DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

Kathleen J. Day
Senior Director
Global Regulatory Affairs, Labeling and Promotion
Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199

DEC 7 2000

RE: Detrol (tolterodine tartrate tablets)
NDA 20-771
MACMIS ID #9318

Dear Ms. Day:

This letter concerns several promotional pieces (flipchart #UX00828.00; journal advertisement #UJ01855.00; and sales aids #UX02331.00, UX02332.00) for Detrol (tolterodine tartrate tablets) disseminated by Pharmacia & Upjohn (P&U). As part of its monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these promotional materials and has concluded that they are false or misleading, in violation of the Federal Food, Drug, and Cosmetic Act and its implementing regulations. Our specific objections follow.

Broadened Indication

The approved product labeling (PI) for Detrol states that "Detrol tablets are indicated for the treatment of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence." Detrol is not indicated for the treatment of stress incontinence. However, in flipchart #UX00828.00, you include a large questionnaire titled "Could you have stress incontinence," followed by the symptoms of stress incontinence. This claim and presentation is misleading because it suggests that Detrol is useful in patients with stress incontinence when such has not been demonstrated by substantial evidence.

Unsubstantiated Patient Satisfaction Claims

In sales aid UX02331.00, you present patient satisfaction claims that are unsubstantiated. For example, you present claims, based on survey results, such as "Patients taking Detrol tolterodine tartrate tablets reported improved sense of well being" and "Detrol had a positive impact on behavior." Claims such as these, concerning the subjective impact of overactive bladder and its treatment need to be supported by substantial evidence, such as adequate and well-controlled trials using validated instruments to measure these

outcomes, along with concurrent evaluations of efficacy and safety. Your claims and representations are misleading because they are not supported by such evidence. Rather, they are based solely on a market research survey of Detrol "users." In this case, you collected outcomes only from patients who remained on Detrol therapy, potentially biasing the results in favor of those who were "satisfied" with their treatment results.

Unsubstantiated Compliance Claims

In journal advertisement UJ01855.00 and sales aid UX02331.00, the claims "Favorable tolerability profile helps patients stay on therapy" and "Tolerability helps patients stay on therapy" are misleading because they lack substantial evidence. There are several factors other than tolerability that influence patient compliance. Therefore, in the absence of Detrol specific compliance data, your suggestions of improved patient compliance are misleading.

Misleading Efficacy Claims

Promotional materials are misleading if they suggest that a drug is more effective than has been demonstrated by substantial evidence. Your sales aid (UX02231.00) prominently presents a graphic that Detrol 2 mg bid demonstrated a 76% median change from baseline in urge incontinence in open-label trials after nine months of treatment. The efficacy found in the open-label trial is inconsistent with the PI, in which three clinical studies demonstrated a median change from baseline in urge incontinence of 50-56%.

Minimizing Risk

In sales aid UX02331.00 you present the incidence of dry mouth to be 39.5% for Detrol compared to 15.9% for placebo treated patients, which is consistent with the PI. However, this statement is followed by a chart depicting the overall incidence of dry mouth and the severity (mild, moderate, and severe). This chart depicts the overall incidence of dry mouth to be 30% with Detrol, which is misleading because it minimizes the risk of dry mouth and is inconsistent with the PI.

In sales aid UX02332.00 the tagline "A CNS safety profile that helps patients stay alert and active" is misleading because it minimizes the risk of somnolence in patients taking Detrol. As you acknowledge, somnolence has been reported by 3% of patients taking Detrol compared to 1.7% of patients taking placebo. Additionally, other adverse effects such as nervousness and dizziness are associated with Detrol therapy and may impact a patient's ability to stay alert and active.

Misleading Graphic Representation of tolterodine concentration in respective tissues

In sales aids #UX02331.00 and UX02332.00, you include a graphic representation of the concentration of tolterodine in the bladder and other elimination organs compared to the

central nervous system and skeletal muscle. This graphic implies that 87% of the tolterodine concentration is selective for the bladder and other elimination organs, while 13% of the tolterodine concentration is selective for the central nervous system and skeletal muscle. However, the difference in tolterodine's selectivity between the organs is unknown. This graphic is also misleading because it suggests clinical significance when, in fact, no such clinical significance has been demonstrated. The PI states that the drug shows selectivity for the urinary bladder over salivary glands in *cats* and the clinical relevance of this finding has not been established.

Requested Action

P&U should immediately discontinue these and all other promotional materials for Detrol that contain the same or similar claims or presentations. We request that P&U respond, in writing, with its intent to comply with the above. We should receive your written response no later than December 21, 2000. This response should list similarly violative materials with a description of the method for discontinuation and the discontinuation date.

If P&U has any questions or comments, please contact me by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #9318 in addition to the NDA number.

Sincerely,

/S/

Barbara S. Chong, Pharm.D., BCPS
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

Could you have overactive bladder?

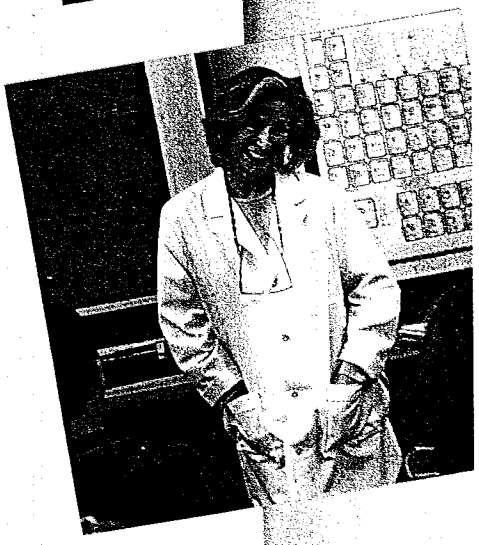
Do you:

- ☐ Use the bathroom frequently (more than 8 times in a 24-hour period)?
- ☐ Have strong, sudden urges to urinate?
- ☐ Wake up to urinate 2 or more times a night?
- ☐ Have wetting accidents?

Could you have stress incontinence?

Do you:

- ☐ Lose urine during physical activities?
- ☐ Have slight losses of urine when sneezing, coughing, or laughing?



Patient Satisfaction

Patient Survey Results

Patients taking DETROL™ tolterodine tartrate tablets reported improved sense of well being

The following data result from a survey of users of DETROL[1]*

DETROL had a positive impact on behavior

- **76%** of patients felt in control about overactive bladder
- **74%** of patients felt more confident when going out
- **73%** of patients felt free from concern about overactive bladder

Patients taking DETROL had confidence in their therapy

- **82%** of patients were satisfied† with therapy
- **67%** of patients stayed home less

90% of patients currently taking DETROL (n=176) said that they were likely to continue therapy

*A total of 280 patients with a new prescription for DETROL (identified from a pharmacy prescription database) were contacted via telephone by an independent market research firm. Of these, 253 had used or were using DETROL.

†Includes patients reporting they were completely, very, or somewhat satisfied.

Patients taking DETROL experienced fewer disruptions of daily living

DETROL improved the symptoms of overactive bladder

- **77%** of patients reported improvement in wetting accidents
- **76%** of patients reported improvement in frequency
- **74%** of patients reported improvement in urgency

Patients taking DETROL reported reduced level of coping activities

- **66%** of patients used pads less frequently
- **50%** of patients reported less frequent limitations of travel or activities
- **50%** of patients reported less frequent limitations of fluid intake

Many patients taking DETROL report they cope less and live more.

DETROL is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who have demonstrated hypersensitivity to the drug or its ingredients.

Reference: 1. Data on file. Pharmacia & Upjohn Company. Peapack, NJ.

Detrol™ tolterodine tartrate tablets

Designed specifically for overactive bladder

Please see full prescribing information.

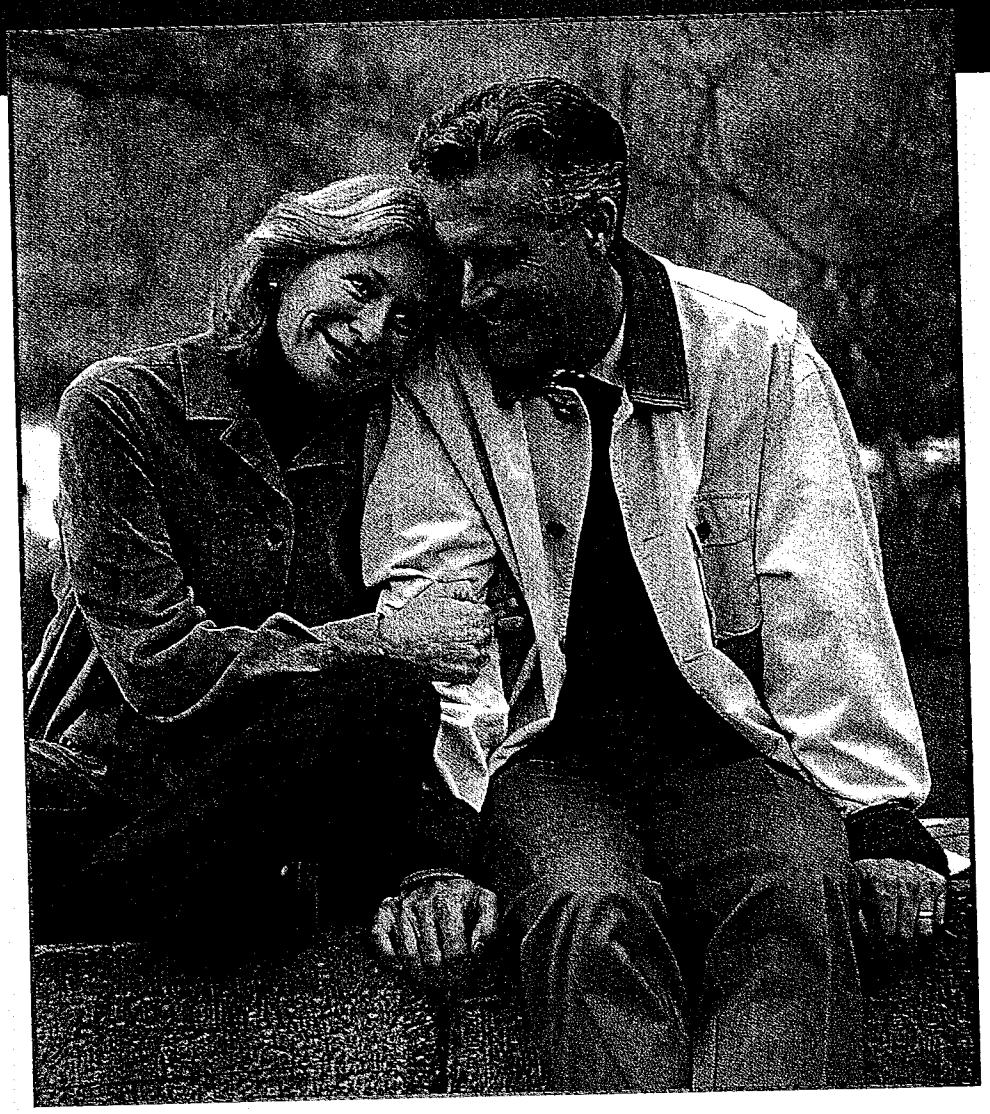
Visit our Web site: **www.detrol.com**

Pharmacia & Upjohn

UX02331.00 May 2000

Ask her about overactive bladder, then tell her about DETROL

Urologists' #1 brand for overactive bladder*



Over 1.5 million patients treated in the United States†

Proven effective for overactive bladder

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

DETROL Tablets are contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma and in patients who have demonstrated hypersensitivity to the drug or its ingredients.

Favorable tolerability profile helps patients stay on therapy

In clinical trials, the most frequently reported adverse event was dry mouth (DETROL 39.5% vs placebo 15.9%)—only 0.8% of patients treated with DETROL discontinued due to dry mouth.

Please see accompanying brief summary of prescribing information.

Detrol™

tolterodine tartrate tablets

Designed specifically for overactive bladder

* Based on total prescription volume. Source: IMS America Monthly NPA *Plus* for the 12 months ending September 1999.

† Source: IMS America Ltd. NDTI/NPA *Plus* patient estimates, 12 months ending September 1999.

Tolerability

helps patients stay on therapy

Generally well tolerated in phase III clinical trials

- In 12-week, placebo-controlled trials, dry mouth was the most frequently reported adverse event (placebo 15.9% vs DETROL 39.5%)
  - —Other adverse events reported that are considered to be treatment related (DETROL vs placebo) were dyspepsia (5.9% vs 1.7%), headache (11.0% vs 7.4%), constipation (6.5% vs 4.5%), and xerophthalmia (3.8% vs 1.7%)
- Discontinuation rate due to dry mouth was low (placebo 1.7% vs DETROL 0.8%)

Tolerability confirmed in large clinical trial

- In the largest study ever of overactive bladder (n=1,022) comparing treatment with DETROL vs placebo, dry mouth was the most commonly reported adverse event[1]

Incidence of Dry Mouth by Severity[1]

	Placebo (n=507)	DETROL 2 mg bid (n=512)
Mild	6%	18%
Moderate	2%	10%
Severe	0%	2%
Overall	**8%**	**30%**

- Other adverse events included constipation (placebo 4% vs DETROL 7%), and headache (placebo 5% vs DETROL 4%)

Effective

week after week, month after month

Change in urge incontinence—at week 12...

- DETROL reduced urge incontinence 50% at week 12 in a clinical trial (n=93) vs 32% for placebo (n=40); *P*=0.0988

  —DETROL median change: -1.2 episodes/24 hours at week 12 from a baseline median of 2.4 episodes/24 hours

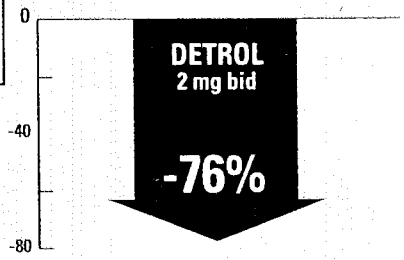
  —Placebo median change: -0.8 episodes/24 hours at week 12 from a baseline median of 2.5 episodes/24 hours

...and after 9 months

- Reduction in urge incontinence continued in open-label trials[1]

Median change from baseline (completer analysis)

9-month data*



Number of incontinence episodes per 24 hours with DETROL		
Median baseline	2.6	(n=508)
Median change from baseline	-1.4	(n=496)
(95% CI)	(-1.7 to -1.4)	

*Open-label, 9-month extension of four 12-week, double-blind, active- and/or placebo-controlled, multicenter phase III studies (N=854). Baseline defined as start of randomized part of trial.

A CNS safety profile that helps patients stay alert and active

- No significant difference vs placebo in psychiatric adverse events reported, *even in the elderly population*
  - —Somnolence was reported by 3% of patients taking DETROL vs 1.7% of patients taking placebo
- No precautions regarding:
  - —Use in elderly
  - —Driving*
  - —Tasks requiring mental alertness
  - —Concomitant use of alcohol or other sedative drugs
  - —Heat prostration

Reference: 1. Chancellor M, Freedman S, Mitcheson HD, et al. Tolterodine, an effective and well tolerated treatment for urge incontinence and other overactive bladder symptoms. *Clin Drug Invest.* 2000;19(2):83-91.

*Patients should be informed that antimuscarinic agents may produce blurred vision.

Detrol™ tolterodine tartrate tablets

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Please see full prescribing information.

Visit our Web site:
www.detrol.com

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UX02332.00 May 2000

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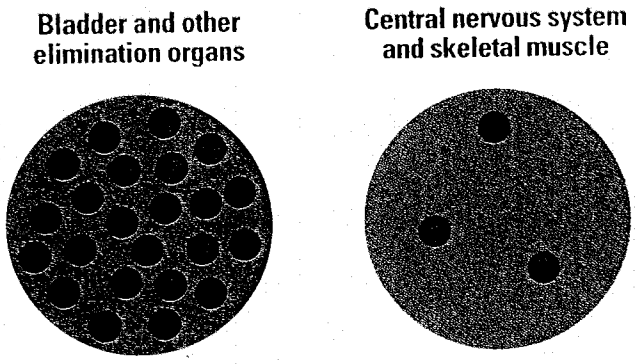
Selectivity demonstrated by greater tissue distribution in bladder vs CNS in an animal model

- Highest concentrations of tolterodine in elimination organs, such as the bladder, kidney, gallbladder, and liver, were seen in the murine model
- Lowest concentrations were seen in the CNS (brain and spinal cord) and skeletal muscles



Artist's depiction of tolterodine concentration in respective tissues

Reference: 1. Nilvebrant L, Andersson K-E, Gillberg P-G, et al. Tolterodine—a new bladder-selective antimuscarinic agent. *Eur J Pharmacol.* 1997;327:195-207.

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