DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR 1 2004

ANDA for Metaxalone Tablets

Dear Applicant:

This letter is to inform you that the FDA has determined that labeling corresponding to the use (U-189) listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for U. S. Patent number 6,407,128 (the '128 patent) may be carved out of the metaxalone labeling. Previously, the FDA may have informed you that such omission would not be permitted. A preliminary decision not to permit omission of this labeling was challenged by an ANDA applicant. The applicant has submitted information and analysis that has persuaded FDA that the fed-state bioavailability information may be carved out of the metaxalone labeling without rendering the drug less safe or effective for the remaining conditions of use. Therefore, FDA has concluded that you may submit proposed labeling that omits the use (U-189) described in the Orange Book. Should you adopt this approach, you must accompany this submission with a "section viii statement" to the '128 patent, pursuant to section 505(j)(2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act (Act)

The listed drug at issue is Elan's Skelaxin (metaxalone) Tablets, NDA 13-217.[1] Metaxalone is approved by FDA for use "as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions." The '128 patent is listed for Skelaxin in the Orange Book. It is identified as a use patent. The use claimed by the patent is listed in the Orange Book as "enhancement of the bioavailability of the drug substance" (U-189). The question presented to the agency was whether a section viii statement with respect to the '128 patent would be permitted. A section viii statement asserts that the labeling in the ANDA does not include any use claimed by the use patent. Section 505(j)(2)(A)(viii); 21 CFR 314.94(a)(12)(iii). A section viii statement is only appropriate when an applicant can carve information protected by the use patent out of the labeling for the product proposed in the ANDA.

ANDA Applicants May Omit from Labeling Method of Use Information Claimed by a Patent if the Omission Will Not Render the Drug Less Safe and Effective

The regulatory principles governing FDA's decision on this matter are well established. FDA has authority to approve ANDAs that omit labeling carried by the listed drug, when such labeling is protected by patent or exclusivity. The Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." Section 505(j)(2)(A)(i). The Act also requires that an ANDA contain "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug . . . ." Section

[1] This NDA is now owned by Jones Pharma, Inc., a subsidiary of King Pharmaceuticals, Inc.

505(j)(2)(A)(v). The Act specifies two exceptions to this requirement. ANDA labeling may differ from that of the listed drug because changes from the listed drug were approved pursuant to an ANDA suitability petition, or because the drugs are produced or distributed by different manufacturers. Section 505(j)(2)(A)(v).

The Act specifically contemplates that an innovator company may submit to FDA patents claiming an approved method of using a drug and that ANDA applicants may omit from proposed labeling methods of use covered by those patents. Sections 505(b)(1) and (c)(2) of the Act state that innovators may submit patents to FDA that claim the approved drug "or method of using such drug." If a method-of-use patent listed by the innovator does not claim a use for which an ANDA applicant is seeking approval (because it is omitted from the proposed ANDA labeling), the ANDA applicant may submit a "section viii statement" to FDA that it is not seeking approval for a use claimed by a listed patent. Section 505(j)(2)(A)(viii). The statutory provisions addressing patent listing and section viii statements use the same "method of use" terminology, and effectively mirror one another; a method of use claimed by a patent is also a method of use that an ANDA applicant may propose to carve out of labeling.

FDA regulations further describe the differences that are permitted between the proposed labeling in the ANDA and the listed drug. 21 CFR 314.94, "Content and format of an abbreviated application," provides:

> Labeling (including the container label and package insert) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, *or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act.*

21 CFR 314.94(a)(8)(iv)(emphasis added). The courts have upheld FDA's authority to approve generic drugs with labeling that omits information protected by exclusivity, *Bristol-Myers v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), and information protected by patent, *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002); *aff'd Purepac Pharm. Co. v. Thompson*, Nos. 02-5410 & 03-5121, 2004 WL 76594 (D.C. Cir. Jan. 20, 2004).

The regulations further provide that to approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, FDA must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use." 21 CFR 314.127(a)(7). Whether a particular ANDA proposing labeling that

omits protected information may be approved depends upon the specific drug product and the labeling at issue. Therefore, whether FDA could approve a metaxalone ANDA that omits certain method of use information from the labeling depends upon whether the agency concludes that the drug will remain safe and effective for all the conditions of use that would remain in the label.

ANDA Applicants May Omit Labeling Related to Fed-State Bioavailability from Metaxalone Labeling

The agency has reviewed the labeling for Skelaxin, and determined that information related to the "enhancement of the bioavailability of the drug substance," may be omitted from the labeling for metaxalone products proposed in ANDAs, without rendering those drug products less safe or effective for the conditions of use that would remain in the label.

Metaxalone is approved by FDA only for use "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 metaxalone has not been clearly identified, but may be related to its sedative properties. The drug has been marketed for approximately 40 years, and is considered to have a favorable safety profile. Until recently, Skelaxin had no information in its labeling related to the effect of administration of the drug with food.

In 2001, Elan conducted a food effect study with metaxalone, and submitted the results to FDA in a labeling supplement. In June 2002, FDA approved changes to the Clinical Pharmacology section of the Skelaxin labeling to incorporate information from the food effect study.[2] It is this pharmacokinetic information that an applicant seeks to delete from its labeling as corresponding to the use claimed in the '128 patent. The bioavailability data submitted by Elan did not result in new Dosing and Administration labeling information for Skelaxin. Nor did it result in any changes to the warnings, precautions, or contraindications in the Skelaxin labeling

The pharmacokinetic information submitted by Elan and included in the labeling demonstrated that administration of metaxalone with a high fat meal enhances drug absorption. See attached Skelaxin labeling. The Skelaxin label includes pharmacokinetic information from dosing following a standardized high fat meal. The results from this study showed that food statistically significantly increased the rate (C_{max}), and extent of absorption (AUC_{0-t}, AUC_{inf}) of metaxalone. The approved Skelaxin labeling further acknowledges that "[t]he clinical relevance of these effects is unknown."[3]

The agency's assessment of whether pharmacokinetic information may be omitted from metaxalone labeling without rendering the drug less safe or effective for the remaining uses focused on whether information about enhanced fed-state bioavailability was necessary to the

[2] Elan did not receive three years of exclusivity for this labeling change under section 505(j)(5)(D)(iii) or (iv) because bioavailability studies are not clinical studies that qualify for exclusivity. 21 CFR 314.108(a).

[3] If Elan had conducted clinical trials to demonstrate a clinical effect arising from the difference in fed- and non-fed-state bioavailability, the inclusion of such information in labeling might have been considered necessary for the safe and effective use of metaxalone. No such study has been submitted.

safe and effective use of the drug. The agency looked specifically at the relationships between bioavailability and efficacy, and bioavailability and the occurrence of known adverse events, particularly drowsiness.

FDA has concluded that omission of information regarding fed-state bioavailability will not negatively affect the safe use of metaxalone. On May 31, 2002, FDA approved an addition to the Skelaxin Clinical Pharmacology labeling that stated "Given the magnitude of the plasma level changes following a high fat meal, Skelaxin tablets should be administered on an empty stomach." The agency had approved this information because it was concerned about enhanced bioavailability and increased adverse events. However, no related changes were made to the Dosing and Administration portion of the labeling. After discussions with Elan and additional review of the available information, the agency later concluded that there were insufficient data to support a correlation between enhanced drug concentrations and increased adverse events. The label was further revised in June 2002, to remove information regarding dosing on an empty stomach, and to state that the clinical effect of the increased bioavailability is unknown.

Because the clinical effect of the increased bioavailability is unknown, omission of fed-state bioavailability information from the labeling will not render the drug less safe for its approved uses. There are no data to support an increase in adverse events related to increased drug concentrations. Even if it were reasonable to conclude that increased bioavailability relates to an increase in adverse events, the labeling already adequately addresses the primary CNS (central nervous system) adverse events by way of the caution that "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." This caution applies to use of metaxalone without reference to the conditions of administration.

The Skelaxin labeling provides no information that links variations in bioavailability to the effectiveness of the drug. In fact, as noted above, the approved labeling specifically states that the clinical relevance of the food effect is unknown. Thus, because the clinical effect of increased bioavailability is unknown, omission of information on this characteristic of the drug will not affect the effective use of metaxalone.

Finally, FDA notes that metaxalone has a long history of safe use. It has been marketed for decades without dosing adjustment information related to fed-state administration. Few adverse event reports have been entered into the Adverse Event Reporting System. Based upon the data available to the agency, there is no reason to believe that metaxalone will not continue to be safe and effective for use as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions.

For the reasons described above, FDA has concluded that an ANDA applicant may delete from its labeling information on fed-state bioavailability claimed by the '128 patent because metaxalone products with such labeling will be no less safe or effective for all of the remaining conditions of use.

If you have further questions regarding this issue, please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at (301) 827-5845.

Sincerely,

Robert Lumpkin /for

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

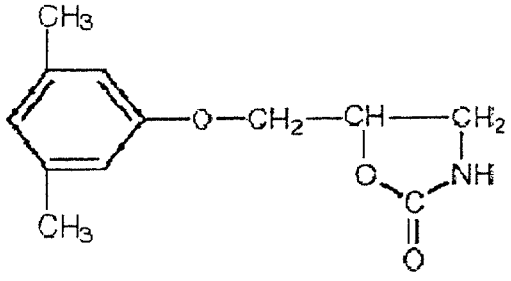
Attachment: Skelaxin Labeling

cc: Jones Pharma, Inc.
Daniel E. Troy, OCC

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 + 1.2 hours after dosing (T_{max}). Metaxalone concentrations declined with mean terminal half-life ($t_{½}$) of 8.0 + 4.6 hours. The mean apparent oral clearance (CL/F) of metaxalone was 66 + 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 ($AUC_{0\text{-}inf}$) of metaxalone by 194% and 142%, respectively. A high fat meal also increased the mean T_{max} to 4.9 +/- 2.3 hours but decreased the mean $t_{½}$ to 4.2 + 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.
Other adverse reactions are:
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_{50} in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD_{50} 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