

CENTER FOR DRUG EVALUATION AND RESEARCH

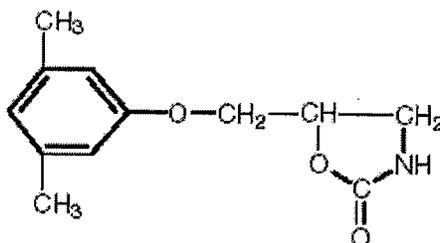
APPLICATION NUMBER:

13-217 / S-044

APPROVED LABELING

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 ($t_{1/2}$) 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-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 $t_{1/2}$ 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;

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 LD₅₀ in rats and mice, progressive sedation, hypnosis and finally respiratory failure were noted as the dosage increased. In dogs, no LD₅₀ 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

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/s/

Lawrence Goldkind
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