





NDA 13-217/S-036

Elan Pharmaceuticals, Inc.  
Attention: Ms. 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 11, 1999, received October 14, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Skelaxin (metaxalone) tablets.

We acknowledge receipt of your submission dated August 13, 2002.

Your submission of July 19, 2002 constituted a complete response to our July 11, 2002, action letter.

This supplemental new drug application provides for an additional strength of the drug product (800 mg tablets) to be manufactured by Mallinckrodt, Inc, Hobart, NY.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

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 ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 13-217/S-036/S-036." Approval of this submission by FDA is not required before the labeling is used.

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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 the 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 Ms. 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

Enclosure

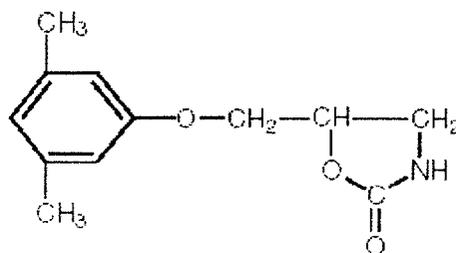
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/s/

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Lawrence Goldkind  
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**SKELAXIN® (Metaxalone)****DESCRIPTION**

SKELAXIN® (metaxalone) has the following chemical structure and name:



5-[(3,5-dimethylphenoxy)methyl]-2-oxazolidinone

SKELAXIN (metaxalone) is available as a 400 mg round, pale rose tablet and an 800 mg oval, pink scored tablet.

**CLINICAL PHARMACOLOGY**

The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate or the nerve fiber.

*Pharmacokinetics:* In a single center randomized, two-period crossover study in 42 healthy volunteers (31 males, 11 females), a single 400 mg SKELAXIN (metaxalone) 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 (S.D.) 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 +/- 34 L/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 SKELAXIN tablets. Relative to the fasted treatment the observed increases were 177.5%, 123.5%, and 115.4%, 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 be 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 SKELAXIN (metaxalone) with a standardized high fat meal, the clinical relevance of these effects is unknown.

In another single center, randomized four-period crossover study in 59 healthy volunteers (37 males, 22 females), the rate and extent of metaxalone absorption were determined after the administration of SKELAXIN tablets under both fasted and fed conditions. Under fasted conditions, the administration of two SKELAXIN 400 mg tablets produced peak plasma metaxalone concentrations ( $C_{max}$ ) of 1653 ng/mL  $3.0 \pm 1.2$  hours after dosing ( $T_{max}$ ). Metaxalone concentrations declined with mean terminal half-life ( $t_{1/2}$ ) of  $8.0 \pm 4.6$  hours. The mean apparent oral clearance (CL/F) of metaxalone was  $66 \pm 34$  L/hr. Except for a 17% decrease in mean  $C_{max}$ , these values were not statistically different from those after the administration of one SKELAXIN 800 mg tablet.

In the same study, the administration of two SKELAXIN 400 mg tablets following a standardized high fat meal showed an increase in the mean  $C_{max}$ , and the area under the curve ( $AUC_{0-inf}$ ) of metaxalone by 194% and 142%, respectively. A high fat meal also increased the mean  $T_{max}$  to  $4.9 \pm 2.3$  hours but decreased the mean  $t_{1/2}$  to  $4.2 \pm 2.5$  hr. The effect of a high fat meal on the absorption of metaxalone from one SKELAXIN 800 mg tablet was very similar to that on the absorption from two SKELAXIN 400 mg tablets in quality and quantity. The clinical relevance of these effects is unknown.

The absolute bioavailability of metaxalone from SKELAXIN 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 SKELAXIN (metaxalone) has not been determined. In the absence of such information, SKELAXIN should be used with caution in patients with hepatic and/or renal impairment and in the elderly.

## **INDICATIONS AND USAGE**

SKELAXIN (metaxalone) is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Metaxalone does not directly relax tense skeletal muscles in man.

## **CONTRAINDICATIONS**

Known hypersensitivity to any components of this product.  
Known tendency to drug induced, hemolytic, or other anemias.  
Significantly impaired renal or hepatic function.

## **WARNINGS**

SKELAXIN may enhance the effects of alcohol and other CNS depressants.

## **PRECAUTIONS**

Metaxalone should be administered with great care to patients with pre-existing liver damage. Serial

liver function studies should be performed in these patients.

False-positive Benedict's tests, due to an unknown reducing substance, have been noted. A glucose-specific test will differentiate findings.

***Information for Patients***

SKELAXIN may impair mental and/or physical abilities required for performance of hazardous tasks, such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants.

***Drug Interactions***

SKELAXIN may enhance the effects of alcohol, barbiturates and other CNS depressants.

***Carcinogenesis, Mutagenesis, Impairment of Fertility***

The carcinogenic potential of metaxalone has not been determined.

***Pregnancy***

Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone. Post marketing experience has not revealed evidence of fetal injury, but such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. Safe use of metaxalone has not been established with regard to possible adverse effects upon fetal development. Therefore, metaxalone tablets should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgement of the physician the potential benefits outweigh the possible hazards.

***Nursing Mothers***

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

***Pediatric Use***

Safety and effectiveness in children 12 years of age and below have not been established.

**ADVERSE REACTIONS**

The most frequent reactions to metaxalone include:

CNS: drowsiness, dizziness, headache, and nervousness or "irritability;"

Digestive: nausea, vomiting, gastrointestinal upset;

Immune system: hypersensitivity reaction, rash with or without pruritus;

Hematologic: leukopenia, hemolytic anemia;

Hepatobiliary: jaundice.

Though rare, anaphylactoid reactions have been reported with metaxalone.

### **OVERDOSAGE**

Deaths by deliberate or accidental overdose have occurred with this class of drugs, particularly in combination with antidepressants and/or alcohol.

When determining the LD<sub>50</sub> in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD<sub>50</sub> could be determined as the higher doses produced an emetic action in 15 to 30 minutes.

*Treatment* - Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

### **DOSAGE AND ADMINISTRATION**

The recommended dose for adults and children over 12 years of age is two 400 mg tablets (800 mg) or one 800 mg tablet three to four times a day.

### **HOW SUPPLIED**

SKELAXIN (metaxalone) is available as a 400 mg pale rose tablet, inscribed with 8662 on the scored side and "C" on the other. Available in bottles of 100 (NDC 0086-0062-10) and in bottles of 500 (NDC 0086-0062-50).

SKELAXIN (metaxalone) is also available as an 800 mg oval, scored pink tablet inscribed with 8667 on the scored side and "S" on the other. Available in bottles of 100 (NDC 59075-068-10) and in bottles of 500 (NDC 59075-068-50).

Store at Controlled Room Temperature, between 15° C and 30° C (59° F and 86° F).

**Rx Only**

Revised: August, 2002