METAXALONE- metaxalone tablet
Preferred Pharmaceuticals Inc.

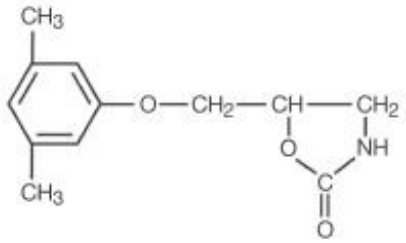
Metaxalone Tablets, USP

Rx Only

DESCRIPTION

Metaxalone Tablets, USP are available as an 800 mg capsule-shaped, scored white to off-white tablet.

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



Metaxalone, USP 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, USP and the following inactive ingredients: alginic acid, ammonium alginate, calcium alginate, corn starch, magnesium stearate and pregelatinized starch (starch 1500 partially pregelatinized maize starch).

USP Dissolution Test Pending.

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 (CNS) 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 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 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)	**t½** (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)

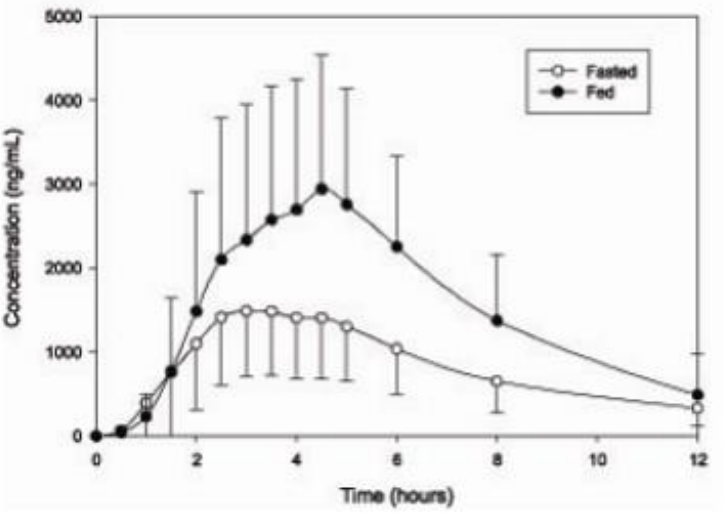
[1]Subjects received 1x400 mg tablet under fasted conditions (N=42)
[2]Subjects received 2x400 mg tablets under fasted conditions (N=59)

Food Effects

A randomized, two-way, crossover study was conducted in 42 healthy volunteers (31 males, 11 females) administered one 400 mg 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 ± 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 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± 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 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



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) Pharmacokinetic 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 ± 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 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∞ (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 should be used with caution in patients with hepatic and/or renal impairment.

INDICATIONS AND USAGE

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.

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

Serotonin Syndrome

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of serotonergic drugs with metaxalone used within the recommended dosage range (see **PRECAUTIONS: Drug Interactions**) and with metaxalone as a single agent taken at doses higher than the recommended dose (see **OVERDOSAGE**). Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT_3 receptor antagonists, opioids (particularly fentanyl, meperidine, and methadone), drugs that affect the serotonergic neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), and drugs that impair metabolism of serotonin (including monoamine oxidase (MAO) inhibitors, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue) (see **PRECAUTIONS: Drug Interactions**).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms generally occurs within several hours to a few days, but may occur later than that. Discontinue metaxalone if serotonin syndrome is suspected.

Risks from Concomitant Use with Alcohol or other CNS Depressants

The sedative effects of metaxalone and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants (TCAs)) may be additive. Exercise caution with patients who take more than one of these CNS depressants simultaneously. Follow patients closely for signs and symptoms of respiratory depression and sedation (see **PRECAUTIONS: Drug Interactions**).

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 metaxalone 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

Driving or Operating Heavy Machinery

Metaxalone 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.

Serotonin Syndrome

Inform patients that metaxalone tablets could cause a rare but potentially life-threatening condition resulting from administration of doses higher than the recommended dose or from concomitant administration of serotonergic drugs with metaxalone tablets used within the recommended dosage range. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their healthcare providers if they are taking, or plan to take, serotonergic medications (see **WARNINGS, PRECAUTIONS: Drug Interactions**, and **OVERDOSAGE**).

Drug Interactions

CNS Depressants

The sedative effects of metaxalone and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants (TCAs)) may be additive. Exercise caution with patients who take more than one of these CNS depressants simultaneously. Follow patients closely for signs and symptoms of respiratory depression and sedation (see **WARNINGS**).

Serotonergic Drugs

Serotonin syndrome has resulted from concomitant use of serotonergic drugs with metaxalone used within the recommended dosage range (see **WARNINGS**). If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue metaxalone if serotonin syndrome is suspected.

Examples of serotonergic drugs include: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT_3 receptor antagonists, opioids (particularly fentanyl, meperidine, and methadone), drugs that affect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

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: anaphylaxis, hypersensitivity reaction, rash with or without pruritus;

Hematologic: leukopenia; hemolytic anemia;

Hepatobiliary: jaundice;

CNS: cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of serotonergic drugs with metaxalone used within the recommended dosage range and with metaxalone as a single agent taken at doses higher than the recommended dose (see **WARNINGS, PRECAUTIONS: Drug Interactions**, and **OVERDOSAGE**).

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-888-838-2872 or FDA at 1-800-FDA-1088 www.fda.gov/medwatch.

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.

Serotonin syndrome has been reported when metaxalone was used at doses higher than the recommended dose (see **WARNINGS** and **ADVERSE REACTIONS**).

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

Metaxalone Tablets, USP are available as an 800 mg capsule-shaped, scored white to off-white tablet, inscribed with “**31 90**” on the scored side and “**WPI**” on the other side. Metaxalone tablets USP, 800 mg has functional scoring.

Bottles of 30 NDC 68788-7018-3
Bottles of 60 NDC 68788-7018-6
Bottles of 90 NDC 68788-7018-9
Bottles of 100 NDC 68788-7018-1
Bottles of 120 NDC 68788-7018-8

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

Manufactured by:
Actavis Laboratories FL, Inc.
Fort Lauderdale, FL 33314 USA

Distributed by:
Actavis Pharma, Inc.
Parsippany, NJ 07054 USA

Rev. A 5/2020

PRINCIPAL DISPLAY PANEL

NDC 68788-7018

Metaxalone Tablets, USP

800 mg

SEALED FOR YOUR PROTECTION.

Actavis

Rx Only

Repackaged By: Preferred Pharmaceuticals Inc.

METAXALONE

metaxalone tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68788-7018(NDC:0591-2341)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
METAXALONE (UNII: 1NMA9J598Y) (METAXALONE - UNII:1NMA9J598Y)	METAXALONE	800 mg

Inactive Ingredients	
Ingredient Name	**Strength**
ALGINIC ACID (UNII: 8C3Z4148WZ)	
AMMONIUM ALGINATE (UNII: Q9QKJ39Q3X)	
CALCIUM ALGINATE (UNII: 8P20S56HZI)	
STARCH, CORN (UNII: O8232NY3SJ)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE (white to off-white)	**Score**	2 pieces
Shape	OVAL (capsule-shaped)	**Size**	19mm
Flavor		**Imprint Code**	31;90;WPI
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**

1	NDC:68788-7018-1	15 in 1 BOTTLE; Type 0: Not a Combination Product	10/11/2017	
2	NDC:68788-7018-2	20 in 1 BOTTLE; Type 0: Not a Combination Product	10/11/2017	
3	NDC:68788-7018-3	30 in 1 BOTTLE; Type 0: Not a Combination Product	10/11/2017	
4	NDC:68788-7018-6	60 in 1 BOTTLE; Type 0: Not a Combination Product	10/11/2017	
5	NDC:68788-7018-0	100 in 1 BOTTLE; Type 0: Not a Combination Product	10/11/2017	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203695	10/11/2017	

Labeler - Preferred Pharmaceuticals Inc. (791119022)

Registrant - Preferred Pharmaceuticals Inc. (791119022)

Establishment

Name	Address	ID/FEI	Business Operations
Preferred Pharmaceuticals Inc.		791119022	REPACK(68788-7018)

Revised: 7/2024 Preferred Pharmaceuticals Inc.