DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 13-217/ S-044

Elan Pharmaceuticals, Inc.
Attention: Linda B. Fischer
Director, Regulatory Affairs
45 Horse Hill Road
Cedar Knolls, NJ 07927

Dear Ms Fischer:

Please refer to your supplemental new drug application dated October 16, 2001, received October 17, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Skelexin (metaxalone) Tablets, 400 mg.

We acknowledge receipt of your correspondence dated June 11, 2002.

This approval will supercede the previous approval letter for this supplemental application.

This supplemental new drug application provides for inclusion of a Pharmacokinetics section in the label.

We have completed the review of this 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 agree upon enclosed labeling text. According the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the following labeling:

Pharmacokinetics

In a single center randomized, two-period crossover study in 42 healthy volunteers (31 males, 11 females), a single 400 mg Skelexin (metazalone) tablet was administered under both fasted and fed conditions.

Under fasted conditions, mean peak plasma concentrations (C_{max}) of 865.3 ng/mL were achieved within 3.3 +/- 1.2 hours after dosing (T_{max}). Metaxalone concentrations declined with a mean terminal half-life ($t_{1/2}$) of 9.2 +/- 4.8 hours. The mean apparent oral clearance (CL/F) of metaxalone was 68 +/- 34L/h.

In the same study, following a standardized high fat meal, food statistically significantly increased the rate (C_{max}) and extent of absorption ($AUC_{(0-t)}$, AUC_{inf}) of metaxalone from Skelexin tablets. Relative to the fasted treatment the observed increases were 177.5%, 123.5%, and 1 15.4%, respectively. The mean T_{max} was also increased to 4.3 +/- 2.3 hours, whereas the mean $t_{1/2}$ was decreased to 2.4 +/ - 1.2 hours. This decrease in half-life over that seen in the fasted subjects is felt to he due to the more complete absorption of metaxalone in the presence of a meal resulting in a better estimate of half-life. The mean apparent oral clearance (CL/F) of metaxalone was relatively unchanged relative to fasted administration (59 +/- 29 L/hr). Although a higher C_{max} and AUC were observed after the administration of Skelexin (metaxalone) with a standardized high fat meal, the clinical relevance of these effects is unknown.

The absolute bioavailability of metaxalone from Skelexin tablets is not known. Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites. The impact of age, gender, hepatic, and renal disease on the pharmacokinetics of Skelexin (metaxalone) has not been determined at this time.

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 10 copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplemental application NDA 13-217/S-044." Approval of this submission is not required before the labeling is used.

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 this letter to this NDA and a copy to the following address:

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

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 Jane A. Dean, RN, MSN, Regulatory Health Project Manager, at 301-827-2090.

Sincerely,

{See appended electronic signature page}

Lawrence Goldkind, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic
Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lawrence Goldkind

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