

**METAXALONE- metaxalone tablet  
DIRECT RX**

---

**METAXALONE**

Metaxalone tablets, USP are available as an 800 mg tablet.

Chemically, metaxalone is 5-[(3,5-dimethylphenoxy)methyl]-2-oxazolidinone. The empirical formula is C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>, which corresponds to a molecular weight of 221.25. The structural formula is:

[Chemical Structure]

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: corn starch, alginic acid, acacia, sodium starch glycolate, magnesium stearate and FD&C red No. 40 aluminum lake.

**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 metaxalone tablets 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 metaxalone tablets from 400 mg to 800 mg results in a roughly proportional increase in metaxalone exposure as indicated by peak plasma concentrations (C<sub>max</sub>) 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

\*

Subjects received 1x400 mg tablet under fasted conditions (N=42)

†

Subjects received 2x400 mg tablets under fasted conditions (N=59)

Dose (mg)

C<sub>max</sub> (ng/mL)

Tmax (h)

AUC $\infty$  (ng•h/mL)

T1/2 (h)

CL/F (L/h)

400\*

983 (53)

3.3 (35)

7479 (51)

9.0 (53)

68 (50)

800†

1816 (43)

3.0 (39)

15044 (46)

8.0 (58)

66 (51)

### Food Effects

A randomized, two-way, crossover study was conducted in 42 healthy volunteers (31 males, 11 females) administered one 400 mg metaxalone tablet under fasted conditions and following a standard high-fat breakfast. Subjects ranged in age from 18 to 48 years (mean age =  $23.5 \pm 5.7$  years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased Cmax by 177.5% and increased AUC (AUC0-t, AUC $\infty$ ) by 123.5% and 115.4%, respectively. Time-to-peak concentration (Tmax) 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 metaxalone tablets (800 mg) were administered to healthy volunteers (N=59, 37 males, 22 females), ranging in age from 18 to 50 years (mean age =  $25.6 \pm 8.7$  years). Compared to fasted conditions, the presence of a high fat meal at the time of drug administration increased Cmax by 193.6% and increased AUC (AUC0-t, AUC $\infty$ ) by 146.4% and 142.2%, respectively. Time-to-peak concentration (Tmax) 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 metaxalone 800 mg tablet was administered in place of two metaxalone 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 1. Mean (SD) Concentrations of Metaxalone Following an 800 mg Dose Under Fasted and Fed Conditions

[Figure 1]

## Distribution, Metabolism and Excretion

Although plasma protein binding and absolute bioavailability of metaxalone are not known, the apparent volume of distribution ( $V/F \sim 800$  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 Metaxalone Tablets (800 mg) Under Fasted and Fed Conditions

Younger Volunteers

Older Volunteers

Age (years)

$25.6 \pm 8.7$

$39.3 \pm 10.8$

$71.5 \pm 5.0$

N

59

21

23

Food

Fasted

Fed

Fasted

Fed

Fasted

Fed

Cmax

(ng/mL)

1816

3510

2719

2915

3168

3680

(43)

(41)

(46)

(55)

(43)

(59)

Tmax (h)

3.0

4.9

3.0

8.7

2.6

6.5

(39)

(48)

(40)

(91)

(30)

(67)

AUC0-t

(ng·h/mL)

14531

20683

19836

20482

23797

24340

(47)

(41)

(40)

(37)

(45)

(48)

$AUC_{\infty}$

(ng·h/mL)

15045

20833

20490

20815

24194

24704

(46)

(41)

(39)

(37)

(44)

(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 metaxalone 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  $AUC_{\infty}$  (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, metaxalone tablets should be used with caution in patients with hepatic and/or renal impairment.

Metaxalone tablets are 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.

Known hypersensitivity to any components of this product.

Known tendency to drug induced, hemolytic or other anemias.

Significantly impaired renal or hepatic function.

Metaxalone tablets may enhance the effects of alcohol and other CNS depressants.

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 metaxalone tablets 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).

#### Information for Patients

Metaxalone tablets 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 metaxalone tablets 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.

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.

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 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.

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

Metaxalone Tablets, USP, for oral administration, are available as

800 mg

Rose-colored, capsule-shaped tablets, debossed "E 448" on one side and scored on the other side

Dispense contents in a tight, light-resistant container as defined in the USP with a child-resistant closure, as required.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

KEEP TIGHTLY CLOSED.

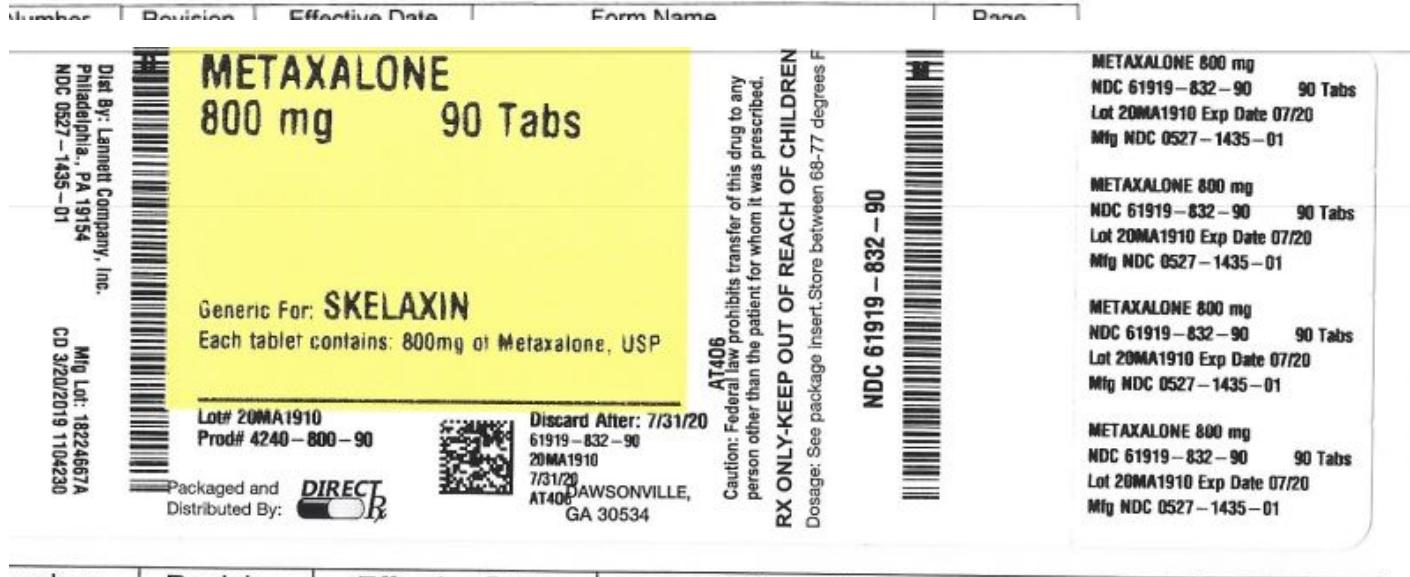
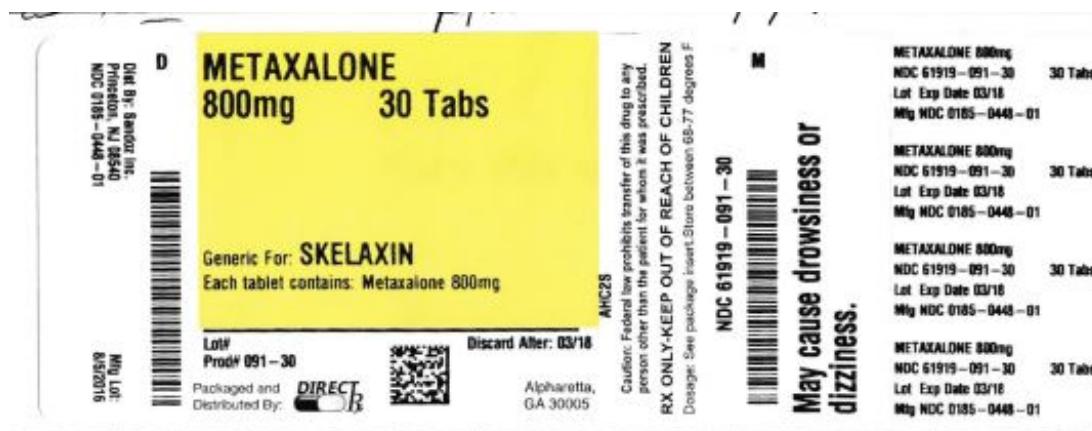
To report SUSPECTED ADVERSE REACTIONS, contact Sandoz Inc. at 1-800-525-8747 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

Manufactured by Sandoz Inc., Princeton, NJ 08540

Rev. May 2016

46188486

MF0448REV05/16



<b>METAXALONE</b>			
metaxalone tablet			
<b>Product Information</b>			
<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:61919-091(NDC:0185-0448)
<b>Route of Administration</b>	ORAL		

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>METAXALONE</b> (UNII: 1NMA9J598Y) (METAXALONE - UNII:1NMA9J598Y)	METAXALONE	800 mg

## Inactive Ingredients

Ingredient Name	Strength
<b>ACACIA</b> (UNII: 5C5403N26O)	
<b>FD&amp;C RED NO. 40</b> (UNII: WZB9127XOA)	
<b>STARCH, CORN</b> (UNII: O8232NY3SJ)	
<b>SODIUM STARCH GLYCOLATE TYPE A POTATO</b> (UNII: 5856J3G2A2)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>ALGINIC ACID</b> (UNII: 8C3Z4148WZ)	

## Product Characteristics

<b>Color</b>	pink	<b>Score</b>	2 pieces
<b>Shape</b>	CAPSULE	<b>Size</b>	19mm
<b>Flavor</b>		<b>Imprint Code</b>	E448
<b>Contains</b>			

## Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-091-30	30 in 1 BOTTLE; Type 0: Not a Combination Product	02/22/2017	12/31/2023

## Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA040445	02/22/2017	12/31/2023

## METAXALONE

metaxalone tablet

## Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:61919-832(NDC:0527-1435)
<b>Route of Administration</b>	ORAL		

## Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
-----------------	-------------------	----------

**Inactive Ingredients**

Ingredient Name	Strength
<b>SILICON DIOXIDE</b> (UNII: ETJ7Z6XBU4)	
<b>FD&amp;C RED NO. 40</b> (UNII: WZB9127XOA)	
<b>ALUMINUM OXIDE</b> (UNII: LMI26O6933)	
<b>HYDROGENATED CASTOR OIL</b> (UNII: ZF94AP8MEY)	
<b>CARBOXYMETHYLCELLULOSE SODIUM</b> (UNII: K679OBS311)	
<b>ALGINIC ACID</b> (UNII: 8C3Z4148WZ)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>SODIUM LAURYL SULFATE</b> (UNII: 368GB5141J)	
<b>STEARIC ACID</b> (UNII: 4ELV7Z65AP)	

**Product Characteristics**

<b>Color</b>	pink	<b>Score</b>	2 pieces
<b>Shape</b>	OVAL (capsule-shaped)	<b>Size</b>	19mm
<b>Flavor</b>		<b>Imprint Code</b>	LCI;1435
<b>Contains</b>			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-832-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	05/03/2019	

**Marketing Information**

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204770	05/03/2019	

**Labeler** - DIRECT RX (079254320)**Registrant** - DIRECT RX (079254320)**Establishment**

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	repack(61919-091) , relabel(61919-832)