DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

FOI

MAY 13 1997

TRANSMITTED VIA FACSIMILE

Ronald J. Garutti, MD
Director, Marketed Products Support
Worldwide Regulatory Affairs
Schering Corporation
2000 Galloping Hill Road
Kenilworth, NJ 07033

RE: **ANDA#** 89-822 (400 mg), 89-823 (600 mg)
Uni-Dur (theophylline) Extended Release Tablets
MACMIS ID# 4636

Dear Dr. Garutti:

As part of its routine monitoring activities, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed promotional materials that have been disseminated by or on behalf of Schering Corporation/Key Pharmaceuticals (Schering) for Uni-Dur (theophylline) Extended Release Tablets. DDMAC has determined that these materials contain unsubstantiated comparative claims to other sustained release theophylline products or are otherwise misleading and thus violative of the Federal Food, Drug, and Cosmetic Act and its implementing regulations.

These materials include, but are not limited to, a Uni-Dur promotional brochure "No Other 1 Is As Consistent...Or As Convenient" (UD400/19216306) and a publication "Allergy & Asthma, Spring 1996" magazine featuring (with one exception for allergic conjunctivitis) articles that are promotional presentations of exclusively Schering allergy and asthma drugs with Schering product photographs and "call-out" claims. The magazine is issued by Healthline Publishing, Inc., and is disseminated by direct mail to physicians and available free to pharmacy chain customers.

DDMAC, in consultation with the Division of Pulmonary Drug Products and the Division of Bioequivalence in the Office of Generic Drugs, objects to the following claims:

> "Uni-Dur, the most recent entry on the market, is unaffected by meals and has the 'flattest' mean plasma concentration curve over time of all the sustained release theophylline preparations." ("Asthma & Allergy, Spring 1996" magazine)

"No other 1 is as consistent" (Uni-Dur brochure)

These broad claims are false and/or misleading because they are not substantiated by adequate comparative pharmacokinetic (PK) data for all possible product comparisons, and because the claims suggest that Uni-Dur confers a clinical benefit when no such clinical significance has been demonstrated by substantial clinical evidence.

"(Uniphyl) Serum Levels: Fluctuations three times that of Uni-Dur"

(Uni-Dur brochure, cited to Oosterhuis, Brannan, Groen, et al. "Biopharmaceutic Characteristics of a New Extended-Release Theophylline Formulation (Uni-Dur)" 1995; Annals of Allergy, Asthma, & Immunol. 75: 158-161.)

This comparative claim about Uniphyl (theophylline) Controlled Release Tablets versus Uni-Dur is misleading because the serum concentration data that were collected from normal subjects in the Oosterhuis PK study are presented in a way that suggests clinical significance of the data when no such clinical significance in patients has been demonstrated. Moreover, this fluctuation claim is ambiguous because "Fluctuation Index" (FI) has been variously calculated to show peak to trough serum concentration differences. Since the Oosterhuis FI equation is not a universally accepted measure, this comparative serum level claim is misleading because it lacks adequate context to define the equational basis of the fluctuation calculation.

DDMAC requests that the distribution and use these promotional materials containing similar claims cease immediately. Schering's written response should be received by DDMAC no later than May 28, 1997, describing the corrective steps that the Company has taken to ensure that these activities and the use of these materials has been suspended.

Please direct your response to the undersigned by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising and Communications, HFD-40, Rm 17-B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Schering that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #4636 in addition to the NDA number.

Sincerely,

Joan Hankin

Joan Hankin, JD
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications