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September 19, 2013

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, rm 1061
Rockville, MD 20852

2013 SEP 20 A 9:25

Citizen Petition

The undersigned submits this petition under 21 CFR 10.25(a) and 21 CFR 10.30 to request the Commissioner of the Food and Drug Administration to determine whether a listed drug (Skelaxin® 400 mg, manufactured by King Pharmaceuticals, Inc. under NDA 013217), that has been discontinued, was not discontinued for safety or effectiveness reasons. In addition, the undersigned submits this application to request permission for approval of an abbreviated new drug application (ANDA) in the event that the listed drug was discontinued for reasons other than concerns with its safety and effectiveness.

A. Action Requested

The petitioner (CorePharma, LLC) requests that the Commissioner of the Food and Drug Administration determine whether Skelaxin® 400 mg, NDA 013217, manufactured by King Pharmaceuticals, Inc has been voluntarily withdrawn from sale for safety and efficacy reasons.

B. Statement of Grounds

The Food and Drug Administration's Orange Book (http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempno.cfm) updated through July 2013 lists Skelaxin® 400 mg (NDA 013217) as a discontinued drug. According to information received online at FDA's Drug Approval Databases website (http://www.fda.gov/Drugs/InformationOnDrugs/ucm091535.htm) under Additions/Deletions for Prescription and OTC Drug Product Lists, this product was discontinued as of May 2005. Copies of online web pages are enclosed.

Under FDA Regulations, the Agency must make a determination as to whether a listed drug is withdrawn from sale for reasons of safety and effectiveness before an ANDA referencing the listed drug may be approved (21 CFR 314.161 (a)(1)).

CorePharma, LLC has no information or evidence concerning the reason that King Pharmaceuticals, Inc. discontinued marketing Skelaxin® 400 mg, but nonetheless contends that the reasons were unrelated to safety and effectiveness. Skelaxin® 800 mg remains listed in the Orange Book (http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempno.cfm) as a Rx (Prescription Drug Product) under the same NDA 013217. In addition, as per the current labeling, Skelaxin® 800 mg is a scored tablet. This allows the tablet to be divided. This further supports our position that Skelaxin ® 400 mg could not have been discontinued because of safety and efficacy. CorePharma, LLC petitions FDA to determine that King Pharmaceutical Inc.'s decision to discontinue Skelaxin® 400 mg was for reasons other than safety or effectiveness. A copy of the online web page and the current labeling of Skelaxin® 800 mg are enclosed.

2013-8006
CP

FDA-2013-P-1199

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C. Environmental Impact

A claim for categorical exclusion of the requirement for submission of an environmental assessment or environmental impact statement is made pursuant to 21 CFR 25.31.

D. Economic Impact

In accordance with 21 CFR 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition. CorePharma hereby commits to promptly provide this information, if so requested.

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

Kimberly D Ernst

Kimberly D. Ernst
Senior Director, Regulatory Affairs

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Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

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Proprietary Name Search Results from "OB_Disc" table for query on "013217."

Displaying records 1 to 1 of 1

Download data

Appl No	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N013217	METAXALONE	TABLET; ORAL	400MG	SKELAXIN	KING PHARMS

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METAXALONE

TABLET; ORAL

SKELAXIN

>D>	JONES PHARMA INC	400MG	N13217 001	May	DISC
>A>	@	400MG	N13217 001	May	DISC

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Start Over[6] | Back to Search Page

Proprietary Name Search Results from "OB_Rx" table for query on "013217."

Displaying records 1 to 1 of 1

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Appl No	TE Code[7]	RLD[8]	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
N013217	AB	Yes	METAXALONE	TABLET; ORAL	800MG	SKELAXIN	KING PHARMS

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U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
Ph. 1-888-INFO-FDA (1-888-463-6332)
Email FDA

Links on this page:

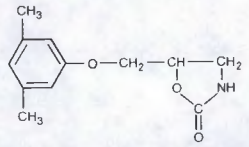
SKELAXIN®

(Metaxalone) Tablets

DESCRIPTION

SKELAXIN® (metaxalone) is available as an 800 mg oval, scored pink tablet.

Chemically, metaxalone is 5-[(3,5- dimethylphenoxy) methyl]-2-oxazolidinone. The empirical formula is $C_{12}H_{15}NO_3$, which corresponds to a molecular weight of 221.25. The structural formula is:



Metaxalone is a white to almost white, odorless crystalline powder freely soluble in chloroform, soluble in methanol and in 96% ethanol, but practically insoluble in ether or water.

Each tablet contains 800 mg metaxalone and the following inactive ingredients: alginic acid, ammonium calcium alginate, B-Rose Liquid, corn starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

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

Pharmacokinetics:

The pharmacokinetics of metaxalone have been evaluated in healthy adult volunteers after single dose administration of SKELAXIN under fasted and fed conditions at doses ranging from 400 mg to 800 mg.

Absorption

Peak plasma concentrations of metaxalone occur approximately 3 hours after a 400 mg oral dose under fasted conditions. Thereafter, metaxalone concentrations decline log-linearly with a terminal half-life of 9.0 ± 4.8 hours. Doubling the dose of SKELAXIN from 400 mg to 800 mg results in a roughly proportional increase in metaxalone exposure as indicated by peak plasma concentrations (C_{max}) and area under the curve (AUC). Dose proportionality at doses above 800 mg has not been studied. The absolute bioavailability of metaxalone is not known.

The single-dose pharmacokinetic parameters of metaxalone in two groups of healthy volunteers are shown in Table 1.

Table 1: Mean (%CV) Metaxalone Pharmacokinetic Parameters

Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	AUC_∞ (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
400[1]	983 (53)	3.3 (35)	7479 (51)	9.0 (53)	68 (50)
800[2]	1816 (43)	3.0 (39)	15044 (46)	8.0 (58)	66 (51)

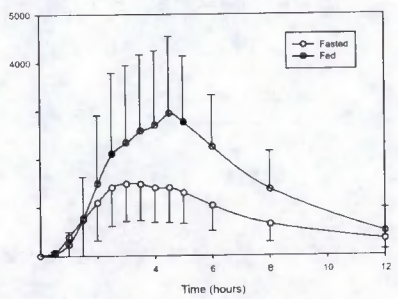
[1]Subjects received 1x400 mg tablet under fasted conditions (N=42)
[2]Subjects received 2x400 mg tablets under fasted conditions (N=59)

Food Effects

A randomized, two-way, crossover study was conducted in 42 healthy volunteers (31 males, 11 females) administered one 400 mg SKELAXIN tablet under fasted conditions and following a standard high-fat breakfast. Subjects ranged in age from 18 to 48 years (mean age = 23.5 ± 5.7 years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased C_{max} by 177.5% and increased AUC (AUC_{0-t}, AUC_∞) by 123.5% and 115.4%, respectively. Time-to-peak concentration (T_{max}) was also delayed (4.3 h *versus* 3.3 h) and terminal half-life was decreased (2.4 h *versus* 9.0 h) under fed conditions compared to fasted.

In a second food effect study of similar design, two 400 mg SKELAXIN tablets (800 mg) were administered to healthy volunteers (N=59, 37 males, 22 females), ranging in age from 18-50 years (mean age = 25.6 ± 8.7 years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased C_{max} by 193.6% and increased AUC (AUC_{0-t}, AUC_∞) by 146.4% and 142.2%, respectively. Time-to-peak concentration (T_{max}) was also delayed (4.9 h *versus* 3.0 h) and terminal half-life was decreased (4.2 h *versus* 8.0 h) under fed conditions compared to fasted conditions. Similar food effect results were observed in the above study when one SKELAXIN 800 mg tablet was administered in place of two SKELAXIN 400 mg tablets. The increase in metaxalone exposure coinciding with a reduction in half-life may be attributed to more complete absorption of metaxalone in the presence of a high fat meal (Figure 1).

Figure ions of Metaxalone follo ing an
800 mg Dose under Fasted and Fed Con ions



Distribution, Metabolism, and Excretion

Although plasma protein binding and absolute bioavailability of metaxalone are not known, the apparent volume of distribution (V/F ~ 800 L) and lipophilicity (log P = 2.42) of metaxalone suggest that the drug is extensively distributed in the tissues. Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites. Hepatic Cytochrome P450 enzymes play a role in the metabolism of metaxalone. Specifically, CYP1A2, CYP2D6, CYP2E1, and CYP3A4 and, to a lesser extent, CYP2C8, CYP2C9, and CYP2C19 appear to metabolize metaxalone.

Metaxalone does not significantly inhibit major CYP enzymes such as CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Metaxalone does not significantly induce major CYP enzymes such as CYP1A2, CYP2B6, and CYP3A4 *in vitro*.

Pharmacokinetics in Special Populations

Age: The effects of age on the pharmacokinetics of metaxalone were determined following single administration of two 400 mg tablets (800 mg) under fasted and fed conditions. The results were analyzed separately, as well as in combination with the results from three other studies. Using the combined data, the results indicate that the pharmacokinetics of metaxalone are significantly more affected by age under fasted conditions than under fed conditions, with bioavailability under fasted conditions increasing with age.

The bioavailability of metaxalone under fasted and fed conditions in three groups of healthy volunteers of varying age is shown in Table 2.

Table 2: Mean (%CV) Pharmacokinetics Parameters Following Single Administration of Two 400 mg SKELAXIN Tablets (800 mg) under Fasted and Fed Conditions

	Younger Volunteers		Older Volunteers			
Age (years)	25.6 ± 8.7		39.3 ± 10.8		71.5 ± 5.0	
N	59		21		23	
Food	Fasted	Fed	Fasted	Fed	Fasted	Fed
C_{max} (ng/mL)	1816 (43)	3510 (41)	2719 (46)	2915 (55)	3168 (43)	3680 (59)
T_{max} (h)	3.0 (39)	4.9 (48)	3.0 (40)	8.7 (91)	2.6 (30)	6.5 (67)
AUC_{0-t} (ng·h/mL)	14531 (47)	20683 (41)	19836 (40)	20482 (37)	23797 (45)	24340 (48)
AUC_∞ (ng·h/mL)	15045 (46)	20833 (41)	20490 (39)	20815 (37)	24194 (44)	24704 (47)

Gender: The effect of gender on the pharmacokinetics of metaxalone was assessed in an open label study, in which 48 healthy adult volunteers (24 males, 24 females) were administered two SKELAXIN 400 mg tablets (800 mg) under fasted conditions. The bioavailability of metaxalone was significantly higher in females compared to males as evidenced by C_{max} (2115 ng/mL *versus* 1335 ng/mL) and AUC_∞ (17884 ng·h/mL *versus* 10328 ng·h/mL). The mean half-life was 11.1 hours in females and 7.6 hours in males. The apparent volume of distribution of metaxalone was approximately 22% higher in males than in females, but not significantly different when adjusted for body weight. Similar findings were also seen when the previously described combined dataset was used in the analysis.

Hepatic/Renal Insufficiency: The impact of hepatic and renal disease on the pharmacokinetics of 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.

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.

Taking SKELAXIN with food may enhance general CNS depression; elderly patients may be especially susceptible to this CNS effect. (See **CLINICAL PHARMACOLOGY: Pharmacokinetics and PRECAUTIONS: Information for Patients** section).

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

The sedative effects of SKELAXIN and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) may be additive. Therefore, caution should be exercised with patients who take more than one of these CNS depressants simultaneously.

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 metaxalone, particularly in combination with antidepressants, and have been reported with this class of drug in combination with 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 one 800 mg tablet three to four times a day.

HOW SUPPLIED

SKELAXIN (metaxalone) is 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 60793-136-01) and in bottles of 500 (NDC 60793-136-05).

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

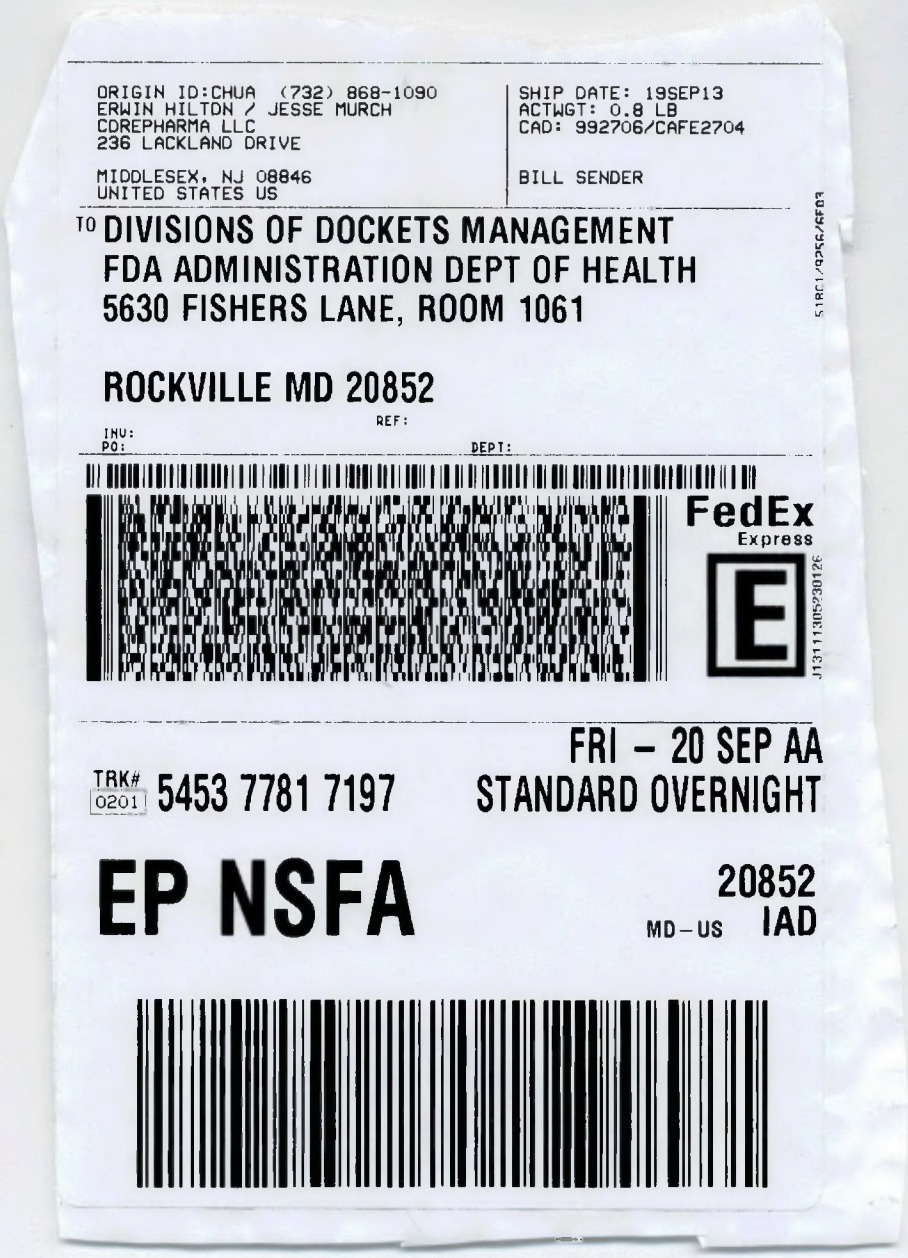
Rx Only

Prescribing Information as of April 2008.

King Pharmaceuticals

Distributed by: King Pharmaceuticals, Inc., Bristol, TN 37620
Manufactured by: Mallinckrodt Inc., Hobart, NY 13788

3000846-F



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