.D. Medical Officer		10/23/00
Mark Hirsch, M.D. <i>Medical Officer</i> Acting Urology Team Leader		10/23/00
David Hoberman, Ph.D. Statistics Reviewer		2/23/00
Lisa Kammerman, Ph.D. Team Leader, Statistics		10/23/00
David Lin, Ph.D. Chemistry Reviewer		1/23/00
Moo-Jhong Rhee, Ph.D. Team Leader, Chemistry		1/23/00
D.J. Chatterjee, Ph.D. Clinical Pharmacology and Biopharmaceutics Reviewer		1/23/00
Ameeta Parekh, Ph.D. Team Leader, Clinical Pharmacology and Biopharmaceutics		1/23/00
Daniel Shames, M.D. Acting Deputy Director		1/23/00
Susan Allen, M.D. Director		10/23/00

137 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-771/S-004**

**FINAL PRINTED LABELING**

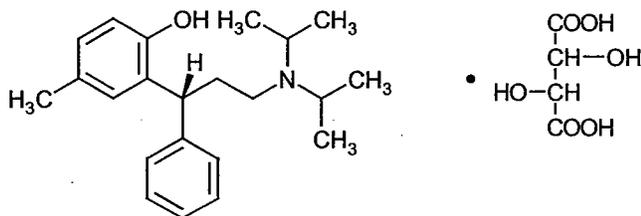
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**Detrol™**  
*tolterodine tartrate tablets*

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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-[bis(1-methylethyl)-amino]-1-phenylpropyl]-4-methylphenol [R-(R\*,R\*)]-2,3-dihydroxybutanedioate (1:1) (salt). 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 Tablets for oral administration contain 1 or 2 mg of tolterodine tartrate. The inactive ingredients are colloidal anhydrous silica, calcium hydrogen phosphate dihydrate, cellulose microcrystalline, hydroxypropyl methylcellulose, magnesium stearate, sodium starch glycolate (pH 3.0 to 5.0), stearic acid, and titanium dioxide.

**CLINICAL PHARMACOLOGY**

Tolterodine is a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors.

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  $^{14}\text{C}$ -tolterodine solution in healthy volunteers who received a 5-mg oral dose, at least 77% of the radiolabeled dose was absorbed. Tolterodine immediate release is rapidly absorbed, and maximum serum concentrations ( $C_{\text{max}}$ ) typically occur within 1 to 2 hours after dose administration.  $C_{\text{max}}$  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  $\alpha_1$ -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  $^{14}\text{C}$ -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 ( $\pm$  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).

**Table 1. Summary of Mean ( $\pm$ SD) Pharmacokinetic Parameters of Tolterodine and its Active Metabolite (5-hydroxymethyl metabolite) in Healthy Volunteers**

Phenotype (CYP2D6)	Tolterodine					5-Hydroxymethyl Metabolite			
	$t_{\max}$ (h)	$C_{\max}^*$ ( $\mu\text{g/L}$ )	$C_{\text{avg}}^*$ ( $\mu\text{g/L}$ )	$t_{1/2}$ (h)	CL/F (L/h)	$t_{\max}$ (h)	$C_{\max}^*$ ( $\mu\text{g/L}$ )	$C_{\text{avg}}^*$ ( $\mu\text{g/L}$ )	$t_{1/2}$ (h)
Single-dose									
EM	1.6 $\pm$ 1.5	1.6 $\pm$ 1.2	0.50 $\pm$ 0.35	2.0 $\pm$ 0.7	534 $\pm$ 697	1.8 $\pm$ 1.4	1.8 $\pm$ 0.7	0.62 $\pm$ 0.26	3.1 $\pm$ 0.7
PM	1.4 $\pm$ 0.5	10 $\pm$ 4.9	8.3 $\pm$ 4.3	6.5 $\pm$ 1.6	17 $\pm$ 7.3	-†	-	-	-
Multiple-dose									
EM	1.2 $\pm$ 0.5	2.6 $\pm$ 2.8	0.58 $\pm$ 0.54	2.2 $\pm$ 0.4	415 $\pm$ 377	1.2 $\pm$ 0.5	2.4 $\pm$ 1.3	0.92 $\pm$ 0.46	2.9 $\pm$ 0.4
PM	1.9 $\pm$ 1.0	19 $\pm$ 7.5	12 $\pm$ 5.1	9.6 $\pm$ 1.5	11 $\pm$ 4.2	-	-	-	-

\* Parameter was dose-normalized from 4 mg to 2 mg.

$C_{\max}$  = Maximum plasma concentration;  $t_{\max}$  = Time of occurrence of  $C_{\max}$ ;

$C_{\text{avg}}$  = 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  $\pm$  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  $\mu\text{g}\cdot\text{h}/\text{L}$  in males versus 7.8  $\mu\text{g}\cdot\text{h}/\text{L}$  in females) and the 5-hydroxymethyl metabolite (10  $\mu\text{g}\cdot\text{h}/\text{L}$  in males versus 11  $\mu\text{g}\cdot\text{h}/\text{L}$  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 (e.g. 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, 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 ( $1.1 \pm 1.7$  L/h/kg) than in the healthy volunteers ( $5.7 \pm 3.8$  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  $C_{\text{max}}$  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 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<sub>i</sub> 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<sub>max</sub> 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 (e.g., itraconazole, miconazole) or macrolide antibiotics (e.g., 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 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, methylchlorothiazide, 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**

	<b>DETROL (SD) N=514</b>	<b>Placebo (SD) N=508</b>	<b>Difference (95% CI)</b>
<b>Number of Incontinence Episodes per Week</b>			
Mean baseline	23.2	23.3	
Mean change from baseline	-10.6 (17)	-6.9 (15)	-3.7* (-5.7, -1.6)
<b>Number of Micturitions per 24 Hours</b>			
Mean baseline	11.1	11.3	
Mean change from baseline	-1.7 (3.3)	-1.2 (2.9)	-0.5* (-0.9, -0.1)
<b>Volume Voided per Micturition (mL)</b>			
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.

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)
<b>Number of Incontinence Episodes per 24 Hours</b>				
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)
<b>Number of Micturitions per 24 Hours</b>				
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)
<b>Volume Voided per Micturition (mL)</b>				
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.

### 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 (e.g., itraconazole, miconazole) or macrolide antibiotics (e.g., erythromycin, clarithromycin) or cyclosporine or vinblastin, 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 four strains of *Salmonella typhimurium* and in two strains of *Escherichia coli*, a gene mutation assay in L5178Y mouse lymphoma cells, and chromosomal aberration tests in human lymphocytes. Tolterodine was also negative in vivo in the bone marrow micronucleus test in the mouse.

In female mice treated for 2 weeks before mating and during gestation with 20 mg/kg/day (corresponding

to AUC value of about 500 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 three-fold higher than that resulting from the human dose. This dose did not result in any embryotoxicity or teratogenicity. There are no studies of tolterodine in pregnant women. Therefore, DETROL should be used during pregnancy only if the potential benefit for the mother justifies the potential risk 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 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.

**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

### Postmarketing Surveillance

The following events have been reported in association with tolterodine use in clinical practice:

anaphylactoid reactions, tachycardia, peripheral edema. 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 "TO") 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).

**Rx only**

US Patent No. 5,382,600

Manufactured by:

Pharmacia & Upjohn S.p.A.

Ascoli Piceno, Italy

For:

Pharmacia & Upjohn Company

Kalamazoo, MI 49001, USA

March 2001

[x-226pi.doc]

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-771/S-004**

**MEDICAL REVIEW**

**HFD-580: DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS****NDA: 20-771 SE8-004****Tolterodine Immediate Release (Detrol™)****Medical Officer's Review****(Original NDA)****Date submitted: 12/22/99****CDER stamp date: 12/23/99****Date assigned: 3/8/00****CDER due date: 10/22/00****Review completed: 10/16/00****Key words:** Tolterodine, urge incontinence, urinary frequency, urgency, overactive bladder, and immediate release**Sponsor:** Pharmacia & Upjohn Company  
7000 Portage Road  
Kalamazoo, MI 49001-0199**Drug names:****Generic:** Tolterodine tartrate immediate release tablets**Trade:** Detrol™**Chemical:** (R)-N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate**Drug class:** Muscarinic receptor antagonist**Administration route:** Oral**Dosage form:** Immediate Release tablets BID**Strength:** 1 mg and 2 mg**Proposed indication:** Treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.**Related INDs:**

IND 46,169 Tolterodine tartrate (DETROL) Pharmacia &amp; Upjohn

IND 56,406 Tolterodine tartrate Prolonged Release; Pharmacia &amp; Upjohn

**Related NDAs:**

NDA 20-771 Tolterodine tartrate (DETROL) Pharmacia &amp; Upjohn

NDA 21-228 Tolterodine tartrate Prolonged Release; Pharmacia &amp; Upjohn

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## 1.0 RESUME

Tolterodine (Detrol™) Tablets were approved by the agency on March 25, 1998 for the treatment of patients with an **overactive bladder** with symptoms of urinary frequency, urgency, or urge incontinence. The sponsor now submits Efficacy Supplement S-004, which contains one study report, **98-TOCR-007**, in the clinical section.

Study **98-TOCR-007** was a multicenter, multinational, randomized, double blind, double-dummy, placebo-controlled, parallel design, phase 3 study in adult patients with an overactive bladder with symptoms of urinary frequency, urgency, and urge incontinence. This study was undertaken since the three previous phase 3 trials (Studies 94-OATA-008, -009 and -010) did **not** demonstrate a statistically significant decrease in the number of incontinence episodes with tolterodine treatment compared with placebo. It should be noted that Studies 94-OATA-008, -009 and -010 were **not designed or powered** to detect statistically significant differences in the number of incontinence episodes. This was because the change in the mean number of incontinence episodes per 24 hours from baseline to end of study (week 12) was a secondary efficacy measurement. The primary efficacy measurement for Studies 94-OATA-008, -009 and -010 was the change in the mean number of micturation per 24 hours from baseline to end of the study (week 12). It should be noted that there was a \_\_\_\_\_ in both 94-OATA-008 and -009 and in both studies, the \_\_\_\_\_ population was statistically superior to placebo in decreasing the number of incontinence episodes.

The primary efficacy variable for Study **98-TOCR-007** was the number of incontinence episodes per week as calculated from the data recorded on the micturition charts. Study **98-TOCR-007** compared tolterodine Immediate Release (IR) tablets 2 mg bid, tolterodine Prolonged Release (PR) capsules 4 mg qd, and placebo during a 12-week treatment period. A highly statistically significant ( $p=0.0005$ ) decrease in the mean number of incontinence episodes per week at end of study (week 12) from baseline was demonstrated by tolterodine IR (-10.6 episodes or 46%)

**Reviewer's comments:**

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- 5) It is the reviewer's opinion that labels for urinary incontinence drugs are not ready to be standardized into class labeling. The goal is to be fair regarding labels for drug products with similar indications.
- 6) The Draft Guidance for Industry "Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics" was distributed for comment purposes in May 2000. It makes several recommendations pertinent to the proposed Detrol Adverse Reaction table:
- "Data in the primary table should be derived from placebo-controlled and/or dose-response studies if these data are available and the databases are sufficiently large to be informative." This recommendation would support including all patients from placebo-controlled or dose-response studies. It would exclude utilizing active-controlled data, single arm trial data (such as from open label extension patients), or the overall database in the table.
  - "Ordinarily, a frequency cut-off appropriate to the size of the database and design of the trial should be identified and only adverse reactions occurring at that frequency and above should be presented in the table." This recommendation would support either continuing to use the  $\geq 1\%$  frequency cut-off or changing to a new frequency cut-off. The Draft Guidance does not recommend a specific frequency cut-off, such as Adverse Events Reported in  $\geq 1\%$ ,  $\geq 2\%$ , or  $\geq 5\%$  of Patients Treated.
  - "Adverse reaction rates from placebo or other comparator arms (e.g., active control, different dosage groups) should be included in the table unless inclusion of such rates would be misleading (for example, if a suboptimal or excessive dose of an active comparator was used) or would constitute or imply an unfair or unsubstantiated comparative safety claim." This recommendation would support listing the incidence of adverse reactions in both treated and placebo patients.
  - "Data presented should be organized by body system and, within body system category, by order of decreasing frequency." This recommendation would support listing both the body system and specific adverse reaction.
  - "To help place in perspective the significance of adverse reactions data obtained from clinical trials, the data presentation should be preceded by the following statement, or an appropriate modification:  
*Because clinical trials are conducted under widely varying conditions, adverse reactions 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.*"  
This recommendation will be incorporated into the Detrol label.
-

- **“In characterizing overall adverse reactions experience, subjective and nonspecific terms (e.g., *well tolerated*) should be avoided, as they have no precise meaning and can be misleading.” This recommendation pertains to the new sentence in the proposed Detrol label which begins:**

7) **Adding the data from study 98-TOCR-007 to the AE 12-week, Phase 3 Clinical Studies Table is desirable since it doubled the numbers of Detrol 2mg bid subjects (from 474 to 986) and quadrupled the number of placebo subjects (from 176 to 683).**

## 2.0 BACKGROUND

The overactive bladder, with symptoms of frequency, urgency and urge incontinence, affects millions of people throughout the world.<sup>1</sup> Tolterodine (Detrol™) Tablets are indicated for the treatment of **overactive bladder** patients with symptoms of urinary frequency, urgency, or urge incontinence. The term “overactive bladder” describes a symptom complex and is an attempt to **“lump” together patients with any or all components of the symptom complex.** It was defined in 1999 as:

Bladder overactivity should be able to be defined either by urodynamic studies or by symptoms. A reasonable definition would be that symptomatic bladder overactivity is a condition referring to the symptoms of frequency, urgency, and urge or reflex incontinence, either singly or in combination, when appearing in the absence of local pathological factors (e.g., urinary tract infection, stones, interstitial cystitis) explaining these symptoms.<sup>1</sup>

The term “overactive bladder” is of such fairly recent vintage that it is **not** listed in the index of Campbell’s Urology<sup>2</sup> or Harrison’s Principles of Internal Medicine<sup>3</sup>. It is **not** listed in the International Continence Society (ICS) classification of voiding dysfunctions<sup>4</sup>, in the Urodynamic Society’s Definition and Classification of Urinary Incontinence<sup>5</sup>, or in the “Expanded Functional Classification” of voiding dysfunction in Campbell’s Urology<sup>6</sup>.

In the past, Urology “split” patients into smaller categories based on diagnosis, test results, or etiology. The International Continence Society (ICS) attempted to standardize the terminology of

<sup>1</sup> Wein AJ and Rovner ES: The Overactive Bladder: An Overview for Primary Care Health Providers. Int J Fertil Womens Med 1999 Mar-Apr; 44 (2): 56-66.

<sup>2</sup> Walsh P et al, editors: Campbell’s Urology 7th edition W.B. Saunders Company, Philadelphia, 1998.

<sup>3</sup> Isselbacher K et al, editors: Harrison’s Principles of Internal Medicine 13<sup>th</sup> edition McGraw-Hill, Inc., New York, 1994.

<sup>4</sup> Abrams P, Blaivas JG, Stanton SL, Andersen JT: The standardization of terminology of lower urinary tract function recommended by the International Continence Society. Int. Urogynecol J 1990; 1:45.

<sup>5</sup> Blaivas JG, Appell RA, Fantl JA, Leach G, McGuire EJ, Resnick NM, Raz S, Wein AJ: Definition and Classification of Urinary Incontinence: Recommendations of the Urodynamic Society. Neurourology and Urodynamics 1997; 16:149-151.

<sup>6</sup> Walsh P et al, editors: Campbell’s Urology 7th edition W.B. Saunders Company, Philadelphia, 1998, p. 925.

lower urinary tract function by heavily relying upon the patient's urodynamic testing results<sup>7</sup>. Other classification systems have relied upon the patient's specific Urologic diagnosis or whether the symptoms had a specific etiology, such as neurogenic. It is important to realize that this "lump" of patients labeled as having an overactive bladder may have many different diagnoses, etiologies, and test results, may be of any age or sex, and may exhibit a wide range in number and severity of symptoms.

In the submitted clinical study 98-TOCR-007, the sponsor included patients with an overactive bladder only if they demonstrate urinary frequency (on average >8 micturition per 24 hours) and urge incontinence (≥5 incontinence episodes per week) and had symptoms of overactive bladder for ≥6 months. Thus study 98-TOCR-007 was performed on a select subgroup of all patients with overactive bladder.

**Reviewer's comments:**

- 1) In order to demonstrate tolterodine efficacy regarding episodes of urinary incontinence, it was reasonable for the sponsor to perform study 98-TOCR-007 on a select subgroup of overactive bladder patients, who all demonstrated ≥5 episodes of urinary incontinence per week.**

**2.1 Regulatory History**

Pharmacia, Inc. submitted the original IND 46,169 for tolterodine tartrate Immediate Release tablets (Detrol™) to HFD-160, Division of Medical Imaging and Radiopharmaceutical Drug Products, on September 2, 1994. The IND was transferred as a result of the CDER restructuring initiative to HFD-510, Division of Metabolic and Endocrine Drug Products (DMEDP), on November 17, 1995. The IND was transferred to HFD-580, Division of Reproductive and Urologic Drug Products (DRUDP), in June 1996 as a result of the formation of this new division from HFD-510. Notice of the change in sponsor name from Pharmacia, Inc. to Pharmacia & Upjohn Company was submitted on June 26, 1996 and was received on September 19, 1996.

The Detrol™ original NDA 20-771 was submitted on March 24, 1997 and was approved on March 25, 1998.

The first supplemental submission for NDA 20-771 is SCM-001 (Supplement-Manufacturing Change or Addition). It was submitted on April 7, 1998 and approved on 8/31/98. The batch size of tolterodine tartrate was increased from \_\_\_\_\_ and the manufacturing facility was changed.

The \_\_\_\_\_ supplement submission for NDA 20-771 is \_\_\_\_\_ (Revision). It was submitted on January 12, 1999 and proposed to update the information in the Package Insert with respect to \_\_\_\_\_. On November 10, 1999, the sponsor was notified that the review of \_\_\_\_\_ had been completed and the agency had two recommendations for revisions to the Package Insert. The sponsor did not accept these

<sup>7</sup> International Continence Society Committee on Standardisation of Terminology: The Standardisation of Terminology of Lower Urinary Tract Function. Scand J Urol Nephrol, Supplementum 114, 1988 p. 5-19.

recommendations and negotiations with DRUDP Clinical Pharmacology and Biopharmaceutics reviewers are continuing to present.

On May 14, 1999, notice of fulfillment of all Phase 4 commitments for NDA 20-771 was sent to the sponsor. On August 12, 1999, guidance on studies required for pediatric exclusivity was provided to the sponsor during a teleconference.

The third supplemental submission for NDA 20-771 is **SCM-003** (Supplement-Manufacturing Change or Addition). It was submitted on December 15, 1999 and was approved May 26, 2000. The Active Pharmaceutical Ingredient (API) source was changed from \_\_\_\_\_ and \_\_\_\_\_ and the API process was changed.

The fourth supplemental submission for NDA 20-771 is the subject of this review. It is submission **SE8-004** (Supplement-Labeling Revision with Clinical Information) and was submitted on December 22, 1999. It presents clinical data from Protocol **98-TOCR-007**, which was performed under IND 56,406. No new information relative to NDA 20-771 is provided in this supplement to the Chemistry, Nonclinical Pharmacology and Toxicology, or Human Pharmacokinetics and Bioavailability sections.

The fifth supplemental submission for NDA 20-771 is **SCM-005** (Supplement-Manufacturing Change or Addition). It was submitted on May 11, 2000 and is currently under review. It gives an alternative drug manufacturing site and was submitted as CBE (Changes Being Effected).

The sixth supplemental submission for NDA-20-771 is **SLR-006** (Supplement-Labeling Revision). It was submitted on May 31, 2000 and is currently under review. It adds a toll-free number and website address to the carton for complimentary samples of Detrol tablets and was submitted as CBE (Changes Being Effected).

The \_\_\_\_\_ supplemental submission for NDA 20-771 is \_\_\_\_\_

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Pharmacia & Upjohn submitted the original IND 56,406 for tolterodine tartrate Prolonged Release (PR) capsules on July 14, 1998. A guidance FDA meeting was held regarding the proposed Phase 3 study, Protocol **98-TOCR-007** on August 12, 1998. The sponsor was advised at this meeting:

- A 15% reduction in dry mouth between tolterodine IR and tolterodine PR was not acceptable; a 25-50% reduction using a visual analog scale was more appropriate.

- An additional 3-month follow-up of approximately 100 patients at 6 months and 50 at one year should be considered for the PR formulation.
- Labeling changes would be based on the study results; statistical as well as clinical differences.

Revisions were made based upon FDA comments and the final sponsor date for Protocol 98-TOCR-007 was October 30, 1998.

Further Protocol 98-TOCR-007 FDA comments were made at an End-of-Phase 2 (EOP2) meeting for NDA 21-228 held with the sponsor on November 30, 1998. The sponsor was advised at this meeting:

- A determination of how many incontinence episode changes from baseline are meaningful to the patient is important. A clinically meaningful difference might be 20-25% decrease in weekly incontinence episodes per week.
- A clinically significant difference for reduction in dry mouth between the PR and IM formulations should be determined.

Alternatively, providing the scientific rationale, which supports a 25% reduction in dry mouth as being clinically significant, would be acceptable.

- Labels will be the same regarding the wording of the indication for all drugs in this class.

There were a total of 4 Amendments to Protocol 98-TOCR-007:

Amendment 1: Sponsor date December 7, 1998; Correspondence date January 20, 1999

Amendment 2: Sponsor date January 22, 1999; Correspondence date May 21, 1999

Amendment 3: Sponsor date March 31, 1999; Correspondence date May 21, 1999

Amendment 4: Sponsor date July 2, 1999; Document could not be located in DFS or Document Room. Sponsor was called on August 16, 2000 and confirmed it was never submitted. Amendment 4 was submitted as Serial Number 040 on August 21, 2000. It was noted upon review that the following new sentence had been inserted into Section 10 STATISTICS 1. Intention to treat population:

*If micturition chart diaries are not completed according to the protocol, the estimations of the micturition variables will be based on the available data*

The sponsor was asked to clarify what was meant by the term "estimation" and provide a listings of patients for which estimations was performed. The sponsor submitted via fax dated September 7, 2000 the clarification that "estimated" meant calculated in this case. They also submitted a listing of 16 placebo subjects, 18 tolterodine PR 4 mg qd subjects, and 18 tolterodine IR 2 mg bid subjects who had estimation of micturition data in protocol 98-TOCR-007 performed because the micturition chart diary was completed for less than 5 days.

There were a Response to FDA Request for Information regarding Supplement SE8-004: Supplemental New Correspondence (SNC-004); Provided Investigator Site #, # of Subjects Enrolled/Completed, and # SAE per site; Correspondence date February 23, 2000

There have been a total of **2 Amendments** to **Supplement SE8-004**:

Amendment 1: Observed Cases Analysis for Protocol **98-TOCR-007**; Correspondence date May 5, 2000

Amendment 2: Adverse Events sorted by subgroups across protocols **94-OATA-008, 94-OATA-009, 94-OATA-010, 94-AOTA-015, and 98-TOCR-007**; Correspondence date July 14, 2000

**Two Final Reports of Phase 3 Trials** were submitted to IND 46,169 as N135-IM, both with the Correspondence date of July 7, 2000:

Protocol **96-OATA-032**: Long-term safety, tolerability and clinical efficacy of tolterodine 2 mg bid. A phase III, open, multinational study for up to two years in patients with detrusor overactivity, symptoms of frequency, urge incontinence and/or urgency.

Protocol **96-OATA-034**: Long-term safety, tolerability and clinical efficacy of tolterodine 1 mg bid. A phase III, open, multinational study for up to two years in patients with detrusor overactivity, symptoms of frequency, urge incontinence and/or urgency.

## **2.2 Clinical Background and Scientific Rationale**

Muscarinic receptor antagonists prevent the effects of acetylcholine by blocking its binding to muscarinic cholinergic receptors at neuroeffector sites on smooth muscle, cardiac muscle, and gland cells.<sup>8</sup> The best known member of the muscarinic receptor antagonist drug class is atropine and the actions of most clinically available muscarinic receptor antagonists differ only quantitatively from those of atropine. Muscarinic receptor antagonists have been used therapeutically in ophthalmology, anesthesia, the cardiovascular and central nervous systems, and the gastrointestinal, respiratory, and genitourinary tracts.

Tolterodine is a muscarinic receptor antagonist used for its antispasmodic effect on the bladder. It reduces the activity of the detrusor muscle. Detrusor muscle contractions are mainly mediated through cholinergic muscarinic receptors, of which there are five known subtypes. Bladder smooth muscle cholinergic receptors are mainly of the M-2 variety. However, it is generally felt that the M-3 variety is responsible for involuntary bladder contractions.<sup>9</sup> Inappropriate detrusor contractions can lead to a sense of urgency, which is a sudden, strong desire to urinate. Increased urgency can lead to urinary frequency and urge incontinence.

Overactive bladder is characterized by its symptoms of urinary frequency, urinary urgency and in many cases urge incontinence. The most bothersome symptom for patients and with the highest consequences to daily life is urge incontinence. Tolterodine immediate release (IR) tablets in a bid dosage regimen have been approved for the treatment of overactive bladder in the United States and for unstable bladder in the European Union countries.

The rationale for trial **98-TOCR-007** was to demonstrate that both tolterodine IR and tolterodine PR decrease the number of incontinence episodes compared with placebo. The three previous

<sup>8</sup> Hardman JG, Editor et al, Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill New York, Ninth Edition, 1996, p. 148.

<sup>9</sup> Wein AJ and Rovner ES; The Overactive Bladder: An Overview for Primary Care Health Providers; *Int J Fertil* 44(2), 1999 p. 64.

Phase 3 tolterodine controlled trials were not designed or powered to detect statistically significant differences in the number of incontinence episodes.

### 2.3 International Marketing Experience

Tolterodine IR tablets in a bid dosage regiment have been approved for the treatment of overactive bladder or unstable bladder in 48 countries, including the United States and the European Union. The International Birthdate for tolterodine IR is September 5, 1997. Tolterodine IR was approved in the European Union Countries on December 23, 1997 for unstable bladder. It was approved in the US (NDA 20-771) on March 25, 1998 for overactive bladder. Per NDA 20,771 Annual Report Y-002 dated May 12, 2000, the total quantity of Detrol distributed from January 1, 1999 through December 31, 1999 was:

Domestic	—————	boxes or bottles of 1.0 and 2.0 mg tablets
International	—————	blisters or bottles of 0.7, 1.0, and 2.0 mg tablets

## 3.0 SUMMARY OF NDA EFFICACY SUPPLEMENT

### 3.1 Summary of Controlled Trials

The clinical section of this efficacy supplement consists of one study report, **98-TOCR-007**. Study 98-TOCR-007 was a multicenter, multinational, randomized, double blind, double-dummy, placebo-controlled, parallel design Phase 3 study in adult patients with urinary frequency and urge incontinence. The study had three equally sized arms: tolterodine IR tablets 2 mg bid, tolterodine PR capsules 4 mg qd, and placebo. The study was comprised of three periods: a 1- to 2-week wash-out/run-in period, a 12-week treatment period, and a 1-week follow-up period. The primary efficacy endpoint was the change in number of incontinence episodes per week from baseline to week 12. A total of 1529 patients were randomized to treatment at 167 sites in 14 countries.

### 3.2 Summary of Uncontrolled Trials

There were no uncontrolled clinical trials submitted in this application.

## 4.0 CLINICAL TRIAL 98-TOCR-007: Clinical efficacy and tolerability/safety of tolterodine prolonged release capsules and tolterodine immediate release tablets vs placebo. A randomized, double blind, placebo-controlled, multinational study in patients with symptoms of overactive bladder.

### 4.1 Objectives

The **primary objective** of this trial was to evaluate the effects of tolterodine immediate release (IR) tablets 2 mg BID and tolterodine prolonged release (PR) capsules 4 mg once daily (OD) on incontinence episodes in adult subjects with urge incontinence over a 12-week treatment period, as compared with placebo.

The **secondary objectives** were to compare efficacy and tolerability/safety of tolterodine IR tablets 2 mg BID and tolterodine PR capsules 4 mg OD with placebo in adult subjects with urge incontinence over a 12-week treatment period.

#### **4.2 Design and conduct of the trial**

This was a multicenter, multinational, randomized, double blind, double-dummy, placebo-controlled, parallel design Phase 3 study in adult patients with urinary frequency, urge incontinence, and overactive bladder symptoms. The study had three equally sized arms: tolterodine IR tablets 2 mg bid, tolterodine PR capsules 4 mg qd, and placebo.

The study was comprised of three periods: a 1- to 2-week wash-out/run-in period, a 12-week treatment period, and a 1-week follow-up period. The expected duration of subject participation was 14 to 15 weeks. The washout period could be omitted for subjects that had no drug treatment for overactive bladder, bladder training or electrostimulation or anticholinergic drugs for the 14 days prior to randomization. All subjects participated in a minimum of a 1-week run-in period when they completed micturition histories to confirm eligibility. The wash-out/run-in period was extended if the subject had a symptomatic urinary tract infection during the wash-out/run-in period or at the day of Visit 2. In such a case, the subject received treatment for the UTI and a new appointment for Visit 2 was given.

#### **Reviewer's comments:**

- 1) Since neither a urinalysis nor a urine culture was obtained on all subjects during the wash-out/run-in period, it would be expected that asymptomatic patients with UTIs were included in this trial. This could bias the study population. Confirming that a patient has a normal urinalysis is recommended before initiating treating for overactive bladder.<sup>10</sup> In this trial, a similar percentage of subjects would be expected to have asymptomatic urinary tract infections at Visit 2 and Visit 4. It is not expected that the efficacy data would be affected.**

Baseline assessments were collected or made at Visit 2, which was 1 day prior to treatment initiation. A baseline cough provocation test was performed on female patients clinically suspected of having stress incontinence, unless they had had a complete urodynamic investigation within 14 days prior to randomization. The cough provocation test was performed with the subject in position for gynecological examination. The bladder volume was confirmed by ultrasound to exceed 100 ml, and subsequently the subject was asked to cough vigorously. If an immediate loss of urine was confirmed, the clinical diagnosis of stress incontinence was made and the subject was excluded from the trial. In Protocol Amendment #3, the subject's position during the cough provocation test was changed to supine.

Micturition charts and QoL questionnaires were completed at baseline and at end of treatment. A pad weight test was performed in centers in the United States and Australia at baseline and at end of treatment. Eligible patients who completed the 12-week treatment period were invited to

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<sup>10</sup> Abrams P and Wein AJ. The Overactive Bladder: A Widespread and Treatable Condition, Stockholm, Sweden: Erik Sparre Medical AB; 1998: p.1-60 as quoted in Hoffman E. Overactive bladder: Diagnosis of a hidden disorder *Contemporary OB-GYN* Summer 2000 Supplement: p. 16

participate in an open label long-term follow-up study that consisted of treatment with tolterodine PR 4 mg qd for 12 months (98-TOCR-007B).

Pharmacia & Upjohn (Stockholm, Sweden) planned 98-TOCR-007. Centers were monitored by local Pharmacia & Upjohn monitors. Pharmacia & Upjohn Clinical Supply Logistics distributed treatments to each participating Pharmacia & Upjohn Market Company, who were responsible for distribution to local pharmacies or investigators.

#### 4.3 Study population

**It was planned that the trial would enroll 1350 subjects at 150 investigator sites with 9 subjects per investigator.**

A total of **1529 subjects** (North American=804, European=608, and Australian/New Zealand=117) were randomized to tolterodine PR (n=507), tolterodine IR (n=514) or placebo (n=508). The study was conducted in a total of **167 sites in 14 countries**. The sites were in North America (Canada=10, United States=64), in Europe (Austria=7, Belgium=7, France=9, Germany=15, Ireland=5, Italy=7, Netherlands=12, Norway=5, Russian Federation/Ukraine=5, United Kingdom=14) and in Australia =4/New Zealand=3. Recruitment per center ranged from 1 patient (9 centers) to 40 patients (1 center) with an **average of 9 subjects per investigator**. Fifty-six sites (34%) enrolled 5 or less subjects. European sites had lower patient recruitment (average 7.1 subjects/site) than North American (average 10.9 subjects/site) or Australian/New Zealand sites (average 16.7 subjects/site).

The first patient was recruited on February 19, 1999 and the last patient completed all study-related assessments on November 8, 1999. The last date a patient was on study drug was October 31, 1999.

##### 4.3.1 Demographics

Demographic data collected on subjects prior to randomization included date of birth, sex, weight, height, and ethnic origin. The study population was approximately 80% female, 20% male, 95% White and 3.7% Black. The mean subject age was 60 years.

##### Reviewer's comments:

- 1) Randomized subjects were overwhelmingly Caucasian. Sex, race and age characteristics were similar in the three treatment groups and in the ITT and PP populations.**
- 2) In the United States, several population studies have found a 20 to 40% higher prevalence of urinary incontinence among white women than among African American women.<sup>11,12,13</sup> However this difference is related to the apparent greater prevalence of**

<sup>11</sup> Thom DH et al. Evaluation of parturition and other reproductive variables as risk factors for urinary incontinence in later life. *Obstet Gynecol.* 1997; 90: 983-989.

<sup>12</sup> Brown JS et al. Prevalence of urinary incontinence and associated risk factors in postmenopausal women. Heart & Estrogen/Progestin Replacement Study (HERS) Research Group. *Obstet Gynecol.* 1999; 94:66-70

<sup>13</sup> Fultz NH et al. Prevalence and severity of urinary incontinence in older African American and Caucasian women. *J Gerontol Biol Sci Med Sci.* 1999; 54: M299-M303.

**stress incontinence among white women.<sup>14</sup> African Americans were twice as likely to have urge incontinence as whites (57% versus 28%).<sup>15</sup> The Clinical Trials section of the**

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#### **4.4 Inclusion and exclusion criteria (includes the one amendment change to the original Exclusion criteria #1)**

##### **Inclusion criteria:**

- 1) Male or female subjects aged  $\geq 18$  years.
- 2) Subjects with urinary frequency (on average  $> 8$  micturitions per 24 hours) and urge incontinence ( $\geq 5$  incontinence episodes per week) as verified in the micturition chart before randomization.
- 3) Subjects with symptoms of overactive bladder for  $\geq 6$  months.
- 4) Subjects able and willing to correctly complete the micturition charts.
- 5) Subjects capable of understanding and having signed the informed consent form after full discussion of the research nature of the treatment and its risks and benefits.

##### **Exclusion criteria:**

- 1) Subjects with stress incontinence as determined by the investigator and for a female subject confirmed by a cough provocation test according to appendix 4.
- 2) Subjects with an average volume voided  $> 200$  ml urine per micturition as verified in the micturition chart before randomization.
- 3) Subjects with a total daily volume of urine  $> 3000$  ml as verified in the micturition chart before randomization.
- 4) Any condition which in the opinion of the investigator makes the subject unsuitable for, or with contraindication for inclusion, i.e. uncontrolled narrow-angled glaucoma, urinary retention and gastric retention.
- 5) Subjects with significant hepatic or renal disease, defined as twice the upper limit of the reference ranges regarding serum concentrations of AST, ALT, ALP or creatinine.
- 6) Subjects with symptomatic acute urinary tract infection (UTI) during the run-in period, or recurrent UTIs defined as treated for symptomatic UTI  $> 5$  times in the last year.
- 7) Subjects with diagnosed interstitial cystitis, uninvestigated hematuria or clinically significant bladder outlet obstruction.
- 8) Subjects treated within the 14 days preceding randomization, or expected to start treatment during the trial with
  - any anticholinergic drug other than trial drug according to randomization
  - any drug treatment for overactive bladder. Estrogen treatment started more than 2 months prior to randomization was allowed.
- 9) Subjects on an unstable dosage of any drug with anticholinergic side effects, or expected to start such treatment during the trial.

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<sup>14</sup> Thom DH et al. Overactive bladder: Epidemiology and impact on quality of life. *Contemporary OB/GYN*. Summer 2000 Supplement; 9.

<sup>15</sup> Bump RC. Racial comparisons and contrasts in urinary incontinence and pelvic organ prolapse. *Obstet Gynecol*. 1993; 81: 421-425.

- 10) Subject on treatment with potent CYP3A4 inhibitors, such as macrolide antibiotics (erythromycin, clarithromycin) or antifungal agents (ketoconazole, itraconazole, miconazole), or expected to start such treatment during the trial.
- 11) Subjects who have received any electrostimulation or bladder training within the last 14 days before randomization, or who are expected to start such therapy during the trial period.
- 12) Subjects with indwelling catheter or the practicing of intermittent self-catheterization.
- 13) Any other investigational drug within 2 months preceding randomization.
- 14) Subjects who are pregnant or nursing.
- 15) Sexually active female subjects of childbearing potential not using reliable contraceptive methods at least 3 months prior to randomization, during the entire trial period and for 1 month thereafter. Reliable contraceptive methods are intrauterine devices (IUD), contraceptive pills of combination type, hormonal implants and injectable contraceptives.

**Reviewer's comment:**

- 1) **Regarding Exclusion #6, subjects were not excluded if they experienced symptomatic acute UTI during their first run-in period. The subjects were treated for the UTI and then repeated their run-in period.**
- 2) **Regarding Exclusion #7, screening urinalysis were not performed as part of the study, thus it would be unlikely that uninvestigated hematuria would be diagnosed during the study.**
- 3) **Regarding Exclusion #8, subjects were not withdrawn if estrogen treatment was changed or stopped during the treatment period.**
- 4) **Regarding Exclusion #8-10, taking a prohibited concomitant medication was considered a protocol deviation and not a protocol violation. Subjects were not withdrawn from the trial unless they violated Exclusions #4, 5, or 15 (per Vol. 2 pg. 27). By comparing the line listings in Vol. 8 Appendix 13-Withdrawn Subjects with the line listings in Vol. 8 Appendix 14-Protocol Deviations, a total of 11 placebo and 5 Tolterodine IR subjects were identified who took a prohibited concomitant medication during the trial. Of these 16 subjects, only one subject (#3114) was withdrawn from the trial. Subject #3114 took the prohibited anticholinergic medication, Atrovent and was withdrawn after 26 days of treatment on August 7, 1999. Subject #3114 was started on Ditropan beginning August 8, 1999. The remaining 15 subjects who took a prohibited concomitant medication were not withdrawn and at least five were taking Atrovent.**

#### **4.5 Procedures**

##### **4.5.1 Screening period**

During the wash-out/run-in period, which lasted 7-14 days, the study design and purpose was explained at Visit 1, and the volunteers were assessed for eligibility. Written informed consent was obtained. Demographic data and vital signs were obtained. The history of any prior treatment(s) for overactive bladder and/or concomitant medication was elicited. Blood samples for clinical chemistry, hematology, and CYP2D6 genotyping were obtained. A urine pregnancy test was performed locally in women of childbearing potential. A measuring jar, micturition chart and instructions were given to all subjects. Every incontinence episode and every micturition associated with a sensation of urgency were to be recorded at the times they occurred for 7 consecutive days prior to Visit 2. In addition for at least 2 complete days, the volume voided (in milliliters) for every micturition, and every pad used were to be recorded at the times

they occurred. In centers in the United States and Australia, approximately 375 subjects who had previously used pads were instructed to collect all pads used over 2 days prior to Visit 2 for the pad weight test. They received standardized pads, zip-lock bags, and a collection bag along with detailed instructions for the pad weight test.

**Reviewer's comment:**

- 1) Studying only subjects who had previously used pads was reasonable, however it would bias the pad weight subgroup toward the more severe urge incontinence patients. This point became irrelevant when the sponsor data.**

**4.5.2 Admission period**

After results of routine laboratory tests qualified a subject for participation, she was seen for Visit 2. The micturition chart and any pads for the pad weight test were collected. Pads were counted and weighed on standardized scales. The investigator together with the subject resolved any micturition chart ambiguities. Eligibility was again determined, which included investigator assessment of the completed micturition charts. The investigator calculated the number of micturitions and incontinence episodes, mean volume voided per micturition, and the total daily urine volume. Concomitant medication information was obtained. Concurrent disease or symptoms present at the day of Visit 2 and their intensity was obtained.

If female subjects were suspected to have stress incontinence as determined by the investigator, they underwent the cough provocation test to confirm the diagnosis. Five weeks after enrolling the first patient, the cough provocation test was changed in protocol Amendment 3 to be performed in the standing rather than supine position. ECGs in a subgroup of approximately 90 subjects  $\geq 65$  years in the United States were planned to be obtained. The investigator assessed the subject's perception of bladder condition and urgency. The subject completed the two QoL assessments: King's Questionnaire and SF-36. Patients in the Netherlands, Norway, Belgium (Flemish speaking), Russian Federation and Ukraine were exempt from filing out the King's Health Questionnaire because validated translations were not available in the appropriate languages.

**Reviewer's comment:**

- 1) To confirm subject eligibility, it would have been optimal for each female subject to undergo the cough stress test. However it is reasonable in a Phase 3 trial to perform the test only in female subjects suspected of stress incontinence, as would likely occur in clinical practice.**
- 2) It is unknown whether or not a cough stress test was performed and what the results were for any enrolled subject. The trial's Case Report Form (CRF) did not collect this data.**

The subjects were then randomized in a block size of six and drug dispensed. Each subject received three bottles, with different content, in a box containing sufficient study medication for 4 weeks of treatment plus 7 surplus doses per bottle. One bottle contained 35 capsules of tolterodine PR or its placebo. The other 2 bottles each contained 35 tablets of tolterodine IR or its placebo. Subjects were instructed to take one capsule and one tablet each morning from the

bottles labeled "morning dose" and one tablet each evening from the bottle labeled "evening dose" beginning the day after Visit 2. There were no dosing restrictions with regard to food or relation to daily activities.

#### **4.5.3 Treatment period**

Subjects were seen for two visits (Visit 3 and Visit 4) during the treatment period.

Visit 3 occurred  $28 \pm 4$  days after Visit 2. Concomitant medication and Adverse Event information was obtained. Micturition charts were dispensed with instructions to complete for 7 consecutive days before the last dose of study medication. Those subjects who had received pads at Visit 1 again received standardized pads at Visit 3 with the instruction to collect each used pad for 2 days before the last dose of study medication. Drug was returned and two boxes of drug were dispensed. The investigator verified subject compliance by capsule/tablet count.

Visit 4 occurred  $84 \pm 4$  days after Visit 2 or upon subject withdrawal from the trial. Concomitant medication and Adverse Event information was obtained. The investigator assessed the Subject's perception of urgency, Subject's perception of treatment benefit, and Subject's perception of urgency. The QoL assessments (King's Questionnaire and SF-36) were completed. The micturition chart and pads were collected. Drug was returned. The investigator verified subject compliance by capsule/tablet count. Clinical chemistry and hematology blood samples were obtained. Urine pregnancy testing was performed locally according to country specific requirements for female subjects of childbearing potential. ECGs were obtained in the subgroup of  $\geq 65$  year old subjects who had ECGs performed at Visit 2 in United States centers. Pads were collected, counted and weighed in the subgroup of subjects who had participated in the pad weight test at Visit 2 in United States and Australian centers.

#### **Reviewer's comment:**

- 1) "During-treatment" efficacy diary data was collected only on the 7 days prior to the last dose of medication. The reviewer considered it unlikely that the prematurely withdrawn subjects (12.2% of all subjects in the study) would have collected "during-treatment" efficacy diary data before withdrawing. In Vol. 2 p. 27 it was stated that if possible any prematurely withdrawn patient was to have completed the micturition chart for the last 7 days on study medication. By analyzing the efficacy diary data, the reviewer determined that only 4 of the 68 placebo and 5 of the 62 tolterodine IR prematurely withdrawn subjects completed at least 5 "during-treatment" diaries. 93% of prematurely withdrawn subjects failed to complete at least 5 "during-treatment" diaries.**
- 2) Five prematurely withdrawn placebo subjects did not complete five "pre-treatment" diaries. Subjects 1577, 1660, and 1696 each completed 2 days "pre-treatment" diaries and no "during-treatment" diaries. Subject 2535 completed 3 days "pre-treatment" diaries and no "during-treatment" diaries. Subject 2926 completed no "pre-treatment" diaries and 2 "during-treatment" diaries.**
- 3) Four prematurely withdrawn tolterodine IR subjects did not complete five "pre-treatment" diaries. Subjects 1578 and 2355 each completed 4 days "pre-treatment" diaries and no "during-treatment" diaries. Subject 1880 completed 2 days "pre-**

treatment” diaries and no “during-treatment” diaries. Subject 2274 completed no “pre-treatment” diaries and 1 “during-treatment” diaries.

- 4) The same percentage (7%) of prematurely withdrawn subjects completed at least 5 “during-treatment” diaries or failed to complete at least 5 “pre-treatment” diaries.

#### **4.5.4 Post-Treatment period**

Visit 5 occurred one week after treatment for post-treatment follow-up. At this visit or telephone contact, concomitant medication and Adverse Event information was obtained. Unresolved adverse events that were judged by the investigator as related to study medication were to be followed until resolved or assessed as chronic or stable.

### **4.6. Evaluation criteria**

#### **4.6.1 Efficacy**

The **primary efficacy variable** was the mean number of incontinence episodes per week.

The **primary efficacy endpoint** was the change in mean number of incontinence episodes per week as determined from the micturition charts taken at baseline and at the end of treatment (week 12 or withdrawal).

The **secondary efficacy variables** were the mean number of micturations per 24 hours, mean volume voided per micturation, number of pads used per 24 hours, subject’s perception of bladder condition, subject’s perception of urgency, subject’s perception of treatment benefit, and QoL variables. Data on an additional secondary efficacy variable (proportion of micturations associated with urgency) were collected but not analyzed due to sponsor concerns that there were misconceptions regarding the term urgency that led to improper completion of the micturition charts. Data on an additional secondary efficacy variable (mean urine weight per incontinence episode) were collected but not analyzed due to technical difficulties with the pad weight test preventing accurate data from incomplete or unreliable information on the weight of the dry pad. Additional secondary efficacy variables (antimuscarinic effects of dry mouth, constipation, and vision abnormalities including accommodation abnormalities using visual analogue scales) were deleted in Amendment 1.

The **secondary efficacy endpoints** were changes from baseline to the end of treatment (week 12 or withdrawal):

- Mean number of micturations per 24 hours (from the micturition charts)
- Mean volume voided per micturition (from the micturition charts)
- Number of pads used per 24 hours (from the micturition charts)
- Proportion of micturations associated with urgency (from the micturition charts-data not analyzed by sponsor)
- Mean urine weight per incontinence episode (from the pad weight test subgroup-data not analyzed by sponsor)
- Subject’s perception of bladder condition
- Subject’s perception of urgency
- Subject’s perception of treatment benefit (assessed only at end of treatment)
- QoL scores

**Reviewer's comments:**

- 1) **Sponsor did not correlate subject's change in perception of bladder condition or urgency with subject's perception of treatment benefit. This resulted in some subjects reporting a worsening of bladder condition on treatment while simultaneously reporting a positive treatment benefit. For example, subject #1097 reported some moderate bladder problems at start of treatment, severe bladder problems at end of treatment, and much benefit from treatment.**
- 2) **Sponsor should have followed protocol analysis plan, analyzed pad weight data, and discussed % of data felt to have be accurate. It is well known that pad tests are fraught with difficulties such as subject noncompliance, need to carefully preweigh all pads used, and need to adjust for weight of any non-urine fluid on pad.**
- 3) **Sponsor should have followed protocol analysis plan, analyzed proportion of micturations associated with urgency, and discussed % of data felt to be accurate.**

Regarding the efficacy endpoints calculated from the micturition chart:

- Volumes voided per micturition and numbers of pads used were averaged for a minimum of 2 days
- All other chart variables were averaged for a minimum of 5 completed days.

**4.6.2 Safety**

The safety variables were adverse events, withdrawals, laboratory variables, and in selected United States centers ECG QT, QTc and QT dispersion.

The secondary safety endpoints were changes from baseline to the end of 12 weeks of treatment in:

- Proportion of subjects with adverse events grouped according to WHO preferred term
- Proportion of withdrawn subjects
- Hematology and clinical chemistry laboratory results
- QT, QTc and QT dispersion on ECG for subjects  $\geq 65$  years of age in selected United States centers

**4.7 Withdrawals, compliance, discontinuations**

Subjects were prematurely withdrawn from the trial if, in the opinion of the investigator, it was medically necessary, or if it was the subject's wish. Subjects who were found to violate the exclusion criteria #4, 5, or 15 regarding contraindicated conditions, significant hepatic or renal disease, pregnancy or lactation, or lack of effective birth control (females of childbearing potential) were immediately withdrawn from the trial for reasons of subject safety. For any prematurely withdrawn subject, all assessments that were related to Visit 4 were to be performed within 3 to 9 hours after the last dose of study medication, if possible. Also, if possible, any prematurely withdrawn subject was to have completed the micturition chart for the last 7 days on study medication.

A total of 187 (12.2%) subjects were prematurely withdrawn from the study for any reason. An adverse event (AE) was the most common reason subjects were prematurely withdrawn (47%). Similar percentages of subjects were prematurely withdrawn and for similar reasons in the three arms of the study (See Table #1)

Table #1-Subjects Prematurely Withdrawn from Study  
(Created by MO from Table 4 Vol. 2 pg. 46)

	Total Number of Subjects	Number Withdrawn (% of total number)	Number due to AEs (% of total number)
Tolterodine IR	514	62 (12.1%)	28 (5.4%)
Placebo	508	68 (13.4%)	33 (6.5%)
Tolterodine PR	507	57 (11.2%)	27 (5.3%)
Total	1529	187	88

Per the protocol (Vol. 2 p.185), subjects who completed the trial according to the protocol i.e., no major violation from the inclusion/exclusion criteria, compliance and have recorded data form both baseline and 12 weeks visit were included in the PP analysis. Per the Final Study Report (Vol. 2 p. 46), these major protocol violations included:

- Randomized but did not take any study medication. One placebo and 2 tolterodine IR subjects were randomized but did not take study medication.
- <4.5 incontinence episodes per week at baseline. Twelve placebo and 17 tolterodine IR subjects reported less than 4.5 incontinence episodes per week at baseline.
- Missing micturition chart (MC). At Visit 2, one placebo subject had a missing MC. At Visit 4, 64 placebo and 57 tolterodine subjects had a missing MC.
- Incomplete micturition chart (defined as less than 5 days completed for 24 hours, or completed after or at first dose of trial medication or completed after last dose of trial medication. At Visit 2, 15 placebo and 10 tolterodine IR subjects had an incomplete MC. At Visit 4, 27 placebo and 20 tolterodine IR subjects had an incomplete MC.
- Invalid micturition chart (defined as symptomatic UTI during the days of completion). At Visit 2, 0 placebo and 1 tolterodine IR subjects had UTIs. At Visit 4, 11 placebo and 8 tolterodine IR subjects had UTIs
- Documentation of missing >25% of the prescribed treatment medication (7 placebo and 20 tolterodine IR subjects) or missing compliance data (18 placebo and 13 tolterodine IR subjects)

A total of 360 (23.5%) subjects had at least one major protocol violation and should have been excluded from the PP analysis. 288 of the 360 subjects (80%) with at least one major protocol violation had a missing, incomplete, or invalid micturition charts. Overall, there were similar numbers of subjects in all three arms of the study having major protocol violations and similar percentages in all three arms for any particular major protocol violation.

Table #2-Subjects with Major Protocol Violations  
(Created by MO from Table 5 Vol. 2 pg. 47)

	Total Number of Subjects	Number Subjects with Major Protocol Violations (% of total number)	Number due to missing, incomplete, or invalid micturition charts
Tolterodine IR	514	117 (22.8%)	92
Placebo	508	134 (26.4%)	108
Tolterodine PR	507	109 (21.5%)	88
Total	1529	360 (23.5%)	288

**Reviewer's comments:**

- 1) It is concerning that the primary efficacy endpoint was taken from the micturition charts and 288 of the 1529 subjects (18.8%) had missing, incomplete, or invalid micturition charts. However similar numbers of subjects in each of the three arms had missing, incomplete, or invalid micturition charts (see Table #2).
- 2) The site monitors should have noticed the micturition chart inadequacies and reeducated the sites. However the rapid trial enrollment and small total numbers of subjects at many sites may have prevented significant improvement due to reeducation from occurring.
- 3) A definition of major protocol violations was not found in the trial protocol or amendments. The definition of major protocol violations should have been prespecified in the protocol.
- 4) I would have included as major protocol violators any subject who failed to meet the inclusion criteria of having an average of  $\geq 8$  micturitions/24 hours. A total of 135 subjects (8.8% of randomized subjects) reported less than 8 micturitions/24 hours at baseline.
- 5) The protocol inclusion criterion was  $\geq 5$  incontinence episodes per week, yet a major protocol violator criteria was  $< 4.5$  incontinence episodes per week. It is unclear why  $< 5$  incontinence episodes per week was not selected as a major protocol violator criteria.
- 6) There is inconsistency regarding whether concomitant use of a prohibited medication excluded a subject from the PP population. The concomitant use of prohibited medications (11 placebo and 5 tolterodine IR subjects) was listed (Table 5 Vol. 2 pg 47) as a major protocol violation, however it was not listed (Vol. 2 pg 46) in the discussion of major protocol violations that could affect the evaluation of treatment. Review of the data determined that subject using a prohibited medication was excluded from the PP population.

Five patients were prematurely unblinded during the study. Site 065 (Dr. Annik Mombet in Paris, France) accidentally unblinded two of the 7 subjects enrolled at the site. Site 220 (Dr. Alan Garely in Great Neck, NY) unblinded two of the 23 subjects enrolled at the site-one due to a nonserious adverse event and one due to a subinvestigators wish to offer other treatment option after withdrawal. Site 170 (Dr. Robert Freeman in Devon, United Kingdom) unblinded one of the 17 subjects enrolled at the site after an overdose by patient's daughter.

## 4.8 Protocol Amendments

### 4.8.1 Protocol Amendment #1

- Visual Analogue Scales were deleted since they had not been validated to measure antimuscarinic effects.
- Pad weight test was changed to being performed in a subset of the trial population; it was changed to being performed in United States centers on subjects who have previously used incontinence pads.
- Hematology laboratory safety assessments were added.
- Exclusion criteria was changed that cough provocation test was only for female subjects.

### 4.8.2 Protocol Amendment #2

- Pad weight test was changed to being performed in Australian centers, as well as in United States centers.
- King's Health Questionnaire completion was deleted for subjects in the Netherlands, Norway, or by Flemish subjects in Belgium since it is not available in Dutch, Norwegian, or Flemish.

### 4.8.3 Protocol Amendment #3

- Cough Provocation test was changed to being done in the standing position, instead of the supine position.

### 4.8.4 Protocol Amendment #4

- Five centers in Russian Federation and Ukraine were added.
- Statistical and analytical plans were changed in response to suggestions from the FDA. An ANOVA replaced the t-test
- King's Health Questionnaire completion was deleted for subjects in the Russian Federation or Ukraine since it is not available in Russian.
- Subgroup analyses on micturition variables with respect to sex and races were added.
- The sentence "If micturition chart diaries are not completed according to the protocol, the estimation of the micturition variable will be based on the available data" was added to the Intention-to-treat population.

## Reviewer's comments:

- 1) **It was initially unclear exactly how and why the micturition variables in the ITT population would be estimated. In a fax dated September 7, 2000, the sponsor clarified that the term "estimation" referred to using less than five complete days of micturition chart diaries to calculate a week of values. The sponsor also explained how the "estimations" were performed and provided a list of subject numbers who had estimations performed.**

## 4.9 Efficacy analyses

### 4.9.1 Statistical Methods

The Final Report of the Trial stated that sample size was calculated on the primary efficacy variable to detect a mean difference of 4.2 incontinence episodes per week between tolterodine IR and placebo and assumed a standard deviation of 18.2 (Vol. 2 pg. 43). It also stated that in the protocol (Vol. 2 pg. 186) the decimal was incorrectly not given for the mean difference, i.e. 4 was mentioned in the protocol text but 4.2 was used for the calculation. **In Appendix 23, the**

sponsor stated that the sample size was based on "a minimum difference worth detecting of four incontinence episodes" (Vol. 22 pg. 188). The sample size was adjusted for an expected dropout rate of 20%. No interim analysis was performed.

**Reviewer's comments:**

**1) Sample size calculations were based on reasonable assumptions as confirmed by the trial results:**

- For the trial's ITT population, the mean difference between tolterodine IR and placebo subjects was 3.7 incontinence episodes per week. The trial results were close to the expected mean difference of 4.2 incontinence episodes per week.
- For the trial's ITT population, the standard deviation was 15.4 for placebo and 16.9 for tolterodine IR subjects regarding the primary efficacy variable change from baseline to week 12. The expected standard deviation was 18.2.
- A total of 12.2 % of subjects were prematurely withdrawn from the trial. The expected drop out rate was 20%.

It was planned to use the t-test for the primary efficacy variable to test the null hypothesis unless assumption of normal distributed data was violated. If that was the case, the Wilcoxon rank sum test was to be used. Adjustment for multiple tests were to be made according to Bonferroni, i.e. each test would be made with a 2.5% significance level to satisfy an overall significance level of 5%. If the mean number of incontinence episodes/week was greater than 168 (>24 incontinence episodes/24 hours), it was truncated at 168 episodes/week (24 episodes/24 hours). Results were also presented as change in mean number of incontinence episodes/24 hours.

For secondary efficacy variables, 95% confidence intervals were planned to be calculated for mean change from baseline to week 12 between the treatment groups. Subgroup analyses of micturition variables were performed for the ITT population based on gender, age (<65 years, ≥65 years), race, and metabolizer type (extensive, poor).

Three populations were to be used for efficacy analyses per the protocol:

- Intent-to-treat (ITT) population-included all randomized subjects. The primary analysis was on the ITT population. Missing values at week 12 were substituted with the last value carried forward (baseline value). Missing baseline values were substituted with the last value carried backward (week 12).
- Observed cases-all subjects who have recorded data from both baseline and 12 weeks visit.
- Per-protocol (PP) population-included all subjects who completed the trial according to the protocol (i.e., had no major violation of the inclusion/exclusion criteria, were compliant, and had data recorded for both baseline and week 12). Analyses on the PP population were supportive data.

There were several changes in the planned analyses made prior to breaking the blind:

- Non-parametric methods were to be used if the assumptions of normality was violated, however it was decided that the parametric analysis would be made as primary analysis but a non-parametric analysis was also to be made which would be considered as a supportive analysis

- The definition of the Per-Protocol population was changed and withdrawn subjects were also included if the patient completed the micturition chart for Visit 4 and all other criteria for Per-Protocol were fulfilled. 12% of subjects in study were prematurely withdrawn.
- Two secondary efficacy variables were not analyzed: the mean urine weight/incontinence episode and the proportion of micturitions associated with urgency.
- On July 2, 1999 in Amendment 4, analysis methods were changed for the ITT population to: If micturition chart diaries were not completed according to the protocol, the estimations of the micturition variables were based on the available data.

The primary efficacy endpoint was analyzed by ANOVA, which included treatment, country, and treatment-by-country factors. Bonferroni's method was used to adjust for multiple testing (tolterodine PR vs placebo and tolterodine IR vs placebo,  $\alpha=0.025$ ). The magnitude of treatment effect for each comparison was determined by the respective 97.5% confidence interval based on the least square means from the ANOVA. The similarity in efficacy between tolterodine PR and IR formulations was described using a 95% confidence interval. Secondary variables were evaluated using 95% confidence intervals for the difference between tolterodine PR and placebo and for tolterodine IR and placebo.

**Reviewer's comments:**

- 1) **The observed cases analyses was omitted from the study final report. The observed cases analyses were requested from the sponsor and were submitted in Amendment No. 1 to S-004 dated May 5, 2000. No significant differences were noted in comparing the observed cases analyses with the ITT and PP analyses.**
- 2) **"During-treatment" diary data was obtained only for the seven days prior to last study medication dose. This necessitated carrying forward baseline values to substitute for missing "during-treatment" values and carrying backward "during-treatment" values to substitute for missing "pre-treatment" values. It penalized the sponsor by making it more difficult for the sponsor to demonstrate a treatment effect. This problem would have been minimized if additional "during-treatment" diary data had been collected, e.g., 7 days of diary data collected during every 28 days of treatment.**
- 3) **In 98-TOCR-007, one subject had no efficacy data for any of the visits and was considered missing in the efficacy analyses (Vol. 2 pg. 53), however Appendix 15 stated no subjects were excluded from the efficacy analysis (Vol. 8 p. 408).**

**4.9.2 Efficacy Results**

**4.9.2.1 ITT Population Efficacy Results**

The baseline primary efficacy variable was well matched in the three treatment arms with a mean of 22.1-23.3 incontinence episodes per week. However all treatment arms had a very wide range of 0 to 168 incontinence episodes per week. At Week 12, there was a mean change from baseline of -10.6 (tolterodine IR), -6.9 (placebo), and -11.8 (tolterodine PR) with large standard deviations of 15.4 to 17.8 incontinence episodes per week. This resulted in a treatment difference for tolterodine IR versus placebo of -3.7 incontinence episodes per week least square estimated mean change (SEM 1.1). It should be noted that the calculation of sample size was based on the primary efficacy variable, a standard deviation of 18.2, and "a minimal difference worth detecting" (Vol. 22 pg. 188) between tolterodine IR and placebo of four incontinence episodes. The tolterodine IR compared to placebo results did not meet the "minimal difference worth

detecting” of four incontinence episodes. The 97.5% CI were (-6.0, -1.3) with a p-value of 0.0005. No subgroup analysis was done based on individual subject race since non-Caucasians races represented only approximately 5% of the population. However analyses were done for White and for the remaining races pooled together.

At Week 12 compared to baseline, there was a statistically significant change of -0.5 micturitions/24 hours with tolterodine IR treatment versus placebo.

At Week 12 compared to baseline, there was a statistically significant increase of 15.3 ml in mean voided volume per micturition with tolterodine IR treatment versus placebo.

At Week 12 compared to baseline, there was very little difference (-0.3) in the number of pads per 24 hours used with tolterodine IR treatment versus placebo.

**Reviewer’s comments:**

- 1) Lack of decrease in number of pads with treatment may be a key issue for reimbursement calculations in some European countries.**

Patient’s perception of bladder condition, perception of urgency, and perception of treatment benefit data was simply listed as percentages in each category with no additional statistical analysis.

Of note regarding their perception of bladder condition at Week 12 compared to baseline:

- 42.9% of placebo subjects reported improvement
- 60.9% of tolterodine IR subjects reported improvement
- 44.3% of placebo subjects reported no change
- 30.7% of tolterodine IR subjects reported no change

Of note regarding their perception of urgency at Week 12 compared to baseline:

- 25.8% of placebo subjects reported improvement
- 40.1% of tolterodine IR subjects reported improvement
- 64.2% of placebo subjects reported no change
- 54.3% of tolterodine IR subjects reported no change

Of note regarding their perception of treatment benefit at Week 12 compared to baseline:

- 22.0 % of placebo subjects reported much benefit
- 40.1 % of tolterodine IR subjects reported much benefit
- 43.5 % of placebo subjects reported no benefit
- 23.7 % of tolterodine IR subjects reported no benefit

Secondary efficacy endpoints of proportion of micturitions associated with urgency and urine weight per incontinence episode were omitted due to sponsor’s assessment of unreliable data.

Subgroup analysis was performed by gender, age (<65 years, ≥ 65 years), race (White, other) and metabolizer type (extensive, poor) for the ITT population with no apparent significant differences noted.

**Reviewer's comments:**

- 1) **Subgroup analysis was not performed by subgroups defined by baseline mean number of incontinence episodes per week. Majority of improvement may have occurred in subjects with large numbers of incontinence episodes.**
- 2) **Subgroup analysis was not performed by subgroups defined by baseline number of micturitions per 24 hours.**

**Quality of Life Data** (NDA Vol. 2 pg. 140-143 and NDA Vol. 22 Appendix 23 pg. 180-315) were reviewed. The King's Health Questionnaire (KHQ) was considered the primary HRQOL measure and the SF-36 a secondary HRQOL measure. The KHQ is a disease-specific HRQOL instrument that was developed specifically for urinary incontinence patients. For the KHQ, 100 indicates the worst possible HRQOL and 0 indicates the best possible HRQOL. Clinically meaningful difference criteria have not been established for the KHQ. The protocol (Section 9.1) stated that all evaluations of the KHQ and the SF-36 were to be performed as specified in the respective manual.

In the KHQ, ten separate scores are generated: one from each of seven domains, two from one-item questions addressing General Health Perceptions and Incontinence Impact, and a separate Symptom Severity scale score. Totaling the ten scores is not part of the KHQ. Three of the ten scores (**Role Limitations** domain, **Emotions** domain, and the one-item **Incontinence Impact** question) showed a clinically meaningful improvement with tolterodine IR treatment compared with placebo. The three scores just exceeded the minimal criteria to be considered a clinically meaningful improvement by 0.07 to 0.85, which were very small margins considering the possible 100 mean change score).

The **Role Limitations** domain score for tolterodine IR treatment compared with placebo showed a difference in mean change score of **-7.6**. The minimal criterion to be considered a clinically meaningful improvement in this domain was **-6.75**.

The **Emotions** domain score for tolterodine IR treatment compared with placebo showed a difference in mean change score of **-5.22**. The minimum criterion to be considered a clinically meaningful improvement in this domain was **-5.15**, which was just exceeded.

Regarding the **Incontinence Impact** question, tolterodine IR was 76.31 at baseline and 58.8 at end of treatment (-17.52 mean change) and placebo was 75.92 at baseline and 67.06 at end of treatment (-8.86 mean change) with a mean change score of **-8.36**. The minimum criterion to be considered a clinically meaningful improvement with this question was **-7.91**, which was just exceeded.

The **Short Form-36** can be analyzed by eight domains or summarized as Physical Component Summary (PCS) and Mental Component Summary (MCS) measures. There were **no statistically significant differences** between treatment groups on the SF-36 PCS and MCS scores. For SF-36, 0 indicates the worst possible HRQOL and 100 indicates the best possible HRQOL. Regarding the SF-36 Physical Summary scores, tolterodine IR was 43.74 at baseline and 44.33 at

end of treatment (0.59 change) and placebo was 43.35 at baseline and 44.08 (0.72 change). The placebo group experienced more improvement in their PCS score than the tolterodine IR group.

In summary regarding the **primary efficacy endpoint ITT Population**, there was a mean decrease of 10.6 incontinence episodes per week (from baseline of 23.2) with tolterodine IR treatment versus a mean decrease of 6.9 incontinence episodes per week (from baseline of 23.3) with placebo. This difference of **3.7 less incontinence episodes per week** with tolterodine IR treatment compared with placebo was a statistically significant decrease and the sponsor concluded that it was also a clinically meaningful decrease. **It is unclear whether it is clinically significant.**

The sponsor utilized a difference of **4.2 less incontinence episodes per week** in determining the sample size (Vol. 2 pg. 43) and stated "a **minimal difference worth detecting of four incontinence episodes**" was used to calculate the sample size (Vol. 2 p. 186). If 4.2 less incontinence episodes were accepted as the minimal difference worth detecting, **the ITT tolterodine IR population did not meet this criterion** when compared to placebo.

The sponsor omitted discussing if the subject considered a mean decrease of one incontinence episode approximately every two days to be of sufficient clinical benefit for them to accept the risks of treatment. During the End of Phase 2 meeting for NDA 21-228 on November 30, 1998, DRUDP advised sponsor to determine what change in incontinence episodes from baseline would be meaningful to the patient. DRUDP stated that a **clinically meaningful difference might be a 20-25% decrease in weekly incontinence episodes per week**. Placebo ITT subjects experienced a 30% decrease in weekly incontinence episodes per week. Tolterodine IR ITT subjects experienced a 46% decrease in weekly incontinence episodes per week. **Tolterodine IR ITT subjects demonstrated a 16% decrease in weekly incontinence episodes per week compared to placebo.**

Regarding the **secondary efficacy endpoints**, there were several statistically significant improvements demonstrated, however **it is unclear if they are clinically significant.**

#### 4.9.2.2 PP Population Efficacy Results

The baseline primary efficacy variable was well matched in the three treatment arms with a mean of 22.9-23.5 incontinence episodes per week. However, placebo and tolterodine PR arms had a very wide range from baseline 5.0 to 168 incontinence episodes per week and tolterodine IR ranged from 5.0 to 141.2. At Week 12, there was a mean change from baseline of -12.8 (tolterodine IR), -8.8 (placebo), and -13.5 (tolterodine PR). This resulted in a treatment difference for tolterodine IR versus placebo of -4.1 incontinence episodes per week least square estimated mean change (SEM 1.3). The 97.5% CI were (-7.9, -1.3) with a p-value of 0.0012.

At Week 12 compared to baseline, there was a statistically significant change of -0.6 micturitions/24 hours with tolterodine IR treatment versus placebo.

At Week 12 compared to baseline, there was a statistically significant increase of 17.8 ml in mean voided volume per micturition with tolterodine IR treatment versus placebo.

At Week 12 compared to baseline, there was very little difference (-0.3) in the number of pads per 24 hours used with tolterodine IR treatment versus placebo.

Of note regarding their perception of bladder condition at Week 12 compared to baseline:

- 47.6% of placebo subjects reported improvement
- 66.2% of tolterodine IR subjects reported improvement
- 39.8% of placebo subjects reported no change
- 26.4% of tolterodine IR subjects reported no change

Of note regarding their perception of urgency at Week 12 compared to baseline:

- 31.6% of placebo subjects reported improvement
- 44.8% of tolterodine IR subjects reported improvement
- 56.7% of placebo subjects reported no change
- 50.4% of tolterodine IR subjects reported no change

Of note regarding their perception of treatment benefit at Week 12 compared to baseline:

- 23.5 % of placebo subjects reported much benefit
- 43.8 % of tolterodine IR subjects reported much benefit
- 44.9 % of placebo subjects reported no benefit
- 19.9 % of tolterodine IR subjects reported no benefit

Subgroup analysis was not presented for the PP population by gender, age (<65 years, ≥65 years), race (White, other) and metabolizer type (extensive, poor). Quality of Life Data was not presented for the PP Population.

**In summary regarding the primary efficacy variable PP Population, there was a mean decrease of 12.8 incontinence episodes per week (from baseline of 23.3) with tolterodine IR treatment versus a mean decrease of 8.8 incontinence episodes per week (from baseline of 23.5) with placebo. This difference of 4.1 less incontinence episodes per week with tolterodine IR treatment compared with placebo was a statistically significant improvement. It is unclear whether this difference is clinically significant.**

**In summary regarding the secondary efficacy variables PP Population, there were several statistically significant improvements demonstrated. It was unclear if they were clinically significant.**

#### 4.9.2.3 Observed Cases Efficacy Results

The baseline primary efficacy variable was well matched in the three treatment arms with a mean of 22.5-22.7 incontinence episodes per week. However, the placebo and tolterodine PR arms had a very wide range from baseline 0 to 168 incontinence episodes per week and tolterodine IR also widely ranged from 0 to 141.2. At Week 12, there was a mean change from baseline of -12.3 (tolterodine IR), -8.2 (placebo), and -13.6 (tolterodine PR). This resulted in a treatment difference for tolterodine IR versus placebo of -4.2 incontinence episodes per week least square estimated mean change (SEM 1.2). The 97.5% CI were (-6.9, -1.5) with a p-value of 0.0004.

At Week 12 compared to baseline, there was a statistically significant change of -0.6 micturitions/24 hours with tolterodine IR treatment versus placebo.

At Week 12 compared to baseline, there was a statistically significant increase of 18.2 ml in mean voided volume per micturition with tolterodine IR treatment versus placebo.

At Week 12 compared to baseline, there was very little difference (-0.3) in the number of pads per 24 hours used with tolterodine IR treatment versus placebo.

Of note regarding their perception of bladder condition at Week 12 compared to baseline:

- 45.9% of placebo subjects reported improvement
- 63.9% of tolterodine IR subjects reported improvement
- 40.4% of placebo subjects reported no change
- 27.3% of tolterodine IR subjects reported no change

Of note regarding their perception of urgency at Week 12 compared to baseline:

- 27.9% of placebo subjects reported improvement
- 42.3% of tolterodine IR subjects reported improvement
- 61.3% of placebo subjects reported no change
- 51.7% of tolterodine IR subjects reported no change

The sponsor failed to submit the Observed Cases-population perception of treatment data. Subgroup analysis was not presented by gender, age (<65 years, ≥ 65 years), race (White, other) and metabolizer type (extensive, poor) for the Observed Cases-population. Quality of Life Data was not presented for the Observed Cases-Population.

**In summary regarding the primary efficacy variable Observed Cases-population, there was a mean decrease of 12.3 incontinence episodes per week (from baseline of 22.5) with tolterodine IR treatment versus a mean decrease of 8.2 incontinence episodes per week (from baseline of 22.6) with placebo. This difference of 4.2 less incontinence episodes per week with tolterodine IR treatment compared with placebo was a statistically significant improvement. It is unclear whether it is clinically significant.**

Regarding the secondary efficacy variables Observed Cases-population, there were several statistically significant improvements demonstrated. **It is unclear whether they are clinically significant.**

**Reviewer's comment:**

- 1) There were no significant differences between the Per Protocol-population and Observed Cases-population efficacy data.**

**4.10 Safety analyses**

The analysis population for safety evaluation included all subjects who received at least one dose of study medication. Demographics, ECG and laboratory variables were analyzed descriptively, and adverse events were summarized. A total of 512 tolterodine IR subjects and 507 placebo subjects were evaluable for safety. Two tolterodine IR and one placebo subjects did not receive

study medication and were excluded from the safety analysis. No unexpected safety concerns were revealed after 12 weeks of treatment. The most common adverse events were those associated with antimuscarinic compounds. Dry mouth was the most common adverse event with tolterodine IR 30.5% compared to placebo 7.7%. The incidences of constipation were tolterodine IR 6.8% compared to placebo 4.3%. One tolterodine IR subject (patient 1136) was withdrawn from the study due to severe urinary retention and it was considered treatment related. The patient recovered after stopping study treatment.

**4.10.1 Serious Adverse Events**

In this study, serious adverse events (SAEs) were defined per FDA standard: death, life-threatening, resulted in hospitalization or prolonged hospitalization, resulted in persistent or significant disability/incapacity or a congenital anomaly/birth defect.

No deaths occurred during the study in subjects on tolterodine IR and one death occurred during the study in subjects on placebo. The placebo death (Patient 1790) was an 84-year-old female with intestinal ischemia due to vascular thrombosis after hospitalization for a fractured hip.

**During treatment**, 14 SAEs were reported in 12 tolterodine IR subjects and 18 SAEs were reported in 18 placebo subjects. A comparison of selected SAEs is presented in Table #2. The SAEs selected were known to be affected by muscarinic receptor antagonists or were cardiovascular SAEs. Five tolterodine IR and 8 placebo subjects prematurely withdrew from treatment due to a serious adverse event. Two of subjects prematurely withdrawn from treatment due to a SAE, both on tolterodine IR, experienced SAEs which were considered by the investigator to be related to study treatment, Patient 2379 (medication error) and patient 2797 (atrial fibrillation). It should be noted that Patient 2797 had a medical history of minor TIA attacks, mitral valve incompetence, atrial fibrillation, and raised TSH.

Table #2-Serious Adverse Events During Treatment by Treatment Group  
(Created by MO from Table 23 Vol. 2 pg. 74)

	Tolterodine IR Subject Number	Placebo Subject Number
Angina pectoris		2821
Cardiac Failure	1032	
Chest Pain		1955
Fibrillation atrial	1564, 2797	
Ileus		2026
Intestinal obstruction		1752
Myocardial infarction	1564	
Nausea/Vomiting		1415
#SAEs Listed Above	4	5
Additional SAEs	10	13
Total # SAEs	14	18

After the end of study treatment, 3 SAEs were reported in 3 tolterodine IR subjects and 5 SAEs were reported in 4 placebo subjects. Table #3 lists the AE WHO preferred term for each of these subjects. In reviewing the subject narratives (Vol. 2 pg. 83-91), tolterodine IR Patients 1880 and 2355 and the placebo Patients 1790 and 2339 experienced a SAE within 24 hours after termination of treatment and they were all prematurely withdrawn from the study due to their SAE.

Table #3-Serious Adverse Events After the End of Treatment by Treatment Group  
(Created by MO from Table 24 Vol. 2 pg. 75)

	Tolterodine IR Subject Number	Placebo Subject Number
Asthenia		1257
Cardiac Failure		2821
Embolism arterial	3016	
Heart block	2355	
Intestinal ischemia		1790
Myocardial infarction	1880	2821
Schizophrenic reaction		2339

**Reviewer's comments:**

- 1) There were similar numbers and types of SAEs reported in the placebo and tolterodine IR arms, which decreases the possibility that the tolterodine IR SAEs were related to the drug. It is the reviewer's opinion that the tolterodine IR SAEs are probably not related to the drug.
- 2) It is the reviewer's opinion that the four subjects experiencing SAEs within 24 hours after the end of treatment should be included in the analysis of subjects experiencing SAEs during treatment. They were all prematurely withdrawn from the study due to their SAE.

**4.10.2 Frequent Adverse Events**

Adverse events that occurred with  $\geq 5\%$  incidence by WHO body system are presented in Table #4.

Table #4-Incidence of Adverse Events  $\geq 5\%$  by WHO Body System  
(Created by MO from Table 19 Vol. 2 pg. 67)

	Tolterodine IR	Placebo
Autonomic nervous	30.9%	7.9%
Gastrointestinal	18.2%	14.2%
General	13.9%	15.2%
Psychiatric	5.5%	5.1%
Respiratory	5.5%	4.9%
Urinary	7.4%	5.9%

Those commonly reported adverse events by WHO preferred term with a  $\geq 1\%$  difference between tolterodine IR and placebo groups are presented in Table #5.

Table #5-Commonly Reported Adverse Events by WHO Body System with a  $\geq 1\%$  Difference between Tolterodine IR and Placebo Groups  
(Created by MO from Table 20 Vol. 2 pg. 69)

	Tolterodine IR	Placebo
Skin dry	1.2%	0.2%
Mouth dry	30.5%	7.7%
Insomnia	0.4%	1.8%
Constipation	6.8%	4.3%
Dyspepsia	3.1%	1.4%
Dysuria	1.6%	0.2%
Urinary tract infection	2.5%	3.9%

The most commonly reported adverse events by relation to treatment (NDA Table 21 Vol. 2 pg. 71) were evaluated. As would be expected, dry mouth and constipation were the adverse events most commonly considered treatment related.

#### 4.10.3 Discontinuations due to AE

Adverse events caused premature withdrawal of 28 tolterodine IR subjects with 76 AEs and 33 placebo subjects with 78 AEs. A comparison of selected adverse events causing premature withdrawal is presented in Table #6. The AEs selected were those known to be affected by muscarinic receptor antagonists or were cardiovascular AEs.

Table #6: Adverse Events Causing Premature Withdrawal  
(Created by MO from Table 25 Vol. 2 pg. 77-82)

	Tolterodine IR Subject Number	Placebo Subject Number
Arrhythmia	1880	
Constipation	1912, 2543	1219, 1495, 1764, 2745
Embolism arterial	3016	
Fibrillation atrial	1564, 2797	
Heart block	2355	
Hypotension postural	1632	
Ileus		2026
Intestinal obstruction		1752
Micturition disorder	1028, 1708	
Mouth dry	1076, 1243, 2355, 2812, 2836, 3142	1219, 1415, 1586, 2615, 2745, 3113
Myocardial infarction	1564, 1880	
Nausea	1243, 2379, 2542, 2760,	1167, 1415, 1696, 1851,

	2836	2293, 2410, 2799
Pericarditis		2117
Urinary Retention	1136	
Vision abnormal	3016	1851
Vomiting		1696, 2410
Additional AEs	51	55
Total AEs	76	78

#### 4.10.4 Changes in lab values

No clinically relevant changes in laboratory assessment or ECG measurements were noted.

A total of 21 ml of blood was withdrawn at Visit 1 and 14 ml at Visit 4. Clinical chemistry and hematology analyses were performed in three central laboratories, one for each continent that contained study centers. The laboratories were \_\_\_\_\_

\_\_\_\_\_ was performed at a single laboratory. \_\_\_\_\_ During the study \_\_\_\_\_ changed its name to \_\_\_\_\_ PK/PD samples were not collected as part of this trial.

\_\_\_\_\_ evaluated all ECGs. ECGs were obtained in 174 patients in selected centers in the United States. The protocol stated the patients in this substudy should be elderly ( $\geq 65$  years). Of the 174 patients that had ECGs, only 154 were  $\geq 65$  years. All ECGs obtained were included in the results regardless of subject age. Mean QTc increased 3.5 msec in the tolterodine IR group and decreased 3.5 msec in the placebo group. A decrease in mean QTc dispersion was observed in all treatment groups. No subject had a QTc on treatment that measured  $>500$  msec at Week 12.

One tolterodine IR subject (#1564) had a normal QTc at baseline (408 msec) and a prolonged QTc at Week 12 (453 msec). Subject #1564 had a medical history of myocardial infarction and hypertension.

Two tolterodine IR subjects (#1084 and #1600) had a prolonged QTc both at baseline and at Week 12. Subject #1084 had a medical history of an unspecified cardiac arrhythmia. Subject #1600 had a medical history of hypertension.

Two tolterodine IR subjects (#1295 and #1401) changed QTc  $>60$  msec from baseline to Week 12. Subject #1295 had a medical history of hypertension. Subject #1401 had a medical history of atrial fibrillation.

#### Reviewer's comment:

- 1) The reported QTc changes do not appear to be clinically significant.
- 2) The sponsor exceeded the goal of obtaining at least 90 ECGs in subjects  $\geq 65$  years.

#### 4.10.5 Changes in physical exam

No physical exam assessments were made in this study at screening, during treatment, or post treatment visits.

#### **4.11 Reviewer's assessment of safety and efficacy**

Tolterodine IR 2 mg bid resulted in a highly statistically significant decrease in the number of incontinence episodes per week after 12-weeks treatment as compared with placebo. **It is unclear whether it is a clinically significant decrease.** Tolterodine IR treatment was also associated with a statistically significant decrease in the number of micturitions per 24 hrs and in the number of pads used per 24 hrs after 12-weeks treatment when compared with placebo. Tolterodine IR treatment resulted in a statistically significant increase in the mean volume of urine voided/micturition at week 12 compared with placebo. **It is unclear whether it is a clinically significant increase.**

More subjects reported a statistically significant improvement in the perception of urgency on tolterodine IR compared to placebo. A greater proportion of subjects on tolterodine IR 2 mg bid compared to placebo reported improvement in the perceptions of their bladder condition over the 12-week treatment period. A statistically significant higher proportion on tolterodine IR reported benefit of treatment at the end of the 12-week treatment.

Tolterodine IR is fairly well tolerated. Dry mouth was the most frequent adverse event with all treatments. No new major safety concerns were evident from serious adverse events, premature withdrawals, clinical laboratory assessments, and ECGs.

#### **5.0 SAFETY UPDATE REPORT**

No Safety Update Report was submitted. All pertinent data for the NDA Supplement is included in the submitted volumes.

#### **6.0 OVERVIEW OF EFFICACY**

Primary variable: There was a statistically significant decrease in mean number of incontinence episodes per week in tolterodine IR subjects compared with the placebo subjects.

##### **Reviewer's comment:**

- 1) It is unclear if this trial demonstrated a clinically significant decrease in the mean number incontinence episodes per week in tolterodine IR subjects compared with the placebo subjects.**

Secondary variables: There were statistically significant improvements in tolterodine IR subjects in micturitions/24 hours, mean volume voided, and pads/24 hours compared with placebo subjects.

##### **Reviewer's comment:**

- 1) It is unclear if this trial demonstrated clinically insignificant decreases in micturitions per 24 hours, mean volume voided, and pads per 24 hours in tolterodine IR subjects compared with the placebo subjects.**



On August 23, 1998, the sponsor was notified that the Division would consider labeling changes the sponsor feels are supported by the completed PK study in children. They were also told that these changes, if accepted, would not affect the sponsor's claim for future pediatric exclusivity because additional safety and efficacy data would still be needed to adequately label Detrol for pediatric use. Additional concerns about the potential for Detrol to cause QT interval prolongations, in particular regarding the reported case of a 12-year old who experienced heart block after receiving 1 mg of Detrol, were transmitted.

In the supplemental submission \_\_\_\_\_, the sponsor updated the information in the package insert with respect to drug interaction. On November 10, 1999, the sponsor was notified that the review of \_\_\_\_\_ had been completed and agency had two recommendations for revisions to the Package Insert. The sponsor did not accept these recommendations and negotiations with DRUDP Clinical Pharmacology & Biopharmaceutics reviewers are continuing to present.

Supplement-Labeling Revision (SLR-006) was submitted on May 31, 2000. It is currently under review. It adds a toll-free number and website address to the carton for complimentary samples of Detrol tablets and was submitted as CBE 0 (Changes Being Effected).

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_ The current approved INDICATIONS AND USAGE section is:

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

\_\_\_\_\_  
\_\_\_\_\_ It would be optimal to address all outstanding Detrol labeling revisions at the same time. This would require completion of the agency's response to \_\_\_\_\_ and completion of the reviews for SLR 006 and \_\_\_\_\_

### 8.2 Proposed versus current labeling:

As stated in Section 1.0 RESUME, the sponsor presents the 98-TOCR-007 data in Efficacy Supplement SE8-004 as the basis for their request to extensively change the **CLINICAL STUDIES** and **ADVERSE REACTIONS** section of the tolterodine IR (Detrol™) label. The sponsor also proposes two minor changes to the **DESCRIPTION** and **CLINICAL PHARMACOLOGY** sections. The **CLINICAL STUDIES** section of the Detrol™ label currently contains a substantial table entitled "95% Confidence Intervals for the Difference between Detrol™ (2 mg bid) and Placebo for the Median Change at Week 12 from Baseline". The middle section of this table demonstrates no statistical difference in the number of incontinence episodes per 24 hours between subjects on tolterodine 2 mg bid versus placebo for

Studies 94-OATA-008, -009, and -010. The sponsor proposes \_\_\_\_\_

The **ADVERSE REACTIONS** section of the current Detrol™ label contains the following statement regarding 2049 patients (Detrol=1619 and Placebo=430) in the Phase 2 and 3 Detrol™ clinical trial program:

No differences in the safety profile of tolterodine were identified based on age, gender, race, or metabolism.

The sponsor proposed to \_\_\_\_\_

During the review of this supplement, sponsor was asked to perform and submit a subgroup analysis of the new pooled safety data, specifically looking for any differences in the safety profile of tolterodine based on age, gender, race, or metabolism. This analysis was submitted on July 14, 2000 as Amendment #2 to S-004 with the sponsor's conclusion that there did not appear to be a difference in safety profile of tolterodine based on metabolism, age, race or sex.

In addition, the **ADVERSE REACTIONS** section currently contains an extensive table entitled "Incidence (%) of Adverse Events Reported in  $\geq 1\%$  of Patients Treated with DETROL (2 mg bid) in 12-week, Phase 3 Clinical Studies". The sponsor proposes to markedly change this table by:

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

No changes to the **INDICATIONS AND USAGE** section in the Detrol™ label are suggested in this submission, however there are differences between the Detrol™ and Ditropan® XL current labeling for this section requiring review. The term "overactive bladder" appears only in the Indications and Usage section of Detrol™ and Ditropan® XL.

Detrol™ Tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.<sup>16</sup>

<sup>16</sup> Detrol™ (tolterodine tartrate tablets) Package Insert June 1, 1999

2 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

---

**This recommendation will be incorporated into the Detrol label.**

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

- 7) Adding the data from study 98-TOCR-007 to the AE 12-week, Phase 3 Clinical Studies Table is desirable since it doubled the numbers of Detrol 2mg bid subjects (from 474 to 986) and quadrupled the number of placebo subjects (from 176 to 683).

**9.0 RECOMMENDATIONS FOR REGULATORY ACTION**

Pending satisfactory negotiations with the sponsor, the reviewer recommends approval of SE8-004. In addition to the Reviewer's comments in Section 8.2 and Attachment C-Label Changes, it would be optimal that negotiations include the labeling changes requested by the sponsor in \_\_\_\_\_

\_\_\_\_\_  
Brenda S. Gierhart, M.D.  
Medical Officer, DRUDP

0/6/00  
Date

\_\_\_\_\_  
Dan Shames, M.D.  
Acting Deputy Director,  
DRUDP

10/6/02  
Date

cc:  
Archival NDA 20-771  
HFD-580 S. Allen/D. Shames/B. Gierhart/E. Farinas  
Division File

**Attachment A-Definition of Terms**

Term	Definition
b.i.d. or bid or BID	Twice a day
tolterodine modified release formulation	Tolterodine PR, tolterodine extended release (ER) or tolterodine once daily is understood to

	indicate the same formulation
q.d. or qd or OD	Once daily

**Attachment B-List of Abbreviations** (Created by MO partially from Definitions Vol. 2 pg. 17)

<b>Abbreviation/ Acronym</b>	<b>Definition</b>
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
CAD	Coronary artery disease
CDER	Center for Drug Evaluation and Research
CI	Confidence interval
CRF	Case Report Forms
CYP2D6	Cytochrome P-450 2D6
CYP3A4	Cytochrome P-450 3A4
DD 01	5-hydroxymethyl metabolite of tolterodine
DMEDP	Division of Metabolic and Endocrine Drug Products
DRUDP	Division of Reproductive Urology Drug Products
DVT	Deep vein thrombosis
ECG	Electrocardiogram
EM	Extensive metabolizer
FDA	Food and Drug Administration
HRQOL	Health-Related Quality of Life
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IR	Immediate release
IRB	Institutional Review Board
ITT	Intent-to-treat (population)
KHQ	King's Health Questionnaire
LPH	Left posterior hemiblock
LS	Least square
MC	Micturition chart
mcg	Micrograms
MCS	Mental Component Summary
mg	Milligrams
MO	Medical Officer
N	Number (of subjects)

13 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

---

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-771/S-004**

**CHEMISTRY REVIEW**

**CHEMIST REVIEW #1  
OF SUPPLEMENT**

1. ORGANIZATION HFD-580
2. NDA NUMBER: 20-771
3. SUPPLEMENT NUMBERS/DATES: SE8-004  
Letterdate: 22-DEC-1999  
Stampdate: 23-DEC-1999
4. AMENDMENTS/REPORTS/DATES:  
Letterdate:  
Stampdate:
5. RECEIVED BY CHEMIST: 10-MAR-2000

**6. APPLICANT NAME AND ADDRESS:**

Pharmacia & Upjohn  
7000 Portage Road  
Kalamzoo, MI 49001

7. NAME OF DRUG: Detrol™ (tolterodine tartrate) Tablets

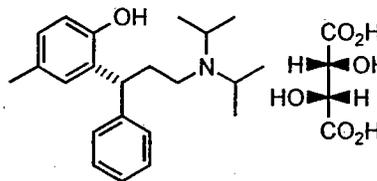
8. NONPROPRIETARY NAME: Tolterodine Tartrate

**9. CHEMICAL NAME/STRUCTURE:**

R-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate

$C_{26}H_{37}NO_7$

M.W. = 475.58



Tolterodine L-(+)-tartrate

10. DOSAGE FORM(S): Tablet

11. POTENCY: 1mg and 2 mg

12. PHARMACOLOGICAL CATEGORY: antimuscarinic

Treatment of patients with overactive bladder with symptoms of frequency, urgency, urge incontinence or any combination of these symptoms

13. HOW DISPENSED: Rx

14. RECORDS & REPORTS CURRENT: Yes

15. RELATED IND/NDA/DMF:

16. SUPPLEMENT PROVIDES FOR: This efficacy supplement provides for changes to product labeling in the "Description" section of the package insert.

**17. COMMENTS**

The changes to the "Description" section of the package insert labeling includes addition of the following statement:

"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."

The "How Supplied" section of the package insert labeling contains an outdated room temperature storage statement.

18. CONCLUSIONS AND RECOMMENDATIONS:

This supplement can be APPROVED from a chemistry, manufacturing and controls perspective.

19. REVIEWER NAME  
Michael Ortwerth, Ph.D.  
Review Chemist

SIGNATURE

DATE COMPLETED

27-MAR-2000

cc: Original: NDA # 20-771  
HFD-580/Division File  
HFD-580/CSO/EFarinas  
HFD-580/Chemist/MRhee/MOrtwerth  
INIT: MJ Rhee

filename: N20771SuppSE8004Rev1.do.

**CHEMIST REVIEW  
OF SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 20-771/SE8-004
3. **SUPPLEMENT NUMBERS/DATES:**  
    **Letterdate:** 22-DEC-1999  
    **Stampdate:** 23-DEC-1999
4. **AMENDMENTS/REPORTS/DATES:**  
    **Letterdate:**  
    **Stampdate:**
5. **RECEIVED BY CHEMIST:** 11-AUG-2000

**6. APPLICANT NAME AND ADDRESS:**

Pharmacia & Upjohn Co.  
7000 Portage Road  
Kalamazoo, MI 49001

**7. NAME OF DRUG:**

Detrol

**8. NONPROPRIETARY NAME:**

Tolterodine tartrate tablets

**9. CHEMICAL NAME/STRUCTURE:**

(R)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate

see USP Dictionary of Drug Names for structure

**10. DOSAGE FORM(S):**

Tablets

**11. POTENCY:**

1 mg, 2 mg

**12. PHARMACOLOGICAL CATEGORY:**

Treatment of overactive bladder with symptoms of frequency, urgency, urge incontinence or any combination of these symptoms.

**13. HOW DISPENSED:**

RX

**14. RECORDS & REPORTS CURRENT:**

Yes

**15. RELATED IND/NDA/DMF:**

none

**16. SUPPLEMENT PROVIDES FOR:**

Efficacy supplement to revise the clinical study section of the package insert.

**17. COMMENTS**

The only CMC issue in this supplement concerns a revision in the Description section of the package insert. The sponsor proposes to delete the following sentence \_\_\_\_\_

and replace it with the following sentences: "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." Based on the physical properties data provided in the original NDA, the revised labeling is acceptable.

Review of the package insert reveals that the storage statement in the How Supplied section should be revised from \_\_\_\_\_

\_\_\_\_\_ "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]". This comment has been conveyed to the sponsor, but the sponsor has not responded.

**18. CONCLUSIONS AND RECOMMENDATIONS:**

From a CMC point of view, this Supplement may be approved pending satisfactory resolution of the above labeling issue.

**19. REVIEWER NAME**

David T. Lin, Ph.D.  
Review Chemist

**SIGNATURE**

\_\_\_\_\_

**DATE COMPLETED**

16-OCT-2000

10/16/00

cc: Original: NDA 20-771/SE8-004  
HFD-580/Division File  
HFD-580/EFarinas  
HFD-580/MRhee/DLin

INIT by MJ Rhee

\_\_\_\_\_

Filename: S20771.004 (doc)

**CHEMIST REVIEW #2  
OF SUPPLEMENT**

- 1. ORGANIZATION:** DRUDP HFD-580
- 2. NDA NUMBER:** 20-771/SE8-004
- 3. SUPPLEMENT NUMBERS/DATES:**  
**Letterdate:** 22-DEC-1999  
**Stampdate:** 23-DEC-1999
- 4. AMENDMENTS/REPORTS/DATES:**  
**Letterdate:** 26-OCT-2000  
**Stampdate:** 27-OCT-2000
- 5. RECEIVED BY CHEMIST:** 11-AUG-2000

**6. APPLICANT NAME AND ADDRESS:**

Pharmacia & Upjohn Co.  
7000 Portage Road  
Kalamazoo, MI 49001

**7. NAME OF DRUG:**

Detrol

**8. NONPROPRIETARY NAME:**

Tolterodine tartrate tablets

**9. CHEMICAL NAME/STRUCTURE:**

(R)-N,N-Diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate

see USP Dictionary of Drug Names for structure

**10. DOSAGE FORM(S):**

Tablets

**11. POTENCY:**

1 mg, 2 mg

**12. PHARMACOLOGICAL CATEGORY:**

Treatment of overactive bladder with symptoms of frequency, urgency, urge incontinence or any combination of these symptoms.

**13. HOW DISPENSED:**

RX

**14. RECORDS & REPORTS CURRENT:**

Yes

**15. RELATED IND/NDA/DMF:**

none

**16. SUPPLEMENT PROVIDES FOR:**

Efficacy supplement to revise the clinical study section of the package insert.

**17. COMMENTS**

The October 26, 2000 amendment is a response to the Division's October 23, 2000 approvable letter. The sponsor has revised the storage statement as requested. See Chemistry Review #1 dated October 16, 2000 for further details.

**All relevant CMC issues have been adequately addressed in the latest label.**

**18. CONCLUSIONS AND RECOMMENDATIONS:**

From a CMC point of view, this Supplement may be approved.

<b>19. REVIEWER NAME</b>	<b>SIGNATURE</b>	<b>DATE COMPLETED</b>
David T. Lin, Ph.D. Review Chemist		26-MAR-2001

cc: Original: NDA 20-771/SE8-004  
HFD-580/Division File  
HFD-580/EFarinas  
HFD-580/MRhee/DLin

INIT by MJ Rhee

Filename: S20771AC.004 (doc)

/s/

-----  
David T. Lin  
3/26/01 02:00:36 PM  
CHEMIST

Labeling supplement: revised storage statement

Moo-Jhong Rhee  
3/26/01 04:53:22 PM  
CHEMIST  
I concur

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-771/S-004**

**CLINICAL PHARMACOLOGY  
BIOPHARMACEUTICS REVIEW**

SEP 20 2000

P11  
SEP 20 2000

<b>DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION</b>	<b>Clinical Pharmacology &amp; Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults</b>
---	--

<b>From: Dhruba J. Chatterjee, Ph.D.</b>	<b>To: DOCUMENT ROOM (LOG-IN and LOG-OUT)</b> <b>Please log-in this consult and review action for the specified IND/NDA submission</b>
--	---

DATE: 4/11/00	NDA No.: 20-771 Supplement No: S 004	NDA No. N/A	DATE OF DOCUMENT 12/29/1999
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NAME OF DRUG Detrol (tolterodine tartarate)	PRIORITY CONSIDERATION S	DATE OF FORMAL REVIEW 4/11/00
--	-----------------------------	----------------------------------

NAME OF THE SPONSOR: Pharmacia and Upjohn

**TYPE OF SUBMISSION**

**CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> PRE-IND<br><input type="checkbox"/> ANIMAL to HUMAN SCALING<br><input type="checkbox"/> IN-VITRO METABOLISM<br><input type="checkbox"/> PROTOCOL<br><input type="checkbox"/> PHASE II PROTOCOL<br><input type="checkbox"/> PHASE III PROTOCOL<br><input type="checkbox"/> DOSING REGIMEN CONSULT<br><input type="checkbox"/> PK/PD- POPPK ISSUES<br><input type="checkbox"/> PHASE IV RELATED | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST<br><input type="checkbox"/> SUPAC RELATED<br><input type="checkbox"/> CMC RELATED<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> SCIENTIFIC INVESTIGATIONS<br><input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others) | <input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> ANNUAL REPORTS<br><input type="checkbox"/> FAX SUBMISSION<br><input type="checkbox"/> OTHER (SPECIFY BELOW):<br><div style="text-align: right;">Supplemental NDA</div> |
|--|--|--|

**REVIEW ACTION**

- |   |  |  |
|---|--|--|
| <input type="checkbox"/> NAI (No action indicated)<br><input type="checkbox"/> E-mail comments to:<br><input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox<br><input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others<br>(Check as appropriate and attach e-mail) | <input type="checkbox"/> Oral communication with<br>Name: [    ]<br><input type="checkbox"/> Comments communicated in<br>meeting/Telecon. see meeting minutes dated:<br>[    ] | <input type="checkbox"/> Formal Review/Memo (attached)<br><input type="checkbox"/> See comments below<br><input type="checkbox"/> See submission cover letter<br><input type="checkbox"/> OTHER (SPECIFY BELOW):<br>[    ] |
|---|--|--|

**REVIEW COMMENT(S)**

NEED TO BE COMMUNICATED TO THE SPONSOR     HAVE BEEN COMMUNICATED TO THE SPONSOR

**COMMENTS/SPECIAL INSTRUCTIONS:**

This supplemental NDA has no apparent PK/Biopharm issues. This was confirmed by the Medical Officer assigned to this NDA, Dr. Gierhart. Hence, no formal review of this S-NDA was conducted.

However, the sponsor is suggesting one minor change in the CLINICAL PHARMCOLOGY section of the label. In the third

---

SIGNATURE OF REVIEWER: \_\_\_\_\_

151

SIGNATURE OF TEAM LEADER \_\_\_\_\_

151

CC.: HFD # 870; TL: Parakh; DD: Huang

Date 9/20/00

Date 9/20/00

Project Manager: \_\_\_\_\_

Date \_\_\_\_\_



**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 20-771/S-004**

**ADMINISTRATIVE DOCUMENTS**

**NDA 20-771/S-004**

**Drug Name:** Detrol (tolterodine tartrate) tablets, 1 and 2 mg

**Sponsor:** Pharmacia & Upjohn

**Subject:** Patent statement

**Action:** Refer to patent information correspondence from sponsor dated  
May 1, 2000

**Date:** April 3, 2001

**PATENT SUBMISSION FORM**

Patent Information Pursuant to 21 C.F.R. 314.53

For

NDA # 020771

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: DETROL
- Active Ingredient(s): Tolterodine Tartrate
- Strength(s): 1 mg, 2 mg
- Dosage Form: Tablet
- Approval Date: March 25, 1998

**A. This section should be completed for each individual patent.**

For more than three patents, copy and paste this section as many times as needed.

**U.S. Patent Number:** 5,559,269

**Expiration Date:** May 5, 2015

**Type of Patent – Indicate all that apply:**

- 1) Drug Substance (Active Ingredient) X Y \_\_\_N
- 2) Drug Product (Composition/Formulation) \_\_\_Y X N
- 3) Method of Use X Y \_\_\_N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: Treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

**Name of Patent Owner:** Pharmacia AB

**U.S. Agent (if patent owner or applicant does not reside or have place of business in the U.S.):**

**B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.**

The undersigned declares that the above stated United States Patent Number 5,559,269 covers the composition, formulation and/or method of use of DETROL (name of drug product). This product is:

\* X currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act

OR

\* \_\_\_ the subject of this application for which approval is being sought

Signed: Don W. Schmitz  
Date: 4/25/00  
Title: Corporate Secretary

---

A copy of the above information should be submitted to the NDA with the original application or as correspondence to an existing NDA. For patents issued after the NDA is filed or approved, the applicant is required to submit the information within thirty (30) days of the date of issuance of the patent.

To expedite publication in "*The Orange Book*," a deskcopy should be submitted to:

Mailing address: (US Mail)

U.S. Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Data Management and Services  
Information Services Team  
HFD-93  
5600 Fishers Lane  
Rockville, MD 20857

OR

Location address: (for FedEx deliveries)

U.S. Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Data Management and Services  
Information Services Team  
Building A  
HFD-93 Room #235  
Nicholson Lane Research Center  
5516 Nicholson Lane  
Kensington, MD 20895

OR

Fax to: (301) 594-6463

\* Please note that patents for unapproved compositions, formulations or uses will NOT be published in *The Orange Book*.

**EXCLUSIVITY SUMMARY** for NDA # 20-771 SUPPL # 004  
Trade Name Detrol Generic Name tolterodine tartrate  
tablets  
Applicant Name Pharmacia & Upjohn Corporation HFD- 580  
Approval Date \_\_\_\_\_

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/\_\_\_/ NO /x\_\_\_/

b) Is it an effectiveness supplement? YES /x\_\_\_/ NO /\_\_\_/

If yes, what type(SE1, SE2, etc.)? SE 8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /\_x\_/ NO /\_\_\_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

\_\_\_\_\_

\_\_\_\_\_

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

\_\_\_\_\_

\_\_\_\_\_

d) Did the applicant request exclusivity?

YES /\_\_\_/ NO /x\_\_\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

---

---

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /x\_\_\_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /x\_\_\_/ NO /\_\_\_/

If yes, NDA # 20-771\_\_\_ Drug Name Detrol

Note: No product other than Detrol (with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule) has been previously approved by FDA for the same use. The clinical studies were submitted to support the change in wording from " Detrol tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency or urge incontinence" to "Detrol tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency and urge incontinence"

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /\_\_\_/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the**

upgrade) .

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_  
NDA # \_\_\_\_\_

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_\_\_/ NO /\_\_\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_\_\_/ NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

\_\_\_\_\_  
\_\_\_\_\_

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/ NO /\_\_\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_\_\_/

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # \_\_\_\_\_

Investigation #2, Study # \_\_\_\_\_

Investigation #3, Study # \_\_\_\_\_

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_\_\_/ NO /\_\_\_/

Investigation #2 YES /\_\_\_/ NO /\_\_\_/

Investigation #3 YES /\_\_\_/ NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_\_\_/  
Investigation #2                      YES /\_\_\_/                      NO /\_\_\_/  
Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_  
NDA # \_\_\_\_\_ Study # \_\_\_\_\_

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #\_\_, Study # \_\_\_\_\_  
Investigation #\_\_, Study # \_\_\_\_\_  
Investigation #\_\_, Study # \_\_\_\_\_

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!	
IND # _____	YES /___/	NO /___/ Explain: _____
	!	_____
	!	_____
Investigation #2	!	
IND # _____	YES /___/	NO /___/ Explain: _____
	!	_____
	!	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____
Investigation #2	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
_____	!	_____
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/      NO /\_\_\_/

If yes, explain: \_\_\_\_\_

\_\_\_\_\_  
\_\_\_\_\_

(S)  
Signature of Preparer  
Title: Project Manager

April 2/01  
Date

(S)  
Signature of Office or Division Director

4/2/01  
Date

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**NDA 20-771/S-004**

**Drug Name:** Detrol (tolterodine tartrate) tablets, 1 and 2 mg

**Sponsor:** Pharmacia & Upjohn

**Subject:** Pediatric Rule

**Action:** Not applicable for this application

**Date:** April 3, 2001

**NDA 20-771/S-004**

**Drug Name:** Detrol (tolterodine tartrate) tablets, 1 and 2 mg

**Sponsor:** Pharmacia & Upjohn

**Subject:** Debarment certification

**Action:** Refer to debarment certification dated  
December 15, 1999

**Date:** April 3, 2001

**DEBARMENT CERTIFICATION FOR TOLTERODINE Efficacy Supplement  
NDA # 20-771**

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

*Ed L. Patt*

*12/15/99*

---

Ed L. Patt  
Associate Director  
Global Regulatory Affairs, CMC

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Date

# MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date:** October 17, 2000  
*LLP 10/17/00*

**From:** Lana L. Pauls, M.P.H.  
Associate Director, Division of Reproductive and Urologic Drug Products (HFD-580)

**Subject:** Review of Financial Disclosure documents

**To:** The file (NDA 20-771)

I have reviewed the financial disclosure information submitted by Pharmacia & Upjohn in support of their supplemental NDA, NDA 20-771/S-004.

One large clinical trial was conducted to support the safety and efficacy for Detrol (tolterodine) for use as monotherapy in the treatment of advanced prostate cancer. The study number and its respective outcome with regard to financial disclosure obligations is summarized below.

Study No.	Study Status	Financial Disclosure Documentation
98-TOCR-007	Ongoing as of February 2, 1999	Appropriate documentation; two investigators reported financial interest (see notes below)

Of those investigators not reporting financial interest, there was a 96% compliance rate in completing the appropriate paper work.

\_\_\_\_\_ reported receiving greater than \_\_\_\_\_ from P & U for "assistance with development of a urodynamic unit. \_\_\_\_\_ Sufficient monitoring of the site was performed, and this receipt of money has no impact on the outcome of the study.

\_\_\_\_\_ reported receiving \_\_\_\_\_ from P & U for "an educational grant for a research nurse." \_\_\_\_\_ Sufficient monitoring of the site was performed, and the site was part of the clinical audit that was conducted by the Agency. This receipt of money has no impact on the outcome of the study.

## Conclusion:

Adequate documentation has been provided to ensure that the sponsor is in compliance with 21 CFR 312.54.

OCT 6 2000

**Deputy Division Director's Memorandum  
Multiple Labeling Revisions**

**NDA: 20-771**

**Tolterodine Immediate Release (Detrol™)**

**Primary**

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**Secondary**

**SE8-004 (Supplement-Labeling Revision with Clinical Information)**

**Submitted: 12/22/99**

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**Sponsor:** Pharmacia & Upjohn Company  
7000 Portage Road  
Kalamazoo, MI 49001-0199

**Drug names:**

**Generic:** Tolterodine tartrate immediate release tablets

**Trade:** Detrol™

**Chemical:** (R)-N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanamine L-hydrogen tartrate

**Drug class:** Muscarinic receptor antagonist

**Administration route:** Oral

**Dosage form:** Immediate Release tablets BID

**Strength:** 1 mg and 2 mg

**Indication:** Treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

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## BACKGROUND

The Detrol™ original NDA 20-771 was submitted on March 24, 1997 and was approved on March 25, 1998. The fourth supplemental submission for NDA 20-771 is submission **SE8-004** (Supplement-Labeling Revision with Clinical Information) which was submitted on December 22, 1999. It presents clinical data from Protocol **98-TOCR-007**, which was performed under IND 56,406. The clinical section of this efficacy supplement consists of one study report, **98-TOCR-007**. Study **98-TOCR-007** was a multicenter, multinational, randomized, double blind, double-dummy, placebo-controlled, parallel design Phase 3 study in adult patients with urinary frequency and urge incontinence. The study had three equally sized arms: tolterodine IR tablets 2 mg bid, tolterodine PR capsules 4 mg qd, and placebo. The study was comprised of three periods: a 1- to 2-week wash-out/run-in period, a 12-week treatment period, and a 1-week follow-up period. The primary efficacy endpoint was the change in number of incontinence episodes per week from baseline to week 12. A total of 1529 patients were randomized to treatment at 167 sites in 14 countries. This supplement proposes major changes to the **CLINICAL STUDIES** and **ADVERSE REACTIONS** sections of the label.

While supplement **SE8-004** was being reviewed, two other Detrol supplements (**SLR-\_\_\_\_\_**) for were being evaluated in the Division. The review team believed that it would be most efficient to review all three supplements and incorporate the changes into one revised label to be offered to the sponsor for consideration. The label with combined revisions from all three supplements was sent to the sponsor on 10/6/00.

**SUMMARY OF IMPORTANT LABELING ISSUES (SE8-004,**

**SE8-004 (See Review by Brenda Gierhart MD dated 10/16/00)**

As mentioned above SE8-004 is supported by data from trial 98-TOCR-007. The sponsor proposed to make extensive changes to the **CLINICAL STUDIES** and **ADVERSE REACTIONS** section of the Detrol label. The sponsor proposed eliminating

The primary reviewer recommended placing data from all four trials into the label (see P. 44-49 of Dr. Gierhart's Review). I agree with the primary reviewer, that it would be most useful for providers to have information from all four placebo controlled trials as proposed by the Division.

The **ADVERSE REACTIONS** section of the currently approved label contains an extensive table entitled "Incidence (%) of Adverse Events Reported in  $\geq 1\%$  of Patients Treated with DETROL (2 mg bid) in 12-week, Phase 3 Clinical Studies". The sponsor proposes to markedly change this table by:

The sponsor's rationale making these changes was "to be consistent with labeling presentations for other drugs in this class"

Recognizing the need to fairly represent information contained in the **ADVERSE REACTIONS** section, an alternative to the sponsor's proposed label (see page 49-54 of Dr. Gierhart's review) was proposed. Dr. Gierhart's proposal was based on thoughtful consideration of communicating the appropriate information to prescribers and information provided in the Draft Guidance for Industry, recently submitted for public comment, entitled "Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics"(see page 39-40 Dr Gierhart's review). I agree with the primary clinical reviewer's labeling comments for this section. I also agreed with other minor changes proposed in this submission by the primary clinical, biopharmaceutics and chemistry reviewers.

[Redacted content]

**OTHER REVISIONS (unrelated to a particular supplement)**

[Redacted content]

**ADDENDUM**

Biopharmaceutics will convey a question to the sponsor regarding dosing recommendations for renally impaired patients in the latest version of the label which will be attached to the approvable letter.

DSI inspections were completed for two of three clinical study sites and results were found to be acceptable. Information from Dr. Sheldon Freedman's site requested by DSI in order to complete their inspection was not received as of October 23, 2000.

**Recommendation:** I agree with the primary reviewers of all disciplines and support the proposed recommended changes in the label as conveyed to the sponsor on 10/6/00. As of 10/20/00 comments on the divisions recommended labeling changes were not received from the sponsor. In a tcon with the sponsor on 10/19/00, the sponsor stated that they wished to continue further labeling negotiations. Therefore an approvable action will be taken at this time pending finalized labeling and successful completion of the DSI inspection of Dr. Freedman's study site.

**ATTACHMENTS**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_ (S)

Daniel A. Shames MD  
Acting Deputy Director, DRUDP

**Memorandum**

**To:** NDA 20-771

**Through:** Dan Shames, M.D.  
Deputy Director, HFD-580

**From:** Brenda S. Gierhart, M.D.  
Medical Officer, HFD-580

**Date:** April 4, 2001

**Re:** **SE8-004**  
Detrol™ (tolterodine tartrate tablets)  
Pharmacia & Upjohn  
MO Review of Division of Drug Marketing, Advertising  
and Communications Comments (dated April 3, 2001)

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Three Detrol labeling comments were submitted by Barbara Chong, Pharm. D., BCPS, Division of Drug Marketing, Advertising and Communications (DDMAC) to HFD-580, Division of Reproductive and Urologic Drug Products (DRUDP) on April 3, 2001 and are summarized as follows:

- 1) The word "pronounced" in the **CLINICAL PHARMACOLOGY** section seems promotional in tone
- 2) Grammatical error in *Absorption* subsection with first sentence reading "In a study with of 14C..."
- 3) Request to change the word "lowered" to \_\_\_\_\_ in the **DOSAGE AND ADMINISTRATION** section regarding Detrol Tablet 2 mg tablets

The three comments have been reviewed.

**Reviewer's comments:**

- 1) **It is acceptable to use the word "pronounced" in the CLINICAL PHARMACOLOGY section, third paragraph, first sentence which reads: Tolterodine has a pronounced effect on bladder function in healthy volunteers. The word "pronounced" is defined as "decided" or "strongly marked". The urodynamic studies in the healthy volunteers showed several "decided" effects that are listed in the second sentence. An identical sentence is in the Detrol LA CLINICAL PHARMACOLOGY section.**
- 

- 2) **The first sentence of the CLINICAL PHARMACOLOGY section, Pharmacokinetics, *Absorption*, subsection of the final Detrol labeling to be submitted to Sponsor correctly reads "In a study with 14C..." No change is needed.**
- 3) **The recommended dosage is accurately stated as lowered, since it is recommended that patients begin on 2 mg twice daily and the dosage lowered to 1 mg twice daily based on individual response.**

**No change is recommended.**

2 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

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/s/

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Brenda Gierhart  
4/4/01 02:35:28 PM  
MEDICAL OFFICER

Daniel A. Shames  
4/4/01 04:33:41 PM  
MEDICAL OFFICER

**Memorandum**

**To:** NDA 20-771

**Through:** Dan Shames, M.D.  
Deputy Director, HFD-580

**From:** Brenda S. Gierhart, M.D.  
Medical Officer, HFD-580

**Date:** April 2, 2001

**Re:** SE8-004  
Detrol™ (tolterodine tartrate tablets)  
Pharmacia & Upjohn  
MO Safety Update

On October 23, 2000 an approvable action letter for NDA 20-771/S-004 was sent to the Sponsor. A complete response to the October 23, 2000 action letter (resubmission) dated October 26, 2000 to NDA 20-771/S-004 was received at the Agency on October 27, 2000. No safety information was included in the resubmission. An Annual Report had been submitted to NDA 20-771 on May 15, 2000 and Periodic Safety Reports had been sent as P010 on April 5, 2000 and P012 on July 5, 2000.

Since receiving the resubmission on October 27, 2000 the Sponsor submitted two Period Safety Reports: P013 on November 3, 2000 and P014 on January 5, 2001. Both Period Safety Reports were reviewed by the Primary Medical Officer assigned to NDA 20-771, Mark Hirsch, MD and were NAI.

**Reviewer's comment:**

- 1) There are no new safety issues for NDA 20-771 since the approvable action letter was sent to the Sponsor on October 23, 2000.

cc: Original NDA 20-771  
HFD-580: Division File, S. Allen, D. Shames, M. Hirsch, B. Gierhart, and E. Farinas

/s/

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Brenda Gierhart  
4/2/01 03:10:51 PM  
MEDICAL OFFICER

Daniel A. Shames  
4/2/01 03:50:47 PM  
MEDICAL OFFICER

**Joint Medical and Clinical Pharmacology and Biopharmaceutics Memorandum**

**To:** NDA 20-771

**Through:** Dan Shames, M.D.  
Deputy Director, HFD-580

Ameeta Parekh, Ph.D.  
Team Leader, Division of Pharmaceutical Evaluation II

**From:** Brenda S. Gierhart, M.D.  
Medical Officer, HFD-580

DJ Chatterjee, Ph.D.  
Division of Pharmaceutical Evaluation II

**Date:** March 28, 2001

**Re:** Detrol™ (tolterodine tartrate tablets)  
Pharmacia & Upjohn

Correspondence Date: March 14, 2000  
Date Received: March 15, 2000  
SE8-004  
Detrol™ Package Insert submitted March 21, 2001

**Background:**

NDA 20-771 for Detrol™ Tablets (tolterodine tartrate) was approved by the agency on March 25, 1998 for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. The \_\_\_\_\_ supplement submission for NDA 20-771 was \_\_\_\_\_ It was dated January 12, 1999, received January 13, 1999, and proposed to \_\_\_\_\_

The Clinical Pharmacology and Biopharmaceutics Review by Soraya Madani, Ph. D. dated April 29, 1999 recommended that all sponsor proposed revisions be accepted except for two sentences in the \_\_\_\_\_

On November 10, 1999, the sponsor was notified that the review of \_\_\_\_\_ had been completed and the agency had two \_\_\_\_\_

**Current submissions:**

The sponsor did not accept these recommendations and submitted correspondence dated March 14, 2000 and received March 15, 2000 with an alternate text for the disputed three sentences and an altered sentence in the \_\_\_\_\_

The Clinical Pharmacology and Biopharmaceutics Review by Dhruba J. Chatterjee, Ph.D. dated August 15, 2000 and finalized on September 13, 2000 recommended revisions to all four of the sponsor proposed sentences. These revisions were incorporated into the Package Insert revisions for SE8-004.

On March 21, 2001, the sponsor faxed the Pharmacia & Upjohn proposed version of the Detrol™ (tolterodine tartrate tablets) Package Insert dated March 20, 2001 to the Agency. This submission was in response to a teleconference held with the Sponsor on March 20, 2001 to convey to the sponsor discrepancies found between the proposed FDA version of the label for NDA 20-771 SE8-004 (faxed on March 9, 2001 to the Sponsor) and that received from the sponsor via facsimile on March 15, 2001. During the teleconference, the sponsor was notified that the proposed label also addressed the label changes proposed in: \_\_\_\_\_

The March 21, 2001 submission was reviewed. The sponsor has accepted all four of the revised sentences as recommended in the Clinical Pharmacology and Biopharmaceutics Review of: \_\_\_\_\_  
— by Dhruva J. Chatterjee, Ph.D. dated August 15, 2000.

**Reviewer's comment:**

- 1) The Pharmacia & Upjohn proposed label dated March 20, 2001 is acceptable for \_\_\_\_\_  
— as well as for SE8-004.

**Recommendation:**

- 1) Recommend sending a regulatory letter to the Sponsor stating that their supplemental new drug application: \_\_\_\_\_ has been superceded by the approval of supplement new drug application SE8-004.

cc: Original NDA 20-771

HFD-580: Division File, S. Allen, D. Shames, M. Hirsch, A. Parekh, B. Gierhart, D.J. Chatterjee, and E. Farinas

/s/

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Brenda Gierhart  
3/29/01 02:53:58 PM  
MEDICAL OFFICER

Dhruba Chatterjee  
3/29/01 03:12:42 PM  
BIOPHARMACEUTICS

Daniel A. Shames  
4/2/01 04:03:46 PM  
MEDICAL OFFICER

nulldate  
MEDICAL OFFICER

Ameeta Parekh  
4/3/01 09:17:23 AM  
BIOPHARMACEUTICS  
I concur.

**Joint Medical and Clinical Pharmacology and Biopharmaceutics Memorandum**

**To:** NDA 20-771

**Through:** Dan Shames, M.D.  
Deputy Director, HFD-580

Ameeta Parekh, Ph.D.  
Team Leader, Division of Pharmaceutical Evaluation II

**From:** Brenda S. Gierhart, M.D.  
Medical Officer, HFD-580

DJ Chatterjee, Ph.D.  
Division of Pharmaceutical Evaluation II

**Date:** March 28, 2001

**Re:** SE8-004 (BL)  
Detrol™ (tolterodine tartrate tablets)  
Pharmacia & Upjohn  
MO Review of Faxed Detrol™ Package Insert  
Correspondence Date: March 21, 2001  
Date Received: March 22, 2001

**Current submission:**

On March 21, 2001, the Sponsor faxed the Pharmacia & Upjohn proposed version of the Detrol™ (tolterodine tartrate tablets) Package Insert dated March 20, 2001 to the Agency. This submission was in response to a teleconference held with the Sponsor on March 20, 2001 to convey to the sponsor discrepancies found between the proposed FDA version of the label for NDA 20-771 SE8-004 (faxed on March 9, 2001 to the Sponsor) and that received from the sponsor via facsimile on March 15, 2001. During the teleconference, the sponsor was notified that the proposed label also addressed the label changes proposed in \_\_\_\_\_

The submission was reviewed. The nine discrepancies discussed during the March 20, 2001 teleconference and documented in the minutes have all been corrected.

**Reviewer's comment:**

- 1) The Pharmacia & Upjohn proposed label dated March 20, 2001 is acceptable. The labeling issues pending at the date the October 23, 2000 Approvable action letter have been resolved.

**Recommendation:**

- 1) Recommend sending an approved letter and copy of the March 20, 2001 proposed label to the Sponsor for their supplemental new drug application SE8-004, which was received December 23, 1999.

cc: Original NDA 20-771

HFD-580: Division File, S. Allen, D. Shames, M. Hirsch, A. Parekh, B. Gierhart, D.J. Chatterjee, and E. Farinas

/s/

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Brenda Gierhart  
3/29/01 02:57:55 PM  
MEDICAL OFFICER

Dhruba Chatterjee  
3/29/01 03:07:45 PM  
BIOPHARMACEUTICS

Daniel A. Shames  
4/2/01 03:58:59 PM  
MEDICAL OFFICER

Ameeta Parekh  
4/3/01 09:07:53 AM  
BIOPHARMACEUTICS  
I concur.

**Joint Medical and Clinical Pharmacology and Biopharmaceutics Memorandum**

**To:** NDA 20-771

**Through:** Dan Shames, M.D.  
Deputy Director, HFD-580

Ameeta Parekh, Ph.D.  
Team Leader, Division of Pharmaceutical Evaluation II

**From:** Brenda S. Gierhart, M.D.  
Medical Officer, HFD-580

DJ Chatterjee, Ph.D.  
Division of Pharmaceutical Evaluation II

**Date:** March 28, 2001

**Re:** Detrol™ (tolterodine tartrate tablets)  
Pharmacia & Upjohn

Correspondence Date: June 9, 2000  
Date Received: June 12, 2000  
**SE8-004**  
Detrol™ Package Insert submitted March 21, 2001

**Background:**

NDA 20-771 for Detrol™ Tablets (tolterodine tartrate) was approved by the agency on March 25, 1998 for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence. The supplemental submission for NDA 20-771 was \_\_\_\_\_). It was dated June 9, 2000 and received on June 12, 2000. It proposes \_\_\_\_\_

\_\_\_\_\_ All the proposed changes were reviewed in my Medical Officer Review Memorandum dated October 6, 2001 and the recommendations incorporated into the Package Insert revisions for SE8-004.

The Clinical Pharmacology and Biopharmaceutics Review by DJ Chatterjee, Ph. D. dated September 18, 2000 and finalized on October 4, 2000 discussed the labeling changes that pertained to three clinical pharmacology issues in the Race, Renal Insufficiency and Drug Interactions subsections. The recommendations made by Dr. Chatterjee were also incorporated into the Package Insert revisions for SE8-004.

**Current submission:**

On March 21, 2001, the sponsor faxed the Pharmacia & Upjohn proposed version of the Detrol™ (tolterodine tartrate tablets) Package Insert dated March 20, 2001 to the Agency. This submission was in response to a teleconference held with the Sponsor on March 20, 2001 to convey to the sponsor discrepancies found between the proposed FDA version of the label for NDA 20-771 SE8-004 (faxed on March 9, 2001 to the Sponsor) and that received from the sponsor via facsimile on March 15, 2001. During the teleconference, the sponsor was notified that the proposed label also addressed the label changes proposed in \_\_\_\_\_

The March 21, 2001 submission was reviewed. The sponsor has incorporated language into the revised labeling that addresses all the issues raised in the Clinical Pharmacology and Biopharmaceutics Review of \_\_\_\_\_ by Dhruba J. Chatterjee, Ph.D. finalized on October 4, 2000 and by myself in the Medical Officer Memorandum dated October 6, 2000.

**Reviewer's comment:**

- 1) **The Pharmacia & Upjohn proposed label dated March 20, 2001 is acceptable for \_\_\_\_\_, as well as for SE8-004.**

**Recommendation:**

- 1) Recommend sending a regulatory letter to the Sponsor stating that their supplemental new drug application \_\_\_\_\_ has been superseded by the approval of supplement new drug application SE8-004.

cc: Original NDA 20-771

HFD-580: Division File, S. Allen, D. Shames, M. Hirsch, A. Parekh, B. Gierhart, D.J. Chatterjee, and E. Farinas

/s/

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Brenda Gierhart  
3/29/01 03:01:06 PM  
MEDICAL OFFICER

Dhruba Chatterjee  
3/29/01 03:11:19 PM  
BIOPHARMACEUTICS

Daniel A. Shames  
4/2/01 04:08:20 PM  
MEDICAL OFFICER

Ameeta Parekh  
4/3/01 09:48:28 AM  
BIOPHARMACEUTICS  
I concur.

**Joint Medical and Clinical Pharmacology and Biopharmaceutics Memorandum**

**To:** NDA 20-771

**Through:** Dan Shames, M.D.  
Deputy Director, HFD-580

Ameeta Parekh, Ph.D.  
Team Leader, Division of Pharmaceutical Evaluation II

**From:** Brenda S. Gierhart, M.D.  
Medical Officer, HFD-580

DJ Chatterjee, Ph.D.  
Division of Pharmaceutical Evaluation II

**Date:** March 28, 2001

**Re:** Detrol™ (tolterodine tartrate tablets)  
Pharmacia & Upjohn

Correspondence Date: October 5, 2000  
Date Received: October 6, 2000  
SE8-004  
Detrol™ Package Insert submitted March 21, 2001

**Background:**

NDA 20-771 for Detrol™ Tablets (tolterodine tartrate) was approved by the agency on March 25, 1998 for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence.

**Current submissions:**

The supplemental submission for NDA 20-771 was \_\_\_\_\_  
Revision)-Changes Being Effected. It was dated October 5, 2000 and was received on October 6, 2000. It stated the \_\_\_\_\_

\_\_\_\_\_ All nine changes were reviewed and the acceptable wording was incorporated into the Package Insert revisions for SE8-004.

The specific changes were as follows:

- **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations, Gender** subsection: the proposed change of the units from  $\mu\text{g}/\text{L}$  to  $\mu\text{g}\cdot\text{h}/\text{L}$  was acceptable and was incorporated into the Package Insert revisions for SE8-004.

- **PRECAUTIONS,** \_\_\_\_\_

\_\_\_\_\_ The original subsection title was retained into the Package Insert revisions for SE8-004.

- **PRECAUTIONS, Information for Patients** subsection: the proposed inclusion of dizziness and drowsiness was acceptable and was incorporated into the Package Insert revisions for SE8-004.
- **PRECAUTIONS, Pregnancy** subsection: the proposed change from \_\_\_\_\_ was not acceptable. The alternative change to "be embryolethal" was acceptable and was incorporated into the Package Insert revisions for SE8-004.
- **ADVERSE REACTIONS** and **OVERDOSAGE** sections: the proposed addition of "Tablets" after the first mention of DETROL was acceptable and was incorporated into the Package Insert revisions for SE8-004.
- **ADVERSE REACTIONS** section: the proposed change of \_\_\_\_\_ was no longer relevant due to the changes to this section in SE8-004 which included eliminating this sentence.
- **ADVERSE REACTIONS** section: the proposed change of \_\_\_\_\_ in the Adverse Events Incidence table was not acceptable. The WHOART term for dry eyes is xerophthalmia. Xerophthalmia was retained in the Package Insert revisions for SE8-004 in the Adverse Events Incidence table.
- **ADVERSE REACTIONS** section: the proposed change of adding \_\_\_\_\_  
\_\_\_\_\_ after the adverse event table was not acceptable. The proposed change was not incorporated into the Package Insert revisions for SE8-004.
- **ADVERSE REACTIONS, Postmarketing Surveillance** subsection: the proposed addition of the subsection and the sentence "The following events have been reported in association with tolterodine use in clinical practice: anaphylactoid reactions, tachycardia, peripheral edema." was acceptable and was incorporated into the Package Insert revisions for SE8-004.

On March 21, 2001, the sponsor faxed the Pharmacia & Upjohn proposed version of the Detrol™ (tolterodine tartrate tablets) Package Insert dated March 20, 2001 to the Agency. This submission was in response to a teleconference held with the Sponsor on March 20, 2001 to convey to the sponsor discrepancies found between the proposed FDA version of the label for NDA 20-771 SE8-004 (faxed on March 9, 2001 to the Sponsor) and that received from the sponsor via facsimile on March 15, 2001. During the teleconference, the sponsor was notified that the proposed label also addressed the label changes proposed in \_\_\_\_\_

The March 21, 2001 submission was reviewed. The sponsor has incorporated language into the revised labeling that addresses all the issues raised in \_\_\_\_\_

**Reviewer's comment:**

- 1) The Pharmacia & Upjohn proposed label dated March 20, 2001 is acceptable for \_\_\_\_\_ as well as for SE8-004.

**Recommendation:**

- 1) Recommend sending a regulatory letter to the Sponsor stating that their supplemental new drug application ~~\_\_\_\_\_~~ has been superceded by the approval of supplement new drug application SE8-004.

cc: Original NDA 20-771

HFD-580: Division File, S. Allen, D. Shames, M. Hirsch, A. Parekh, B. Gierhart, D.J. Chatterjee, and E. Farinas

/s/

-----  
Brenda Gierhart  
3/29/01 03:04:24 PM  
MEDICAL OFFICER

Dhruba Chatterjee  
3/29/01 03:10:01 PM  
BIOPHARMACEUTICS

Daniel A. Shames  
4/2/01 04:06:18 PM  
MEDICAL OFFICER

Ameeta Parekh  
4/3/01 09:24:50 AM  
BIOPHARMACEUTICS  
I concur.

**MEMORANDUM**

**To:** NDA 20-771 S-004

**Through:** Dan Shames, MD  
Deputy Director, HFD-580

**From:** Brenda S. Gierhart, MD  
Medical Officer, HFD-580

**Date:** March 6, 2001

**Re:** Resubmission to NDA 20-771 Efficacy Supplement  
S-004  
Correspondence Date: February 27, 2001  
Date Received: February 28, 2001  
PDUFA Date: April 27, 2001

**Current submission:**

Pharmacia & Upjohn has submitted a revised Detrol™ label, dated February 26, 2001. This submission is in response to the Division draft label, dated February 12, 2001, which was faxed to the Sponsor on February 15, 2001. The Sponsor has also provided four attachments:

- Attachment #1 is provided in support of their proposed changes to Table 2
- Attachment #2, 3, & 4 are provided in support of their proposed modification to two numerical values in Table 3 and to one sentence in the Adverse Reactions section. The sentence discusses the expected side effects of antimuscarinic agents.

There are a total of nine MARKED proposed revisions. The Sponsor made additional changes to the label that were NOT marked as revisions. All revisions/changes made will be discussed in the order they occur in the draft label.

**Unmarked Changes #1 (pg. 1) DESCRIPTION** section; second sentence; the Sponsor

**Reviewer's comment:**

- 1) This revision is not acceptable per review by Dr. David Lin, Chemistry. The Sponsor should return the

**Unmarked Changes #2 (pg. 2) CLINICAL PHARMACOLOGY Pharmacokinetics Absorption** section; first sentence; the Sponsor changed

**Reviewer's comment:**

- 2) This revision is not acceptable. The Sponsor should first sentence, to be consistent with the Detrol LA label.

**Marked Revision #1** (pg. 4) **CLINICAL PHARMACOLOGY** Pharmacokinetics in Special Populations *Renal Insufficiency* section; third sentence; proposes to change the word “subjects” to “volunteers” for consistency within that section.

**Reviewer’s comment:**

3) **This revision is acceptable.**

**Marked Revision #2** (pg. 6) **CLINICAL STUDIES** section; second and third paragraphs; proposes to reverse the order of the studies when discussing the efficacy endpoints. The Sponsor wishes to first present the efficacy endpoints for study 007 and then follow with the sentence discussing the efficacy endpoints for studies 008, 009, and 010.

**Reviewer’s comment:**

1) **This change is acceptable if the order of the efficacy endpoints is changed and the location of the words “Table 3” is changed. The number of incontinence episodes per week should become the new first bullet, since it was the primary efficacy endpoint for study 007. The location of the words “Table 3” should be changed to be consistent with the location of “Table 2” in the first sentence.**

**Unmarked Changes #3 and Marked Revision #3** (pg. 7) **CLINICAL STUDIES** section **Table 2.;**

The Sponsor made several changes to Table 2, which were NOT marked as changes including:

- “2 mg bid” was added to the second column title
- \_\_\_\_\_ ’ was deleted from the fourth column title
- the location of numbers were moved in the fourth column to align with the row “Mean Baseline”
- the number alignment in the second, third, and fourth columns were changed from left alignment to centered alignment
- — was removed six times in the second and third columns

In addition to the above changes, the Sponsor proposes to add “SD” to the second and third column titles, and insert corrected SD values into the row labeled “Number of incontinence episodes/week”.

**Reviewer’s comment:**

1) **The Sponsor wishes to revise Table 2’s format to make it consistent with Table 3’s format. This is acceptable. To accomplish this, several changes are necessary, which have been made in the attached revised label.**

**Unmarked Changes #4** (pg. 8) **CLINICAL STUDIES** section **Table 3.;**

The Sponsor made several changes to Table 3, which were NOT marked as changes including:

- in final column, asterisk was moved from after to before difference
- alignment was changed for columns with numbers from left alignment to centered alignment

**Reviewer’s comment:**



reported events from the worldwide postmarketing experience, the frequency of events and the role of tolterodine in their causation cannot be reliably determined.

**Revision #8** (pg. 13) **OVERDOSAGE Management of Overdosage** section, second paragraph, final sentence; the words "of tolterodine" was deleted as an editorial change.

**Reviewer's comment:**

1) This revision is acceptable.

**Revision #9** (pg. 13) **DOSAGE AND ADMINISTRATION** section, first sentence; the word "Tablets" was added after DETROL. The Sponsor noted that this was in accordance to good company trademark practices (i.e. first mention in each major section).

**Reviewer's comment:**

1) This revision is acceptable.

**Recommendation:**

- 1) Attachment #1 should be sent to the Sponsor. Attachment #1 is DRUDP's response (3/2/01) to Pharmacia's proposed changes (2/26/01) to the Detrol Package Insert. It should be noted that additions to Pharmacia's 10/25/00 Detrol Package Insert are marked as double underlining, deletions are marked as strikethroughs, and comments to the Sponsor are marked as bracketed, bolded, and in italics.
- 2) If the Sponsor accepts Attachment #1, an approved action for NDA 20-771 SE8-004 is anticipated by March 12, 2001.

cc: Original NDA 20-771

HFD-580: Division File

HFD-580: S. Allen, D. Shames, M. Hirsch, B. Gierhart, and E. Farinas

Attachment #1:

***Detrol™***  
*tolterodine tartrate*  
*tablets*

13 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

/s/

-----  
Brenda Gierhart  
3/6/01 03:02:30 PM  
MEDICAL OFFICER

Daniel A. Shames  
3/9/01 02:36:17 PM  
MEDICAL OFFICER

Farinas

AUG 31 2000

**MEMORANDUM**

**To:** IND 56,406 Tolterodine Prolonged Release  
NDA 20-771 Tolterodine Immediate Release  
NDA 21-228 Tolterodine Prolonged Release

**Through:** Dan Shames, MD  
Acting Deputy Director, HFD

**From:** Brenda S. Gierhart, MD  
Medical Officer, HFD-580

**Date:** August 31, 2000

**Re:** Submission N040 PC  
Submitted August 21, 2000  
Received August 22, 2000  
Omitted Submission of Protocol Amendment

**Current submission:**

DRUDP recently notified Sponsor of the omitted submission of Protocol 98-TOCR-007 Amendment #4 issued on July 2, 1999. Sponsor now submits Amendment #4 which:

- Added five centers in the Russian Federation and Ukraine.
- Replaced the t-test with an ANOVA analysis with treatment, center, and treatment by country as factors.
- Deleted King's Health Questionnaire completion for subjects in the Russian Federation or Ukraine, since it is not available in Russian.
- Added subgroup analyses on micturition variables with respect to sex and races.
- Added the sentence "If micturition chart diaries are not completed according to the protocol, the estimation of the micturition variable will be based on the available data" to the analysis plan for the Intention-to-treat population.

Per Sponsor, the statistical and analytical plans were changed in response to suggestions from the FDA.

**Reviewer's comments:**

- 1) It is unclear exactly how and why the micturition variables in the ITT population would be estimated. The Sponsor should clarify what was meant by "estimation", how the estimations were performed, and provide a list of subjects who had their micturition chart diary data estimated.

**Recommendation:**

The Sponsor should be called or sent a brief regulatory letter with the following requests for information:

- 1) Please clarify what was meant by the term "estimations" as used in Protocol 98-TOCR-007, Protocol Amendment #4, 10 STATISTICS, 1. Intention-to treat population.
- 2) Describe how the estimations were performed.
- 3) Please provide list of subjects who had their micturition chart diary data estimated.

cc: Original IND 56,406

Original NDA 20-771

Original NDA 21-228

HFD-580 Division File

S. Allen, D. Shames, B. Gierhart, E. Farinas, HFD-580

# Teleconference Minutes

**Date:** March 20, 2001      **Time:** 8:30-9:00 AM, EDT      **Location:** Parklawn; 17B-43  
**NDA 20-771/S-004**      **Drug:** Detrol (tolterodine tartrate) tablets      **Indication:** overactive bladder

**Sponsor:** Pharmacia & Upjohn Company

**Type of Meeting:** Clarification

**Meeting Chair:** Brenda Gierhart, M.D., Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

**External Lead:** Mark Mannebach, Ph.D. – Associate Director, Global Regulatory Affairs

**Meeting Recorder:** Evelyn R. Farinas, RPh, M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

**FDA Attendees:**

Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)

Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

**External Participant:**

Mark Mannebach, Ph.D. – Associate Director, Global Regulatory Affairs, Pharmacia & Upjohn Company  
Dora Cohen – Pharmacia & Upjohn Company

**Meeting Objective:** To convey to the sponsor discrepancies found between the proposed FDA version of the label for NDA 20-771 S004, (faxed on March 9, 2001 to the sponsor) and that received from the sponsor via facsimile on March 15, 2001.

**Background:** On March 9, 2001, DRUDP sent the sponsor a proposed version of the label for NDA 20-771/S-004, which included comments from DRUDP reviewers. This proposed label was sent via electronic mail as well as via facsimile. The sponsor submitted a response via facsimile on March 15, 2001, accepting the March 9, 2001, FDA label recommendations. It was noted that the wording in the version attached to the March 15, 2001, facsimile did not agree with the wording in the FDA March 9, 2001, proposal.

**Discussion:**

- the sponsor was notified that the proposed label addressed the label changes proposed in \_\_\_\_\_, S-004, \_\_\_\_\_
- the sponsor was notified of discrepancies noted in the March 15, 2001 facsimile, and also of additional information and corrections which should be incorporated into the label; the discrepancies and additional information are:
  - a bracket should be added immediately before “bis” in the chemical name, in the second sentence under the **DESCRIPTION** section

- the spelling should be corrected in the third sentence under the **Renal Insufficiency** subsection to correctly read "N-dealkylated"
- the wording should be changed from "N-dealkylated ~~terodine~~ olterodine" to "N-dealkylated hydroxylated tolterodine" in the third sentence under the **Renal Insufficiency** subsection
- in Table 2, under the **CLINICAL STUDIES**, in the first section "Number of Incontinence Episodes per Week" the word "Week" was capitalized, and in the same table the decimal alignment was not maintained throughout the table; however, the Division does not object to capitalizing the word "Week" in the table, and if it is not technically possible to maintain the decimal alignment, the Division will accept the format of Table 2 as listed in the March 15, 2001 facsimile
- in Table 3, under the **CLINICAL STUDIES** section, the figure "93" has been omitted as the first entry under the "Detrol" column, in the "008 Number of patients" line; the decimal alignment was not maintained throughout the table; and the asterisks in the first, fourth, fifth, seventh, eighth, and ninth entry under the "Difference" column were not placed between the figure and the parenthesis
- in the **Pregnancy** subsection, under the **PRECAUTIONS** section, a new paragraph was created incorrectly between the second and third sentence
- in the fifth paragraph under the **ADVERSE REACTIONS** section, an unnecessary comma was introduced between the words "dizziness" and "and" in the last sentence of this paragraph
- in Table 4, under the **ADVERSE EVENTS** section, the width of the margins in the last two was increased; if it is not technically possible to decrease the width of these columns, the Division will accept the format of Table 4 as listed in the March 15, 2001, facsimile
- the date of last printing (i.e. March 2001) had a strike over under the **HOW SUPPLIED** section
- the sponsor indicated that a revised label will be sent correcting the errors noted and including the additional information and revisions provided today

**Decisions made:**

- the sponsor agreed to amend the March 15, 2001, proposed label to conform with the changes discussed in today's teleconference

**Action Items:**

- DRUDP will send via facsimile and e-mail the revised FDA proposed label for Supplement 004 (*revised version sent to the sponsor via facsimile on March 20, 2001*)
- the sponsor will send via e-mail as soon as possible their response to the March 20, 2001, proposed FDA label (*response received electronically on March 20, 2001*)

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**Minutes Preparer**

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**Concurrence, Chair**

**Note to sponsor:** These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

IND  
Teleconference Minutes  
Page 3

cc:  
Original IND  
HFD-580/DivFile  
HFD-580/Allen/Shames/Hirsch/Gierhart/Rumble/Farinas

drafted: erf/3.20.01  
concurrence: Rumble 3.20.01/Gierhart 3.20.01  
final: erf/3.22.01

MEETING MINUTES

/s/

-----  
Evelyn Farinas  
3/22/01 11:40:10 AM  
CSO

tcon march 20 label revisions

Brenda Gierhart  
3/22/01 11:47:10 AM  
MEDICAL OFFICER

42 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

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## Teleconference Minutes

**Date:** October 19, 2000

**Time:** 1:45-2:00 PM, EDT

**Location:** Parklawn; 17B-45

**NDA 20-771/S-004**

**Drug:** Detrol (tolterodine tartrate)

**Indication:** overactive bladder

**Sponsor:**

Pharmacia & Upjohn Corporation

**Type of Meeting:**

Clarification

**Meeting Chair:**

Daniel Shames, M.D., Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

**External Lead:**

Gregory Shawaryn, Regulatory Manager, Regulatory Affairs

**Meeting Recorder:**

Evelyn R. Farinas, RPh, M.G.A., Regulatory Project Manager

**FDA Attendees:**

Daniel Shames, M.D. - Acting Deputy Director, DRUDP (HFD-580)

Evelyn R. Farinas, RPh, M.G.A. - Regulatory Project Manager, DRUDP (HFD-580)

**External Participants:**

Gregory Shawaryn - Regulatory Manager, Regulatory Affairs

Mark Mannavath - Regulatory Affairs

**Meeting Objective:** To communicate to the sponsor the status of Supplement 004 review.

**Background:** Sponsor submitted an efficacy supplement (S-004) to NDA 20-771 for tolterodine immediate release formulation, on December 22, 1999. This labeling supplement requires review of clinical data (Study Report 98-TOCR-007). In this study, the sponsor plans to demonstrate a statistically significant decrease in the number of incontinent episodes with tolterodine treatment compared with placebo. The 10-month goal date for this submission is October 23, 2000.

**Discussion:**

- the sponsor will most likely receive an Approvable letter for Supplement 004 for NDA 20-77, because labeling discussions for Supplement 004 between DRUDP and Pharmacia & Upjohn will not be finalized prior to the 10-month goal date of October 23, 2000
- the intent of DRUDP is to craft a label that addresses Supplements — and 004 for NDA 20-771, as well as the pending NDA 21-228 for the tolterodine extended release product
- the time frame for labeling discussions should accommodate both parties; DRUDP's intent is to provide a response within four weeks after receipt of the sponsor's revisions
- the sponsor should submit the rationale for their preferred name for the extended release product, (i.e. Detrol XL); the final decision for an approved name for this product rests with DRUDP

**Decisions made:**

- DRUDP will probably send an Action letter to the sponsor on October 23, 2000
- the sponsor will submit rationale for the preferred name for the extended release product

**Action Items:**

- minutes of this teleconference will be faxed to sponsor with

Minutes Preparer

Concurrence, Chair

10/20/00

**Note to sponsor:** These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

NDA 20-771/S-004  
Teleconference Minutes October 19, 2000  
Page 3

cc:  
Original IND  
HFD-580/DivFile  
HFD-580/Allen/Shames/Rumble/Farinas

drafted: erf/10.20.00  
concurrence: Shames 10.20.00/Colangelo for TR 10.20.00  
final: erf/10.20.00

MEETING MINUTES

## Labeling/Status Meeting Minutes

Date: October 16, 2000 Time: 2:00-3:00 PM, EST Location: PKLN; 17B43

NDA 20-771/S-004 Drug: Detrol Indication: overactive bladder

Sponsor: Pharmacia & Upjohn Corporation

Type of Meeting: Status/Labeling discussion

Meeting Chair: Brenda Gierhart, M.D., Medical Officer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager

### FDA Attendees:

Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)

David Lin, Ph.D. – Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)

Terri Rumble, B.S.N. – Chief, Project Management Staff, DRUDP (HFD-580)

Evelyn R. Farinas, R.Ph., M.G.A. - Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss status of this NDA and label revisions to the sponsor's proposed label in supplement \_\_\_\_\_ S-004, and \_\_\_\_\_.

Background: Pharmacia & Upjohn Corporation has submitted to DRUDP several label supplements, \_\_\_\_\_, S-004 (December 22, 1999) and \_\_\_\_\_ for tolterodine immediate release tablets. In \_\_\_\_\_ the sponsor proposed changes \_\_\_\_\_ section, and to the \_\_\_\_\_ section of the label. In this supplement, the sponsor provided literature data and \_\_\_\_\_ to support the proposed changes. In S-004 the sponsor proposed changes to the DESCRIPTION, CLINICAL PHARMACOLOGY, CLINICAL STUDIES and ADVERSE REACTIONS sections. In support of the changes for the first two sections, the sponsor did not submit any new data, and referred to the Original NDA (Item 6); for the remaining two sections, the sponsor submitted Protocol 98-TOCR-007 as supporting documentation. In \_\_\_\_\_, the sponsor

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_. No references were provided in support of the changes to the other sections. DRUDP's revised version of the proposed label was faxed to the sponsor on September 29, 2000. The same label was refaxed on October 3, 2000, when the sponsor indicated that it had not been received.

Discussion:

- An Approvable action pending resolution of the label is being considered for this application
- Sponsor indicated via telephone conversation on October 16, 2000 between Ms. Farinas and Mr. Shawaryn, that DRUDP's proposed label revisions were being discussed internally, but that additional discussions were still required; sponsor did not indicate a specific time-frame for submitting their response to the DRUDP's revised label; Mr. Shawaryn indicated that Pharmacia & Upjohn was not aware that this application was on a 10-month clock
- DSI report is pending; Dr. Roy Blay has been notified
- Chemistry review is pending; Dr. David Lin is finalizing this report (*final review submitted October 16, 2000*)
- Statistics report is pending; Dr. David Hoberman indicated previously that information necessary for review had not been submitted by the sponsor, despite his request (*sponsor was asked to submit another set of statistic data via overnight delivery; diskette received October 17, 2000 and delivered to Dr. Hoberman*)

Action Items:

- Call Dr. Blay for an update on receipt of DSI report (*draft copy sent electronically on October 16, 2000*)
- Contact Dr. Hoberman for status of Statistics review
- Review Action Package for completeness

(E)

(SJ)  
Minutes Preparer

(SJ)  
Concurrence, Chair

Cc:

IND Arch:

HFD-580/Div File

HFD-580/Allen/Shames/Hirsch/Gierhart/Rhee/Lin/Rumble

Drafted: October 18, 2000

Concurrence: Gierhart 10.18/00/Lin 10.18.00/Rumble

Finalized: 10.19.00

MEETING MINUTES

## Labeling Meeting Minutes

Date: September 18, 2000      Time: 2:00-3:00 PM, EST      Location: PKLN; 17B43  
NDA 20-771/S-004      Drug: Detrol      Indication: overactive bladder  
Sponsor:      Pharmacia & Upjohn Corporation  
Type of Meeting:      Status/Labeling discussion  
Meeting Chair:      Daniel Shames, M.D., Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)  
Meeting Recorder:      Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager

### FDA Attendees:

Daniel Shames, M.D. – Medical Team Leader, DRUDP (HFD-580)  
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)  
David Lin, Ph.D. – Chemistry Reviewer, @ DRUDP (HFD-580)  
Ameeta Parekh, Ph.D. – Clinical Pharmacology and Biopharmaceutics Team Leader, @ DRUDP (HFD-580)  
D.J. Chatterjee, Ph.D. - Clinical Pharmacology and Biopharmaceutics Reviewer, @ DRUDP (HFD-580)  
Barbara Chong – Reviewer, DDMAC  
Evelyn R. Farinas, R.Ph., M.G.A. - Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective:      To discuss label revisions to the sponsor's proposed label in supplements S-004, and

Background:      Pharmacia & Upjohn Corporation has submitted to DRUDP several label supplements, S-004 (December 22, 1999) and S- for tolterodine immediate release tablets. In , the sponsor proposed changes to the

s. In S-004 the sponsor proposed changes to the DESCRIPTION, CLINICAL PHARMACOLOGY, CLINICAL STUDIES and ADVERSE REACTIONS sections. In support of the changes for the first two sections, the sponsor did not submit any new data, and referred to the Original NDA (Item 6); for the remaining two sections, the sponsor submitted Protocol 98-TOCR-007 as supporting documentation. In the sponsor proposed changes to

section changes. No references were provided in support of the changes to the other sections.

Discussion:

Comments and recommendations to the sponsor's proposed label, per section, were:

- DESCRIPTION:

- approve the addition of these three sentences proposed in [redacted] "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."

- HOW SUPPLIED:

- change existing storage statement to "store at 25° C (77° F); excursion permitted to...."
- ask the sponsor to make this change to all their carton labels; the sponsor may use existing supply of carton labels before implementing changes

- CLINICAL PHARMACOLOGY:

- the changes proposed in [redacted] to the third paragraph [redacted] are unacceptable as written. Alternative wording will be sent to the sponsor.

- Pharmacokinetics in Special Population:

- the concepts proposed in [redacted] are acceptable
- further language revisions are necessary to the sponsor's proposed language ([redacted])

- Drug-Drug Interactions:

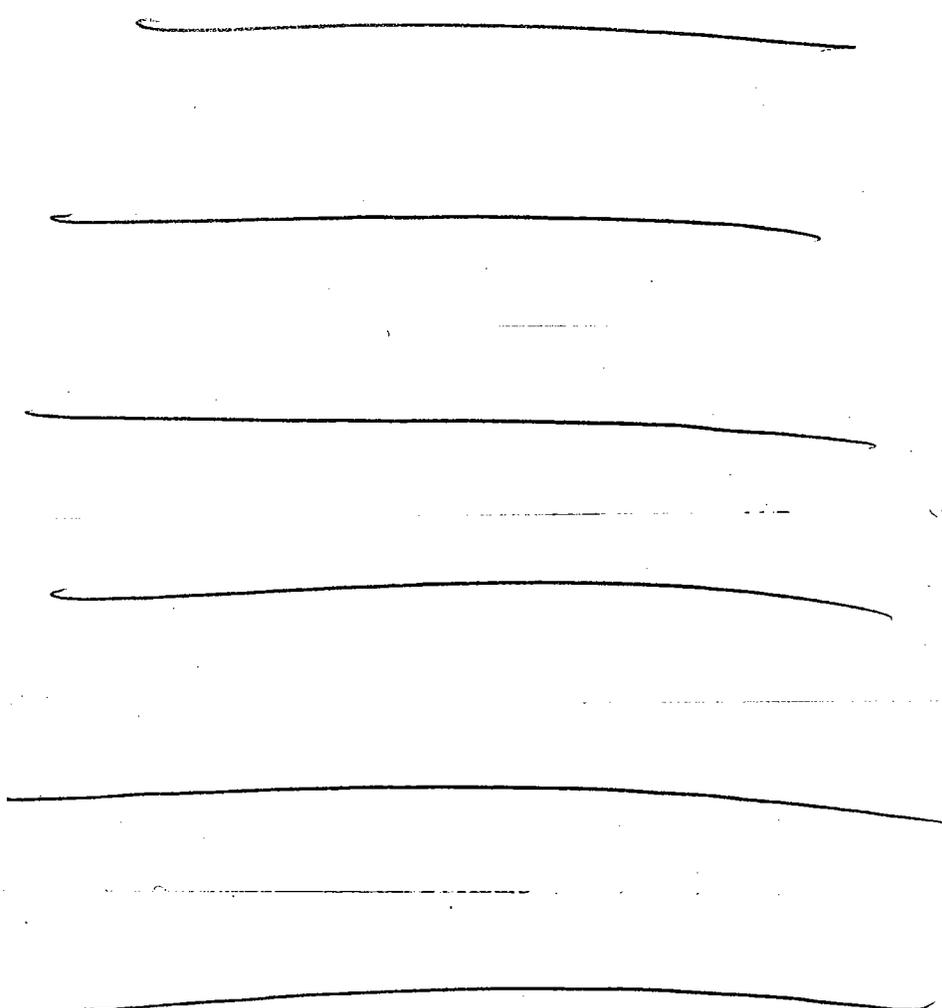
- the concepts proposed in [redacted] are acceptable
- further language revisions are necessary to the sponsor's proposed language in [redacted]

- the concepts proposed in [redacted] are acceptable
- the following exact text should be inserted in the label to address the [redacted] proposal:

- Clinical Studies:

- proposed language and tables should be changed to “DETROL Tablets were evaluated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency in four 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%), female (78%), and 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 studies 008, 009, and 010 included the change from baseline for:
  - Number of micturitions per 24 hours (averaged over 7 days)
  - Number of incontinence episodes per 24 hours (averaged over 7 days)
  - Volume of urine voided per micturition (averaged over 2 days)

The efficacy endpoints for study 007 were identical to the above endpoints with the exception that the number of incontinence episodes was per week. Efficacy results for the four placebo-controlled, 12-week studies are presented in the following figure:



[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

• **INDICATIONS AND USAGE:**

[Redacted]

• **PRECAUTIONS**

- **General subsection:** same comments as in Pharmacokinetics in Special Population section (see above)
- **Drug Interactions subsection:** same comments as in Drug-Drug Interactions section (see above)

[Redacted]

[Redacted]

[Redacted]

• **ADVERSE REACTIONS**

- reject the sponsor's proposed language for this section in S-004

- the language in this section should be changed to: 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 \_\_\_\_\_ 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 reactions 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.
  - 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; 1.0% 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. 7% of patients treated with DETROL 2 mg bid discontinued treatment due to adverse events versus 6% of placebo patients; the most common adverse events leading to discontinuation 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 \_\_\_\_\_ changes in QT and QT<sub>c</sub> have not been demonstrated in clinical study patients treated with Detrol 2 mg bid. The following table 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.

<u>Incidence* (%) of Adverse Events Exceeding Placebo Rate and Reported in &gt;1% of Patients Treated with DETROL (2 mg bid) in 12-Week, Phase 3 Clinical Studies</u>			
<u>Body System</u>	<u>Adverse Event</u>	<u>% DETROL 2 mg bid N=986</u>	<u>% Placebo N=683</u>
<u>Autonomic Nervous</u>	<u>Accommodation abnormal</u>	<u>2</u>	<u>1</u>
	<u>dry mouth</u>	<u>35</u>	<u>10</u>
<u>General</u>	<u>chest pain</u>	<u>2</u>	<u>1</u>
	<u>fatigue</u>	<u>4</u>	<u>3</u>
	<u>Headache</u>	<u>7</u>	<u>5</u>
	<u>Influenza-like symptoms</u>	<u>3</u>	<u>2</u>
<u>Central/Peripheral Nervous</u>	<u>Vertigo/dizziness</u>	<u>5</u>	<u>3</u>

<u>Gastrointestinal</u>	<u>Abdominal pain</u>	<u>5</u>	<u>3</u>
	<u>Constipation</u>	<u>7</u>	<u>4</u>
	<u>Diarrhea</u>	<u>4</u>	<u>3</u>
	<u>Dyspepsia</u>	<u>—</u>	<u>—</u>
<u>Urinary</u>	<u>Dysuria</u>	<u>2</u>	<u>1</u>
<u>Skin/Appendages</u>	<u>skin dry</u>	<u>1</u>	<u>0</u>
<u>Musculoskeletal</u>	<u>Arthralgia</u>	<u>2</u>	<u>1</u>
<u>Vision</u>	<u>Xerophthalmia</u>	<u>3</u>	<u>2</u>
<u>Psychiatric</u>	<u>Somnolence</u>	<u>3</u>	<u>2</u>
<u>Metabolic/Nutritional</u>	<u>weight gain</u>	<u>1</u>	<u>0</u>
<u>Resistance Mechanism</u>	<u>Infection</u>	<u>1</u>	<u>0</u>
<u>* in nearest integer</u>			

• **OVERDOSAGE/MANAGEMENT OF OVERDOSAGE**

- no change should be made in the current wording of this section

• **DOSAGE AND ADMINISTRATION**

- the following exact text for the third sentence of this section should be: \_\_\_\_\_

**Chemistry comments:**

- review to be finalized within two weeks of this meeting

**Biopharmaceutics comments:**

- review to be finalized within two week of this meeting

**Action Items:**

- a single label revision with DRUDP's recommendations for \_\_\_\_\_, S-004 and \_\_\_\_\_ will be sent to the sponsor for discussion prior to the October 23, 2000, goal date
- additional comments from the Statistical reviewer will be requested by the Medical Officer and incorporated into label recommendations prior to sending DRUDP's revisions to the sponsor  
(Medical officer conveyed request to Dr. Hoberman)

(S)  
Minutes Preparer

(S)  
Concurrence, Chair

cc:

IND Arch:

HFD-580/DivFile

HFD-580/ Allen/Shames/Gierhart/Hoberman/ Parekh/Chatterjee/Lin/Rumble

drafted: Farinas, 9.19.00

concurrence: Shames 9.21.00/Gierhart 9.22.00/Parekh/Chatterjee/Lin/Rumble 9.20.00

final: Farinas, 10.17.00

MEETING MINUTES

ADDENDUM: October 20, 2000

Dr. Barbara Chong confirmed via e-mail that at the September 18, 2000 status meeting she recommended that the following sentence from the Clinical Pharmacology section be deleted from the labeling:

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151  
Evelyn R. Farinas

151  
Daniel Shames

10/20/00

Gierhart

## Meeting Minutes

**Date:** August 11, 2000      **Time:** 9:00-9:30 EST      **Location:** Parklawn; 17B43  
**NDA 20-771/S-004**      **Drug:** tolterodine      **Indication:** overactive bladder  
**Sponsor:**      Pharmacia & Upjohn  
**Type of Meeting:**      Status  
**Meeting Chair:**      Daniel Shames, M.D., Acting Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)  
**Meeting Recorder:**      Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

### FDA Attendees:

Daniel Shames, M.D. – Acting Deputy Director, DRUDP (HFD-580)  
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)  
Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)  
D.J. Chatterjee, Ph.D. Biopharmaceutics Reviewer, OCPB @ DRUDP (HFD-580)  
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manger, DURDP (HFD-580)

**Meeting Objective:**      To discuss status of review.

**Background:**      Sponsor submitted an efficacy supplement (S-004) to NDA 20-771 for tolterodine immediate release formulation, on December 22, 1999. This labeling supplement is coded as an SE8 which requires review of clinical data (Study Report 98-TOCR-007). In this study, the sponsor plans to demonstrate a statistically significant decrease in the number of incontinent episodes with tolterodine treatment compared with placebo. The goal date for this submission is October 23, 2000.

### Discussion:

#### Biopharmaceutics:

- no issues
- background material will be obtained by the Medical Officer (Dr. Gierhart) and reviewed by the Biopharmaceutics Reviewer ( Dr. Chatterjee) to assess the adequacy of the sponsor's proposal for additional wording to the clinical Pharmacology section of the label

#### Clinical:

- adequacy of proposed tables
  - statistical review is needed to determine adequacy of the proposed tables
  - submitted table format suggests greater safety of tolterodine; as proposed, the adverse events text does not adequately address the frequency of adverse events nor the placebo information
  - submission of tables which are similar and consistent with previously approved labeling may be recommended
- adverse event section

- draft adverse event guidance document is not clear
- standardization of the adverse events section of the labeling for incontinence products should be pursued
- will consult DDMAC as to which form of reporting adverse events, i.e. specific adverse events listing versus body system listing, is preferred
- multiplicity of supplements, i.e. S-004, S-006, —
- concurrent review of all labeling supplement is recommended

Chemistry:

- chemistry reviewer (Dr. Lin) will be asked to comment on the proposed addition of three sentences to the Description section describing the physical chemistry for tolterodine

**Action Items:**

- contact Dr. Lisa Kammerman (statistician) for review and comments on adequacy of tables
- contact Nancy Ostrove (DDMAC) for review and comments on preferred Adverse Event section format
- investigate possibility of exchanging label comments with sponsor in electronic format, via diskettes

(S)

Minutes Preparer

(S)

Concurrence, Chair

cc:

NDA Arch: 20-771  
HFD-580/DivFile

HFD-580/ Allen/Mann/Shames/Gierhart/Kammerman/Lin/Rhee/ Parekh/Chatterjee/Rumble

drafted: Farinas, 8.14.00

concurrence: Shames 8.23.00/Gierhart 8.16.00/Parekh/Chatterjee 8.16.00/Rumble (KC) 8.15.00

final: Farinas, 8.23.00

filename: NDA 20771 S004 status meeting Aug.doc  
MEETING MINUTES

FARINAS

# Meeting Minutes

**Date:** February 7, 2000      **Time:** 3:10 PM, EST      **Location:** Parklawn; 17B-45

**NDA 20-771/S-004      Drug:** Detrol (tolterodine immediate release)

**Indication:** urinary incontinence

**Sponsor:** Pharmacia & Upjohn

**Type of Meeting:** Filing meeting

**Meeting Chair:** Daniel Shames, MD – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

**Meeting Recorder:** Evelyn R. Farinas, RPh – Regulatory Project Manager

**FDA Attendees:**

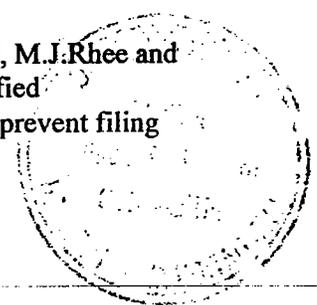
- Daniel Shames, MD – Medical Team Leader, DRUDP (HFD-580)
- Alexander Jordan, Ph.D. – Pharmacologist Team Leader, DRUDP (HFD-580)
- Moo-Jhong Rhee, Ph.D. – Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
- Ameeta Parekh, Ph.D. – Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
- Mark Hirsch, MD – Medical Officer, DRUDP (HFD-580)
- David Lin, Ph.D. – Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
- Soraya Madani, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
- Evelyn R. Farinas, RPh, MGA – Regulatory Project Manager, DRUDP (HFD-580)

**Meeting Objective:** To discuss fileability of NDA 20-771/S-004.

**Background:** This efficacy supplement (S-004) was submitted on December 22, 1999. The sponsor indicated that study results demonstrate a highly statistically significant difference between Detrol (tolterodine tartrate tablets) and placebo for improvement in incontinence episodes with Detrol. Study results also showed statistically significant improvement in secondary efficacy variables, number of micturitions and mean volume voided. The sponsor is proposing a labeling update of the Clinical Studies and Adverse Reactions sections based on these data. DRUDP held a virtual filing meeting (via e-mail) on February 7, 2000 to determine if this supplement was fileable.

**Discussion:**

- e-mail sent to D. Shames, M. Hirsch, A. Jordan, A. Parekh, S. Madani, M.J.Rhee and D. Lin on February 7, 2000, requesting that fileability issues be identified
- the reviewers did not indicate that there were any issues which would prevent filing this supplement



**Decisions reached:**

- Supplement 004 is fileable

**Action Items:**

- none

ISI  
\_\_\_\_\_  
Minutes Preparer

ISI  
\_\_\_\_\_  
Concurrence, Chair

cc:

NDA Arch:  
HFD-580/DivFile

HFD-580/Allen/Mann/Shames/Hirsch/Gierhart/Jordan/Rhee/Lin/Parekh/Rumble/Farinas

drafted: Farinas 3.28.00

concurrence: Shames 4.11.00/Hirsch 3.30.00/Jordan 4.10.00/Parekh 4.12.00  
/Madani/Rhee 4.12.00/Lin 3.30.00/Rumble 3.29.00

final: Farinas, 4.12.00

FILING MEETING MINUTES

**NDA 20-771/S-004 – Action Package (second cycle)**

**Drug Product:** Detrol (tolterodine tartrate) Tablets

**Sponsor:** Pharmacia & Upjohn Company

**Indication:** Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

**Goal Date:** April 27, 2001

**Review Team:** Brenda Gierhart, M.D. – Clinical  
Alexander Jordan, Ph.D. – Toxicology  
D. J. Chatterjee, Ph.D. – Biopharmaceutics  
David Lin, Ph.D. – Chemistry  
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager

**Division:** Division of Reproductive and Urologic Drug Products (HFD-580)  
Susan Allen, M.D., M.P.H.  
Director

**Reviewer:** Evelyn R. Farinas, R.Ph., M.G.A.  
Regulatory Health Project Manager

**Through:** Jeanine Best for Terri Rumble  
Acting Chief, Project Management Staff

**Date:** April 3, 2001

On October 23, 2000, the Division issued an Approvable letter to the sponsor for Supplement 004. The letter stated that approval was dependent upon two conditions: the sponsor's submission of a draft label in accordance with the label enclosed in the October 23, 2000, letter; and satisfactory completion of the Division of Scientific Investigations' inspection of all study sites.

The sponsor's letter of October 26, 2000 constituted a complete response to our October 23, 2000, Approvable letter. The draft label submitted via facsimile to the sponsor on March 20, 2001, was accepted by Pharmacia & Upjohn, and is enclosed with the Approval letter that completes the review of this application. Please note that the Division of Scientific Investigations issued a final report on November 3, 2000, stating that the data submitted in support of this NDA by the three sites inspected (Drs. Antoci, Mitcheson, and Freedman) are acceptable.

In addition to the labeling recommendations for S-004, this package also includes labeling recommendations for Supplement \_\_\_\_\_ . These changes include \_\_\_\_\_ in \_\_\_\_\_ and revisions to th \_\_\_\_\_

Acknowledge and Retain letter indicating that the approved label for Supplement 004 supercedes Supplements \_\_\_\_\_ will be issued. . An

/s/

-----  
Evelyn Farinas  
4/3/01 10:24:04 AM  
CSO

cover letter for action package first cycle

Jeanine Best  
4/3/01 12:18:58 PM  
CSO  
Signing for Terri Rumble, CPMS

**NDA 20-771/S-004 – Action Package (first cycle)**

**Drug Product:** Detrol (tolterodine tartrate) Tablets

**Sponsor:** Pharmacia & Upjohn Company

**Indication:** Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency.

**Goal Date:** October 23, 2000

**Review Team:** Brenda Gierhart, M.D. – Clinical  
Alexander Jordan, Ph.D. – Toxicology  
D. J. Chatterjee, Ph.D. – Biopharmaceutics  
David Lin, Ph.D. – Chemistry  
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager

**Division:** Division of Reproductive and Urologic Drug Products (HFD-580)  
Susan Allen, M.D., M.P.H.  
Director

**Reviewer:** Evelyn R. Farinas, R.Ph., M.G.A.  
Regulatory Health Project Manager

**Through:** Jeanine Best for Terri Rumble  
Acting Chief, Project Management Staff

**Reviewer:** Evelyn R. Farinas, R.Ph., M.G.A.  
Regulatory Health Project Manager

**Date:** October 23, 2000

Pharmacia & Upjohn submitted this SE-8 application (labeling application requiring review of clinical data) on December 23, 1999, to update the product labeling for the Clinical Studies and Adverse Reactions sections. This application did not include preclinical nor CMC data, not did it include Phase 4 commitments. Please note that foreign labeling, tradename review and pediatric information are not required for this application.

This abbreviated Action Package includes Clinical, Statistical, Biopharmaceutics and Chemistry Reviews, labeling (sponsor's proposal and FDA revisions), correspondence between the sponsor and the Division, and minutes of meetings and teleconferences.

In addition to the labeling recommendations on S-004, this package also includes labeling recommendations from DRUDP for \_\_\_\_\_ . These changes include revisions to the \_\_\_\_\_

Please note that the indication will be modified from "Detrol tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or

urge incontinence” to “Detrol tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.”

/s/

-----  
Susan Allen

4/6/01 02:00:40 PM



Pharmacia & Upjohn

Pharmacia & Upjohn  
7000 Portage Road  
Kalamazoo, MI 49001-0199  
USA  
Telephone: (616) 833-4000

March 15, 2001

Division of Reproductive Health and Urologic Drug Products, HFD-580  
Center for Drug Evaluation and Research  
Document Control Room 17B-20  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

RE: NDA 20-771/S-004  
Detrol<sup>tm</sup>  
Tolterodine tartrate tablets

Amendment #6

Dear Sir/Madam:

Reference is made to the package insert proposal faxed to Pharmacia Corporation on March 9, 2001. We have accepted the Division's proposals and have enclosed a final version of the package insert incorporating the proposed text. We are also sending an electronic version of the insert via secure e-mail to farinase@cder.fda.gov.

If you should have any questions regarding this information, please contact Gregory G. Shawaryn at (616) 833-8239. Please address correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPIJOHN COMPANY

A handwritten signature in cursive script that reads "Gregory Shawaryn".

Gregory G. Shawaryn  
Regulatory Manager  
Regulatory Affairs

GGG:kmv

Attachments

50 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

---

ORIGINAL



Pharmacia & Upjohn

Pharmacia & Upjohn  
7000 Portage Road  
Kalamazoo, MI 49001-0199  
USA  
Telephone: (616) 833-4000

February 27, 2001

**NDA SUPP AMEND**

Division of Reproductive Health and Urologic Drug Products, HFD-580  
Center for Drug Evaluation and Research  
Document Control Room 17B-20  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

AJ 3/15/01  
NAA



5E8604 (BL)

**Re: NDA 20-771/S-004  
DETROL™  
tolterodine tartrate tablets**

**Amendment #5 to Supplement**

Dear Sir or Madam:

Reference is made to the Division's draft label faxed on February 15, 2001 concerning the above supplement. We have reviewed the Division's proposal and have provided our response in this submission. Enclosed please find a Marked Version, and a Clean Version of the PI.

In addition to the Marked Version and Clean Version of the PI, please find included in this submission the following attachments:

- Attachment 1: Study 98-TOCR-007. Table 10, Mean Number of Incontinence Episodes/Week - ITT Population
- Attachment 2: Pooled Adverse Event Table for Studies 94-OATA-008, -009, -010, 015, and 98-TOCR-007.
- Attachment 3: Brown JH, Taylor P. Muscarinic receptor agonists and antagonists. In *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th edition. Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. New York: McGraw-Hill 1996:148-154.
- Attachment 4: Peters NL. Snipping the thread of life: Antimuscarinic side effects of medications in the elderly. *Arch Intern Med* 1989;149:2414-2430.

If you have any questions regarding this submission, please contact Gregory Shawaryn.  
Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Gregory G. Shawaryn  
Regulatory Manager  
Regulatory Affairs

GGs:lmf

Attachments

*Not of  
NFI  
JTC  
3/15/01*

*(3/6/01)  
Reviewed  
See Memo  
for comments  
of (label)  
for sponsor*

REVIEWS COMPLETED	
GSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
GSO INITIALS	DATE

14 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

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NDA 20-771/S-004

Pharmacia & Upjohn Company  
Attention: Gregory G. Shawaryn  
Regulatory Manager, Regulatory Affairs  
7000 Portage Road  
Kalamazoo, MI 49001-0199

Dear Mr. Shawaryn:

We acknowledge receipt on October 27, 2000 of your October 26, 2000 resubmission to your supplemental new drug application for Detrol (tolterodine tartrate) tablets.

This resubmission contains additional revisions to the proposed label and the requested DSI information submitted in response to our October 23, 2000 action letter.

With this amendment, we have received a complete response to our October 23, 2000 action letter.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri Rumble  
Chief, Project Management Staff  
Division of Reproductive and Urologic Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

/s/

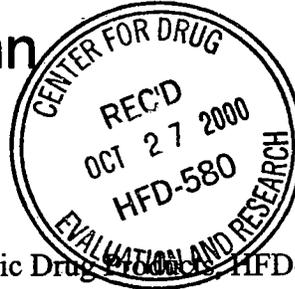
-----  
Terri F. Rumble  
11/2/00 02:48:09 PM



Pharmacia & Upjohn

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

October 26, 2000



Division of Reproductive Health and Urologic Drugs, HFD-580  
Center for Drug Evaluation and Research  
Document Control Room 17B-20  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

**NDA SUPP AMEND**

**ORIGINAL**

SE 8-004-AL

Re: **NDA 20-771/S-004**  
**DETROL™**  
**tolterodine tartrate tablets**

**Amendment #4 to Supplement**

Dear Sir or Madam:

Reference is made to the approvable letter dated October 23, 2000 concerning the above supplement.

This amendment addresses the comments included in this letter as follows:

1. We have reviewed the labeling included with the approvable letter (faxed to Pharmacia on October 4, 2000) and have proposed an alternate text to the Division's proposal. A strikethrough/underlined version as well as a clean version of the package insert are provided in Attachment 1. Support for our proposals is appended to the strikethrough/underlined version. Electronic copies, in Word, of both versions of the package insert are also included in this submission.
2. We have recently (October 17, 2000) received a request for additional information from DSI. This information was provided to DSI on October 25, 2000. It is our understanding that there are no outstanding issues with regard to site inspections.
3. There is no new safety information that has been collected directly pertinent to this supplement. The tolterodine tablets portion of the protocol (98-TOCR-007) that was the basis of this supplement was complete at the time of the original submission. Other safety data relative to this compound is routinely reported through periodic safety updates and

annual reports to NDA 20-771 and through information amendments and annual reports to IND 46,169. Since this submission, a Periodic Safety Update Report has been submitted to NDA 20-771 on July 5, 2000, an annual report to NDA 20-771 has been submitted on May 12, 2000. The annual report to IND 46,169 is in preparation and should be submitted to the Division in the next week.

We consider this amendment to be a complete response to the October 23, 2000 approvable letter.

If you have any questions regarding this submission, please contact Gregory Shawaryn. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Gregory G. Shawaryn  
Regulatory Manager  
U.S. Regulatory Affairs

GGs:lmf

Attachment

*AP letter to be issued  
in April 01 based  
on label faxed by  
spanx 3/20 GMR*

REVIEWS COMPLETED	
CSO ACTION:	
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
<i>en</i>	<i>3-27-01</i>
CSO INITIALS	DATE

15 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

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**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** October 3, 2000 *vs*

**TO:** Mr. Gregory G. Shawaryn, Regulatory Manager,  
Regulatory Affairs, Pharmacia & Upjohn

**FROM:** Dornette Spell-LeSane, Regulatory Project Manager  
Division of Reproductive and Urologic Drug Products (HFD-580)

**SUBJECT:** NDA 20-771, Pharmacia & Upjohn Company, Detrol™

The following are additional Clinical Pharmacology and Biopharmaceutical labeling comments and request for information related to the review of your NDA 20-771 for Detrol™.

1. Please provide a rationale for addressing the issue of risk (if any) associated with the exceptionally high levels of metabolites in renally impaired patients.
2. A recommendation for dosage adjustment (for renally impaired patients) in the final label will be provided.

If you have any questions please call me at 301-827-4260,

Sincerely,



DORNETTE SPELL-LESANE

cc:

Archival IND/NDA 20-771

HFD-580/Div. Files

HFD-580/Allen/Shames/Geirhart/Parekh/Chaterjee

Drafted by: Spell-LeSane, 10.3.00

Initialed by: Chatterjee, 10.3.00

Final: Spell-LeSane, 10.3.00

Filename: memo.doc

**MEMORANDUM**

Gierhart

SEP 29 2000

NDA 20-771, S-004,

**INFORMATION REQUEST LETTER**

Pharmacia & Upjohn Corporation  
Attention: Gregory Shawaryn  
Regulatory Manager, Regulatory Affairs  
7000 Portage Road  
Kalamazoo, MI 49001-0199

Dear Mr. Shawaryn:

Please refer to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Detrol (tolterodine tartrate) tablets.

We also refer to your submissions dated January 12, March 14, and December 22, 1999, and June 9, 2000.

We are reviewing your proposed Physician Package Insert for this application. Note that there will be additional comments to the Clinical Pharmacology section sent to you at a later date.

Please review the attached document and provide your prompt written response to continue our evaluation of your supplemental application.

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

LSI

9/28/00

Terri Rumble, B.S.N.  
Chief, Project Management Staff  
Division of Reproductive and Urologic Drug Products  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

Attachment

NDA 20-771 ———, S-004, ———

Page 2

cc:

Archival NDA 20-771

HFD-580/Div. Files

HFD-580/E.Farinas

HFD-580/Allen/Shames/Hirsch/Gierhart/Parekh/Chatterjee/Rhee/Lin/Jordan

DISTRICT OFFICE

Drafted by: erf/September 27, 2000

Initialed by: rumble/

final:erf

filename: N20771.DOC

INFORMATION REQUEST (IR



15 page(s) of  
revised draft labeling  
has been redacted  
from this portion of  
the review.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

*Greerhast  
Hirsch*

Food and Drug Administration  
Rockville MD 20857

SFP 1 3 2000

David Mitcheson, M.D.  
Bay State Urologists, Inc.  
11 Nevins Street  
Brighton, Massachusetts 02135

Dear Dr. Mitcheson:

Between May 23 and June 1, 2000, Mr. Gary Hagan, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #98-TOCR-007) of the investigational drug, Detrol<sup>®</sup> (tolterodine tartrate) tablets, performed for Pharmacia & Upjohn Company. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Hagan during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

*/s/*

John R. Martin, M.D.  
Branch Chief  
Good Clinical Practice I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research,  
7520 Standish Place  
Rockville, Maryland 20855

cc:

HFA-224  
HFD-580/Doc. Rm. NDA 20-771/S-004  
HFD-580/Farinas  
HFD-580/Hirsch  
HFD-45/Reading File  
HFD-46/Chron File  
HFD-46/GCP File #010136  
HFD- 46/Blay  
HFD-46/Huff  
HFD-46/Martin  
HFR-NE252/Kraychuk  
HFR-NE250/Levitt  
HFR-NE250/Hagan

CFN #

Field Classification: NAI

Headquarters Classification:

<input checked="" type="checkbox"/> 1)NAI	
<input type="checkbox"/> 2)VAI	no response required
<input type="checkbox"/> 3)VAI-R	response requested
<input type="checkbox"/> 4)VAI-RR	adequate response received prior to issuance of VAI-R letter
<input type="checkbox"/> 5)OAI-WL	warning letter
<input type="checkbox"/> 6)OAI-NIDPOE	

Note to the File:

This inspection covers both NDA 20-771/S-004 and NDA 21-228. The difference is that the latter provides for an extended release formulation of the drug.

E:/blay/mitcheson.rab  
drafted/rab/8.30.00  
reviewed:/  
final:mgk 9/6/00

Note to Review Division and DSI Recommendation:

The field inspector reviewed the study-related records for 7 of the 37 patients enrolled in protocol #98-TOCR-007 at Dr. Mitcheson's site. The inspector reviewed an additional 6 records of the 30 subjects who continued into the open-label portion of the study. The data appear acceptable for use in support of drug claims.

ORIGINAL



Pharmacia & Upjohn

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

August 28, 2000

Division of Reproductive Health and Urologic Drug Products, HFD-580  
Center for Drug Evaluation and Research  
Document Control Room 17B-20  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

SUPPL NEW CORRESP

SAIC-004

Re: **NDA 20-771/S-004**  
**DETROL™**  
**tolterodine tartrate tablets**

**Amendment #3 to Supplement**

Dear Sir or Madam:

Pharmacia and Upjohn has recently submitted IND amendment Serial No. 40 to IND 56, 406 which contained amendment 4 to protocol 98-TOCR-007. Since this protocol was a significant component of the above submission, we provide a copy of this IND amendment to the above file for completeness.

If you have any questions regarding this submission, please contact Gregory Shawaryn. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory G. Shawaryn  
Regulatory Manager  
U.S. Regulatory Affairs

GGS:mlw

Attachment

REVIEWS COMPLETED
CSC ACTION
<input type="checkbox"/> LETTER <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> MEMO
CSO INITIALS <i>GGS</i> DATE <i>8-31-00</i>



Pharmacia & Upjohn

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

August 21, 2000

Division of Reproductive Health and Urologic Drug Products, HFD-580  
Center for Drug Evaluation and Research  
Document Control Room 17B-20  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Serial No. 040

Re: IND 56,406  
Tolterodine Prolonged Release Capsules  
for treatment of overactive bladder

Protocol Amendment  
Change in Protocol

Sir/Madam:

We are amending the above referenced IND to provide information as described below:

Item 6-Protocols

**Change in Protocol**

**Protocol 98-TOCR-007**, Clinical efficacy and tolerability/safety of tolterodine prolonged release capsules and tolterodine immediate release tablets vs placebo. A randomized, double-blind, placebo-controlled, multinational study in patients with symptoms of overactive bladder. (*Protocol and Amendment 1 submitted in Serial No. 008, dated 1/20/99, amendments 2 and 3 submitted in Serial No. 016, dated 5/21/99*).

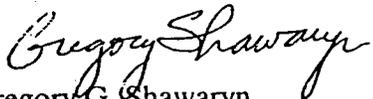
Protocol Amendment 4 issued on July 2, 1999 is attached. It provides for the addition of clinical sites and an update of the statistical and analytical plans.

It is Pharmacia and Upjohn's standard procedure to submit changes to protocols in a timely manner, unfortunately, due to an administrative oversight, submission of this amendment was inadvertently omitted. We have just recently learned of this omission and are now submitting the amendment to the IND. A copy of this submission is being submitted to NDA 20-771 (S-004) and NDA 21-228. Protocol 98-TOCR-007 is a significant part of these submissions.

If you should have any questions regarding this information, please contact Gregory G. Shawaryn at (616) 833-8239. Please address correspondence to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

  
Gregory G. Shawaryn  
Regulatory Manager  
U.S. Regulatory Affairs

GGs:mlw

cc Desk copy to Evelyn Farinas HFD-580, Room 17B-45

# MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Date:** August 16, 2000

**To:** Gregory G. Shawaryn, Regulatory Manager, Regulatory Affairs  
Pharmacia & Upjohn Company

**From:** Evelyn R. Farinas, R.Ph., M.G.A.  
Regulatory Project Manager

**Subject:** NDA 20-771, S-004, Detrol (tolterodine tartrate) tablets

The sponsor was asked (via telephone conversation between Ms. Farinas and Mr. Shawaryn) to submit a copy of Amendment 4 to Protocol 98-TOCR-007. This submission arrived on August 29, 2000. Upon review, the sponsor was requested via regulatory IR letter to IND 56,406 dated September 12, 2000, to provide the following clarifications:

1. Define what was meant by the term "estimations" in this protocol (i.e. Protocol Amendment #4, 10 Statistics, 1. Intention-to-treat population).
2. Describe how the estimations were performed.
3. Provide the list of subjects who had their micturition chart diary data estimated.

SJ

Evelyn R. Farinas  
Regulatory Project Manager

~~Hirsch~~ Gerhart  
Doc Rm

Food and Drug Administration  
Rockville MD 20857

AUG 8 2000

Joseph P. Antoci, M.D.  
Connecticut Clinical Research Center  
160 Robbins Road  
Waterbury, Connecticut 06708

Dear Dr. Antoci:

Between July 10 and July 18, 2000, Ms. M. Patricia Murphy, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol #98-TOCR-007) of the investigational drug, Detrol® (tolterodine tartrate) tablets, performed for Pharmacia & Upjohn Company. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you adhered to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Murphy during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

JS

JOHN K. MARTIN, M.D.  
Branch Chief  
Good Clinical Practice I, HFD-46  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, Maryland 20855

cc:

HFA-224  
HFD-580/Doc. Rm. NDA 20-771/S-004  
HFD-580/Farinas  
HFD-580/Hirsch  
HFD-45/Reading File  
HFD-46/Chron File  
HFD-46/GCP File #010152  
HFD- 46/Blay  
HFD-46/Huff  
HFD-46/Martin  
HFR-NE252/Kraychuk  
HFR-NE250/Levitt  
HFR-NE2530/Murphy

CFN #

Field Classification: NAI

Headquarters Classification:

<input checked="" type="checkbox"/> 1)NAI	
<input type="checkbox"/> 2)VAI	no response required
<input type="checkbox"/> 3)VAI-R	response requested
<input type="checkbox"/> 4)VAI-RR	adequate response received prior to issuance of VAI-R letter
<input type="checkbox"/> 5)OAI-WL	warning letter
<input type="checkbox"/> 6)OAI-NIDPOE	

E:/blay/antoci.rab  
drafted/rab/8.4.00  
reviewed:/  
Final:mgk 8/7/00

Note to Review Division and DSI Recommendation:

The field inspector reviewed the study-related records for 21 of the 38 patients enrolled in protocol #98-TOCR-007 at Dr. Antoci's site. The data appear acceptable for use in support of drug claims.

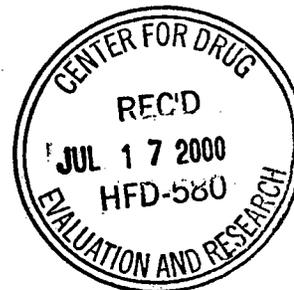


# Pharmacia & Upjohn

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

July 14, 2000

Division of Reproductive Health  
and Urologic Drug Products, HFD-580  
Center for Drug Evaluation and Research  
Document Control Room, 17B-20  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 20-771/S-004  
**DETROL™**  
tolterodine tartrate tablets

**NDA SUPP AMEND**

Amendment #2 to S-004

*SE8-004-*

Dear Sir or Madam:

In response to Evelyn Farinas's June 28 request, please find the following attachments relative to evaluation of adverse events relative to certain subgroups pooled across protocols 94-OATA-008, 94-OATA-009, 94-OATA-010, 94-AOTA-015 and 98-TOCR-007.

- Attachment 1: Events sorted relative to poor or extensive metabolizers
- Attachment 2: Events sorted by age
- Attachment 3: Events sorted by race
- Attachment 4: Events sorted by sex

Based upon Pharmacia & Upjohn's review of these data, there does not appear to be a difference in safety profile of tolterodine base on metabolism, age, race or sex.

If you have any questions regarding this submission, please contact Gregory Shawaryn at (616) 833-8239. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

*Gregory Shawaryn*

Gregory G. Shawaryn  
Regulatory Manager  
Regulatory Affairs

GGs:LMF  
Enclosure

*(9/13/00)  
Reviewed  
in MO  
Review  
of SE8-004  
NAI  
BSG*

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE



Pharmacia & Upjohn

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

May 5, 2000

ORIGINAL



Division of Reproductive Health  
and Urologic Drug Products, HFD-580  
Center for Drug Evaluation and Research  
Document Control Room, 17B-20  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

NDA SUPP AMEND

Re: NDA 20-771/S-004  
DETROL™  
tolterodine tartrate tablets

Amendment No. 1 to S-004

Dear Sir or Madam:

SE8-004-BM

In response to Evelyn Farinas's April 27 request, please find in Attachment 1 the Observed Cases analysis described in protocol 98-TOCR-007. This analysis was not included in the study report for reasons described in the Attachment.

If you have any questions regarding this submission, please contact Gregory Shawaryn at (616) 833-8239. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory G. Shawaryn  
Regulatory Manager  
Regulatory Affairs

GGs:lmf

Enclosure

(9/13/00)  
Reviewed  
in MO Review  
of SE8-004;  
NAT  
BSB

REVIEWS COMPLETED
CDO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CDO INITIALS _____ DATE _____



Pharmacia & Upjohn

ORIGINAL



Global Intellectual Property

May 1, 2000

Via Airborne Express  
Central Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Park Bldg., Rm. 2-14  
12420 Parklawn Drive  
Rockville, MD 20857

NEW CORRESP  
NC



Re: NDA 020771  
DETROL (tolterodine tartrate)

Time Sensitive Patent Information

To Whom It May Concern:

Enclosed please find duplicate originals of patent information for the above-referenced product.

Very truly yours,

Bruce A. Pokras

Enclosures

Pharmacia & Upjohn  
100 Route 206 North  
Peapack, NJ 07977

Bruce A. Pokras  
Senior Patent Counsel  
Voice: (908) 306-8453  
Fax: (908) 306-8650  
bruce.a.pokras@am.pnu.com

REVIEWS COMPLETED
CSO ACTION:
<input type="checkbox"/> LETTER <input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
<i>AMP</i> <i>5-9-00</i>
CSO INITIALS <span style="float: right;">DATE</span>



DEPARTMENT OF HEALTH & HUMAN SERVICES

Farinas

Public Health Service

Food and Drug Administration  
Rockville MD 20857

NDA 20-771/S-004

Pharmacia Inc  
7000 Portage Road  
Kalamazoo, MI 49001

DEC 29 1999

Attention: Gregory G. Shawaryn,  
Regulatory Affairs

Dear Mr. Shawaryn

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Detrol™ (tolterodine tartrate) Tablets

NDA Number: 20-771

Supplement Number: S-004

Date of Supplement: December 22, 1999

Date of Receipt: December 23, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 21, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research  
Division of Reproductive and Urologic Drug Products, HFD-580  
Office of Drug Evaluation III  
Attention: Document Control Room 17B-20  
5600 Fishers Lane  
Rockville, MD 20857

Sincerely,

*TS*  
Terri F. Rumble  
Chief, Project Management Staff  
Division of Reproductive and Urologic  
Drug Products, HFD-580  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

**NDA 20-771/S-004**

**Page 2**

**cc:**

**Original NDA 20-771/S-004**

**HFD-580/Div. Files**

**HFD-580/CSO/E. Farinas**

**SUPPLEMENT ACKNOWLEDGEMENT**

NDA NO. 20-771 REF. NO. SE8-004  
NDA SUPPL FOR Labeling



**Pharmacia & Upjohn**

7000 Portage Road  
Kalamazoo, MI 49001-0199  
Telephone: (616) 833-4000

December 22, 1999

Division of Reproductive Health and Urologic Drug Products, HFD-580  
Center for Drug Evaluation and Research  
Document Control Room 17B-20  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Re: **NDA 20-771**  
**DETROL™**  
**tolterodine tartrate tablets**

**Efficacy Supplement**

Dear Sir/Madam:

Under the provisions of 21 CFR 314.70, Pharmacia & Upjohn is submitting this Supplement to the above referenced NDA.

As part of the development program for the prolonged release formulation of tolterodine (subject of IND 56,406), a large placebo-controlled double blind study (study 007) was conducted to compare the effects of tolterodine immediate release (Detrol), tolterodine prolonged release, and placebo on the primary efficacy variable of urinary incontinence. More than 500 patients were treated in each arm of this study. The study report is now complete and results indicate a highly statistically significant difference between Detrol and placebo for improvement in incontinence episodes with Detrol. Treatment with Detrol also resulted in statistically significant improvement in secondary efficacy variables, number of micturitions and mean volume voided. Adverse event frequencies were similar to those reported as part of the original NDA 20-771. As such we have prepared this supplemental application to update the product labeling (Clinical Studies and Adverse Reactions sections) to reflect these new findings and additional experience in this study, which enrolled more patients than the combined total for the 3 registration studies included in the original NDA.

This application contains:

Items 1, 2, 8, 10, 11, 12, 16, 18, and 19.

Items 1, 2 (paper and electronic), 11 (electronic only), 12 (electronic only), 16, 18 and 19 are included in volume 1. Items 8/10 (final report for study 007) are included in volumes 2 through 23. An electronic copy of this study report is also included.

Only an electronic archival copy of Items 11 and 12 is being submitted. They are provided on 1 ISO 9660 CD in PDF format and organized according to FDA's Guidance for Industry, Archiving Submissions in Electronic Format—NDA's, September 1997. The total size of the electronic files on CD-Rom is 394 megabytes, Item 11, 51 megabytes and Item 12, 343 megabytes. These files have been scanned with Network Associates' McAfee Virus Scan software for Windows, version 4.01. All electronic information is contained in the directory N20771 and a copy of this letter and the 356H form are also provided as a PDF files (cover.pdf and 356H.pdf respectively) in this directory.

Attachment 1 contains an abbreviated Table of Contents (TOC) for the NDA and is also provided as a PDF file (ndatoc.pdf) in directory N20771. The abbreviated NDA TOC provides hyperlinked connections to Tables of Contents for Case Report Tabulations and Case Report Forms. The table of contents are then either bookmarked or hyperlinked to individual profiles or CRF's.

A User Fee check made payable to the Food and Drug Administration in the amount of \$144, 878 was sent to the Mellon Bank, Pittsburgh, PA. on December 17, 1999.

If you have any questions regarding this submission, please contact Gregory Shawaryn. Please send correspondence addressed to Unit 0635-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY



Gregory G. Shawaryn  
Regulatory Manager  
Regulatory Affairs

GGG:lmf

Attachments

cc: Nancy Ostrove DDMAC

**regfiles**

---

**From:** regfiles [regfiles@gateway.pnu.com]  
**Sent:** Tuesday, March 20, 2001 10:17 AM  
**o:** Evelyn Farinas 301-827-4260 FAX 301-443-9288  
**Subject:** DETROL PI T-Con with FDA

**ArchiveCopy:** regfiles@gateway.pnu.com  
**Product Name:** DETROL  
**Product Number:** NDA 20-771



PNU320PI.DOC

Dear Evelyn,

Per the telephone contact March 20, 2001, between Pharmacia and FDA, we agree with all requested revisions discussed regarding the DETROL Tablets package insert (PI). Supplements -004, have been considered, with changes to the PI incorporated. The attached WORD version of the Detrol Tablets PI reflect the changes discussed today (with the exception of the decimal alignment in Tables 2 and 3 -- these will be decimal aligned in the 'printed' PI as discussed).

Thank you and best regards,

Dora

Attachment

**PHARMACIA & UPJOHN, INC. FACSIMILE**

7000 Portage Road  
Kalamazoo, MI 49001  
Facsimile #: 616-833-8237

TO: Evelyn Farinas

DATE: September 21, 2000

FACSIMILE # 301-827-4267

SUBJECT: NDA 20-771 S-004

FROM: Gregory Shawaryn  
PHONE: 616-833-8239**TOTAL PAGES IN THIS TRANSMISSION (Includes this sheet): 1**

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Message:

Dear Evelyn,

On September 15 you asked me to check if the following statement is accurate:

---

to make the statement accurate it would need to be revised in either of the following ways:

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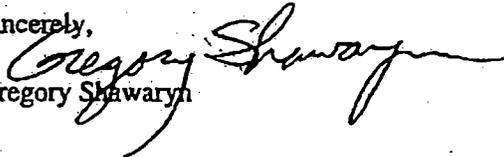
OR

2. "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"

The 2133 figure included 70 patients on 0.5mg Detrol BID and 58 patients treated with 4 mg BID as well as 2005 patients on 2 or 4 mg/day.

Please give me a call at 616-329-8239 if you have any questions or concerns.

Sincerely,

  
Gregory Shawaryn

---

**Confidentiality Note:** The documents accompanying this telecopy transmission contain information belonging to Pharmacia & Upjohn, Inc., which is intended only for the use of the addressee. If you are not the intended recipient, you are hereby notified that any disclosure, copying, distribution or the taking of any action in reliance on the contents of this telecopied information is strictly prohibited. If you have received this telecopy in error, please immediately notify us by telephone to arrange for the return of the original documents to us. Thank you.

Freedman

**MEMORANDUM**

---

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**CLINICAL INSPECTION SUMMARY**

**DATE:** November 3, 2000

**TO:** Evelyn Farinas, Regulatory Project Manager, HFD-580  
Dan Shames, M.D. Medical Officer, HFD-580  
Division of Reproductive and Urologic Drug Products, HFD-580

**THROUGH:** John R. Martin, M.D.  
Branch Chief  
Good Clinical Practice I, HFD-46  
Division of Scientific Investigations

**FROM:** Roy Blay, Ph.D.,  
Senior Regulatory Review Officer  
Good Clinical Practices Branch 1, HFD-46  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 20-771/S-004 and 21-228

**APPLICANT:** Pharmacia & Upjohn

**DRUG:** Detrol<sup>®</sup> (tolterodine tartrate) tablets

**THERAPEUTIC CLASSIFICATION:** 1(S)

**INDICATION:** Treatment of overactive bladder

**REVIEW DIVISION GOAL DATE:** September 22, 2000  
**ACTION GOAL DATE (PDUFA Date):** October 22, 2000

**I. BACKGROUND:**

The goal of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events. The indication for this drug is the treatment of overactive bladder.

II. RESULTS (by site):

NAME	CITY, STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
David Mitcheson, M.D.	Brighton, MA	3 May 2000	12 July 2000	NAI/010136
Joseph Antoci, M.D.	Waterbury, CT	3 May 2000	3 Aug 2000	NAI/010152
Sheldon Freedman, M.D.	Las Vegas, NV	3 May 2000	2 Oct 2000	VAI-R/010202

Site #1

David Mitcheson, M.D.  
Bay State Urologists, Inc.  
11 Nevins Street  
Brighton, Massachusetts 02135  
Acceptable

- a. The field investigator inspected the study-related records for 7 of the 37 subjects enrolled at Dr. Mitcheson's site.
- b. There were no limitations on the inspection.
- c. The inspection of this site was unremarkable. No Form 483 was issued.

Site #2

Joseph P. Antoci, M.D.  
Connecticut Clinical Research Center  
160 Robbins Road  
Waterbury, Connecticut 06708  
Acceptable

- a. The field inspector inspected the study-related records for 21 of the 38 subjects entered into the study at Dr. Antoci's site.
- b. There were no limitations on the inspection.
- c. The inspection of this site was unremarkable. No Form 483 was issued.

Site #3

Sheldon Freedman, M.D.  
3006 S. Maryland Parkway  
Las Vegas, Nevada 89109  
Acceptable

- a. The field investigator inspected the study-related records for 8 of the 40 subjects enrolled at Dr. Freedman's site.
- b. There were no limitations on the inspection.

- c. A Form 483 was issued for several instances of failure to follow protocol and maintain adequate and accurate records, as well as failure to retain an informed consent form for one patient. These deficiencies are of relatively minor importance. Original subject diaries were requested from the sponsor. These diaries were reviewed to substantiate the observations made by the inspector (who conducted the inspection using photocopies of the original diaries). An additional four diaries were reviewed in their entirety and compared against the database submitted in the NDA. No additional discrepancies were observed. Because of the nature and number of violations observed, a VAI-R letter was sent to Dr. Freedman requesting assurances that these violations would not occur in ongoing or future studies.

### III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data submitted in support of this NDA by Drs. Antoci, Mitcheson, and Freedman are acceptable.

Follow-up action: None needed.

151  
\_\_\_\_\_  
Roy Blay, Ph.D., Clinical Reviewer  
DSI/GCPBI

### CONCURRENCE:

1  
c. 151  
\_\_\_\_\_  
John R. Martin, M.D.  
Branch Chief  
Good Clinical Practice I, HFD-46  
Division of Scientific Investigations

**DISTRIBUTION:**

NDA 20-771 and 21-228

HFD-45/Division File

HFD-46/Program Management Staff (electronic copy)

HFD-580/Farinas

HFD-46/Blay

HFD-46/Huff

HFD-46/CIB File #s 010136, 010152, and 010202

HFD-46/Reading File

**MEMO: Sites for FDA Inspections (NDA 20-771 SE8-004 and NDA 21-228 both Detrol)**

**To:** Evelyn Farinas, Project Manager, HFD-580 and Roy Blay, Ph. D., DSI

**From:** Brenda Gierhart, Medical Officer, HFD-580

**Date:** 3/10/00

19  
3/10/00

I recommend that the following three sites be inspected. They are the sites with the largest enrollments. There was the same one large randomized comparative placebo-controlled clinical trial in NDA 20-771 SE8-004 and NDA 21-228. The trial had three arms: Detrol immediate release, Detrol extended release, and placebo.

**Protocol 98-TOCR-007**

- |    |  |                      |
|----|--|----------------------|
| 1) | Site #203-Joseph Antoci, MD<br>Medical Practice<br>160 Robbins Street<br>Waterbury, CT 06708 USA                 | 34 Enrolled Subjects |
| 2) | Site #219-Sheldon Freedman, MD<br>3006 South Maryland Parkway, #430<br>Las Vegas, NV 98109, USA                  | 40 Enrolled Subjects |
| 3) | Site #239-David Mitcheson, MD<br>Bay State Urologist Inc<br>11 Nevin Street, Suite 501<br>Brighton, MA 02135 USA | 37 Enrolled Subjects |
- cc Original NDA 20,771  
Original NDA 21,228  
B. Gierhart, MD HFD-580  
E. Farinas, PM HFD-580  
R. Blay, PhD DSI

**NDA 20-771/S-004**

**Drug Name:** Detrol (tolterodine tartrate) tablets, 1 and 2 mg

**Sponsor:** Pharmacia & Upjohn

**Subject:** Clinical Pharmacology and Toxicology Review

**Action:** Not applicable for this application

**Date:** April 3, 2001

**NDA 20-771/S-004**

**Drug Name:** Detrol (tolterodine tartrate)tablets, 1 and 2 mg

**Sponsor:** Pharmacia & Upjohn

**Subject:** Advisory Committee

**Action:** Not applicable for this application

**Date:** April 3, 2001

**NDA 20-771/S-004**

**Drug Name:** Detrol (tolterodine tartrate)tablets, 1 and 2 mg

**Sponsor:** Pharmacia & Upjohn

**Subject:** Advisory Committee

**Action:** Not applicable for this application

**Date:** October 23, 2000

**NDA 20-771/S-004**

**Drug Name:** Detrol (tolterodine tartrate) tablets, 1 and 2 mg

**Sponsor:** Pharmacia & Upjohn

**Subject:** Foreign Labeling

**Action:** Not applicable for this application

**Date:** October 23, 2000

**NDA 20-771/S-004**

**Drug Name:** Detrol (tolterodine tartrate) tablets, 1 and 2 mg

**Sponsor:** Pharmacia & Upjohn

**Subject:** Tradename Review

**Action:** Not applicable for this application

**Date:** April 3, 2001

**NDA 20-771/S-004**

**Drug Name:** Detrol (tolterodine tartrate) tablets, 1 and 2 mg

**Sponsor:** Pharmacia & Upjohn

**Subject:** Tradename Review

**Action:** Not applicable for this application

**Date:** October 23, 2000