DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

TRANSMITTED VIA FACSIMILE

MAY 29 1998

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

RE: NDA 20-771
Detrol (tolterodine tartrate tablets)
MACMIS ID #6710

Dear Ms. Day:

Reference is made to Pharmacia & Upjohn's (P&U) May 8, 1998 submission of promotional materials under cover of Form FDA 2253 for Detrol (tolterodine tartrate tablets) to the Division of Drug Marketing, Advertising and Communications (DDMAC). This submission includes the following promotional items for Detrol:

- (USX101400)
- (USX101500)
- (USX891100)

DDMAC has reviewed these materials and finds them to be in violation of the Federal Food, Drug and Cosmetic Act and its implementing regulations for the following reasons.

Overstatement of Efficacy

The claim "Encourage continued use to achieve and maintain therapeutic control" is misleading because it suggests that Detrol is more effective in treating overactive bladder than has been demonstrated. Three pivotal studies (008, 009, and 010) cited in the approved product labeling (PI) did not show a statistically significant difference between Detrol and placebo in reducing the number of incontinence episodes per 24 hours in patients with overactive bladder. Furthermore, patients receiving Detrol experienced approximately one less micturition per 24 hours compared to patients taking placebo. Specifically, the median baseline range for patients enrolled in studies 008, 009, and 010 was 10.4 to 11 micturitions per 24 hours, and the median change from baseline ranged between -1.5 to -2.2 for patients receiving Detrol versus -1.1 to -1.2 for patients receiving placebo. Thus, the suggestion that Detrol therapy achieves and maintains therapeutic control in these patients is an overstatement of efficacy.

Selective Presentation of Data

"Detrol reduced abnormally increased urinary frequency by a median 1.6 to 2.2 micturitions per 24 hours from baseline (median ranged from 10.4 to 11.0). Results were significantly better than placebo in two of three studies."

"Detrol reduced median (urge) incontinence episodes per 24 hours by 1.2 to 1.5 from baseline (median ranged from 2.4 to 2.7). This result was not significantly different compared to placebo."

"...Detrol 2 mg bid reduced urinary frequency by a median 1.6 to 2.2 micturitions per 24 hours, from baseline."

"...Detrol 2 mg bid reduced urge incontinence episodes by 1.2 to 1.5 episodes per 24 hours, from baseline."

These claims are misleading because they omit material facts and are, therefore, a selective presentation of the data. The three placebo-controlled, 12 week studies described in the PI compared Detrol versus placebo. The efficacy endpoints for these studies 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 PI lists specific values (Detrol vs placebo) for baseline and median change from baseline with respect these endpoints. Therefore, claims such as these that describe Detrol's efficacy in terms of change from baseline and omit the specific values representing the efficacy of placebo are misleading.

In order to address these objections, DDMAC requests that P&U immediately cease its use of promotional materials that contain these or similar claims or representations. P&U should respond in writing by June 8, 1998, including a list of all similarly violative material and a description of its method for discontinuing their use

If you have any questions or comments, please contact the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-240, 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 #6710 in addition to the NDA number.

Sincerely,

Mark W. Askine, R.Ph.
Regulatory Review officer
Division of Drug Marketing,
Advertising, and Communications