DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FASCIMILE

Stephen W. Sherman
Director, Advertising and Labeling
Regulatory Affairs
ALZA Corporation
1900 Charleston Road
PO Box 7210
Mountain View, CA 94039-7210

NOV 16 2000

RE: Ditropan® XL (oxybutynin chloride) Extended Release Tablets
NDA 20-897
MACMIS ID#8996

Dear Mr. Sherman:

This letter concerns several promotional pieces (sales aid # 0008699-2, uncoded sales aid, file cards # 0010171, 0010175) for Ditropan XL (oxybutynin chloride) disseminated by ALZA Corporation (ALZA). As part of its monitoring program, the Division of Drug Marketing, Advertising and Communications (DDMAC) has reviewed these promotional materials and 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.

Unsubstantiated Superiority Claim

Promotional materials are misleading if they suggest that a drug is superior to other products when such has not been demonstrated by substantial evidence. In your materials, you present side by side comparisons of Ditropan XL and Detrol's mechanism of action, indication, safety, efficacy, and dosing under taglines such as "Let your patients try Ditropan XL and be convinced," "Compare and be convinced," or "Ditropan XL delivers a difference." These presentations are misleading because they suggest that Ditropan XL is superior to Detrol when such has not been demonstrated by substantial evidence (generally, two adequate and well-controlled head-to-head comparative studies). Rather, your suggestions of Ditropan XL's superiority appear to be based on an "across label" comparison of the two products.

Omission of Material Facts

In file card (0010175), you present several efficacy claims and presentations about Ditropan XL, such as "In one clinical study, significant reductions in UI episodes were demonstrated at the 5-mg starting dose in only 2 weeks." This claim is misleading

because it omits material facts. The approved product labeling (PI) for Ditropan XL states that the controlled studies included patients known to be responsive to oxybutynin or other anticholinergic medications. That is, the clinical studies were designed to include only patients who were known to have had improved symptoms on oxybutynin, the active ingredient in Ditropan XL, or other similar medications used to treat overactive bladder. These facts are not disclosed in the file card.

Misleading Efficacy Presentations

File card 0010171 is misleading because it overstates the effectiveness of Ditropan XL. Specifically, you present the claim "Up to 90% reduction in urge incontinence episodes across four studies" along with four prominent graphs depicting efficacy rates between 83-90% on the front of the card. However, you fail to present that patients randomized to the placebo arm experienced up to a 51% reduction in urge incontinence episodes in the same trials. Without the presentation of the placebo arm, the efficacy of Ditropan XL is overstated.

Requested Action

In order to address these violations, DDMAC recommends that ALZA immediately discontinue these, and all other promotional materials for Ditropan XL that contain the same or similar claims or presentations. We request that ALZA respond, in writing, with its intent to comply with the above. DDMAC should receive your written response no later than December 1, 2000. This response should list similarly violative materials with a description of the method for discontinuation and the discontinuation date.

If you have 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. We remind you that only written communications are considered official.

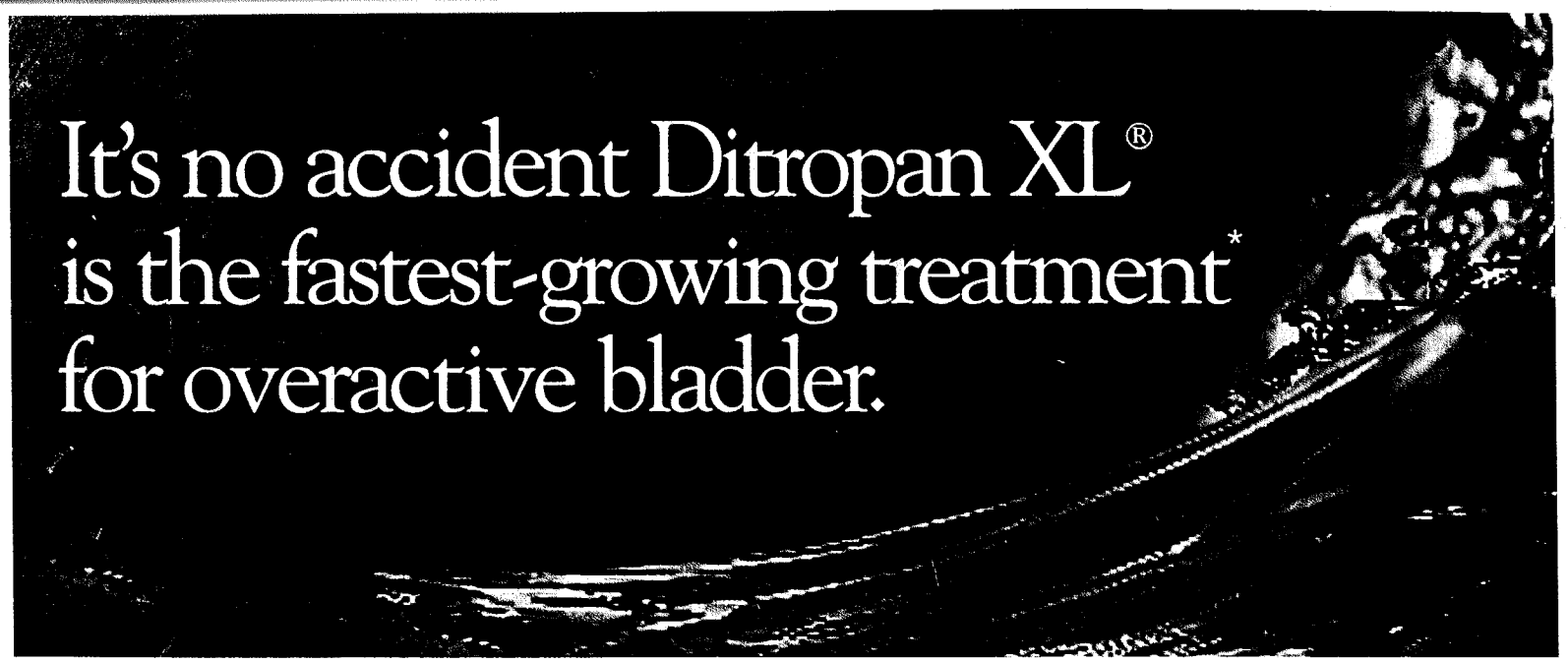
In all future correspondence regarding this particular matter, please refer to MACMIS ID #8996 in addition to the NDA number.

Sincerely,

/S/

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

It's no accident Ditropan XL® is the fastest-growing treatment* for overactive bladder.



Let your patients try Ditropan XL® and be convinced

	Ditropan XL®	Detrol™†
Mechanism of action	Anticholinergic Antispasmodic	Anticholinergic
Superior to placebo in reduction of urge urinary incontinence	YES	NO
Incidence of dry mouth	32% 5 mg qd 44% 10 mg qd 64% 15 mg qd	40% 2 mg bid
Dosing	qd	bid
Price/day for the most commonly prescribed dose‡	$2.31	$2.59
Dosing flexibility	5 mg qd 10 mg qd 15 mg qd	1 mg bid 2 mg bid

* IMS Monthly Data.

† Detrol™ (tolterodine tartrate tablets) is a trademark of Pharmacia & Upjohn.

‡ Based on the current published average wholesale price. *1999 Drug Topics® Red Book®*. Montvale, NJ: Medical Economics Company Inc. December. Comparison may not represent the actual price to pharmacies or paid by customers.

Ditropan® and Ditropan XL® are registered trademarks of ALZA Corporation.

Ditropan XL® is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma, and in patients who are at risk for these conditions. Ditropan XL® is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

Please see accompanying full prescribing information.

Once-a-day
DITROPAN XL®
(oxybutynin chloride) Extended-release tablets 5, 10, 15 mg

Delivers a difference

Manufactured/ Distributed/Marketed by
ALZA Corporation
Mountain View, CA 94043

Marketed by
UCB Pharma, Inc
Smyrna, GA 30080

For more information, call 1-888-DXL-1-A-DAY, or visit www.DitropanXL.com

Ditropan 15-mg tab

Once-a-day
DITROPAN® XL
(oxybutynin chloride) Extended-release tablets 5, 10, 15 mg

Compare and be convinced.

	Ditropan® XL	Tolterodine
MECHANISM OF ACTION		
Antimuscarinic	✓	✓
Antispasmodic	✓	—
INDICATION		
Overactive bladder with symptoms of:		
Urge urinary incontinence	✓	✓
Urinary urgency	✓	✓
Frequency	✓	✓
SAFETY		
~1% discontinuation rate due to dry mouth	✓ (1.2%)	✓ (0.8%)
~7% overall discontinuation rate	✓ (6.8%)	✓ (8.0%)
No difference in side effects in elderly patients	✓	✓
ONCE-DAILY DOSING*	✓	—
PRICE†	$2.13 (5 mg qd) $2.38 (10 mg qd) $2.63 (15 mg qd)	$2.52 (2 mg bid $2.59 (1 mg bid —

* Ditropan® XL recommended starting dose is 5 mg/day. Tolterodine initial recommended dose is 2 mg twice daily.

† Based on the current published average wholesale price. *1999 Drug Topics® Red Book®*. Montvale, NJ: Medical Economics Company Inc. July 1999. Comparison may not represent the actual price to pharmacies or paid by customers.

References: 1. Ditropan® XL [package insert]. Palo Alto, Calif.: ALZA Corporation; 1998. **2.** Data on file, ALZA Corporation. **3.** Norton PA, MacDonald LD, Sedgwick PM, Stanton SL. Distress and delay associated with urinary incontinence, frequency, and urgency in women. *BMJ*. 1988;297:1187-1189. **4.** *Physician Drug & Diagnosis Audit (PDDA)* April 1997-March 1998, Scott-Levin, a division of PMSI Scott-Levin Inc.

Please see literature for full prescribing information inside flap on back cover.

0008699-2 July 1999

Manufactured/ Distributed/Marketed by
alza PHARMACEUTICAL
ALZA Corporation
Palo Alto, CA 94304

Marketed by
ucb Pharma
UCB Pharma, Inc
Smyrna, GA 30080

Effective, well-tolerated therapy.

- **Ditropan XL® decreases urgency and frequency of both incontinence episodes and voluntary urination.**
- **In one clinical study, significant reductions in UI episodes were demonstrated at the 5-mg starting dose in only 2 weeks.**

Ditropan XL® is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma, and in patients who are at risk for these conditions. Ditropan XL® is also contraindicated in patients who have demonstrated hypersensitivity to the drug substance or other components of the product.

Please see accompanying literature for full prescribing information.

Reference: 1. Kachur JF, Peterson JS, Carter JP, Rzeszotarski WJ, Hanson RC, Noronha-Blob L. R and S enantiomers of oxybutynin: pharmacological effects in guinea pig bladder and intestine. *J Pharmacol Exp Ther.* 1988;247:867-872.

The most common side effect experienced by patients treated with Ditropan XL® in clinical trials was dry mouth (61%), which was dose related. However, only 1% of 429 patients studied discontinued therapy due to dry mouth. Other common adverse events reported included constipation (13%), somnolence (12%), diarrhea (9%), blurred vision (8%), dry eyes (6%), dizziness (6%), and rhinitis (6%). The overall discontinuation rate was 7%.

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

Manufactured/ Distributed/Marketed by

ALZA Corporation
Mountain View, CA 94043

Marketed by

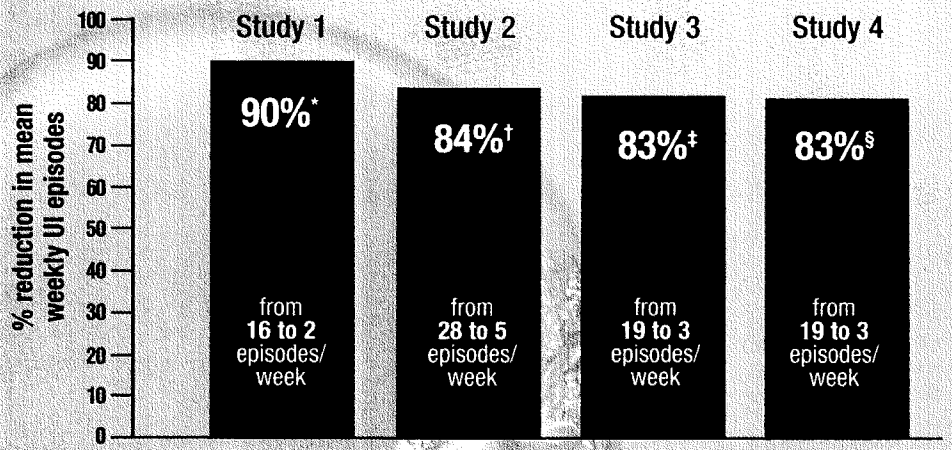
UCB Pharma, Inc
Smyrna, GA 30080

Once-a-day
DITROPAN XL®
(oxybutynin chloride) Extended-release tablets 5, 10, 15 mg
Delivers a difference

Efficacy that's no accident.

Once-a-day
DITROPAN XL®
(oxybutynin chloride) Extended-release tablets 5, 10, 15 mg
Delivers a difference

Up to 90% reduction in urge incontinence (UI) episodes across four studies (n=685).[1,2]



- Across all studies, consistent efficacy (83%-90%) was seen in studies of patients known to be responders to oxybutynin or other anticholinergic medications[1] as well as naive patients.[2]

References: 1. Ditropan XL® [package insert]. Mountain View, Calif.; ALZA Corporation; 2000. **2.** Gleason DM, Susset J, White C, Munoz DR, Sand PK, for the Ditropan XL® Study Group. Evaluation of a new once-daily formulation of oxybutynin for the treatment of urinary urge incontinence. *Urology*. 1999;54:420-423.