

METAXALONE- metaxalone tablet

Amneal Pharmaceuticals of New York LLC

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use METAXALONE TABLETS safely and effectively. See full prescribing information for METAXALONE TABLETS.

METAXALONE tablets, for oral use

Initial U.S. Approval: 1962

RECENT MAJOR CHANGES

Dosage and Administration (2) 06/2024

INDICATIONS AND USAGE

Metaxalone is a muscle relaxant indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions in adults and pediatric patients 13 years of age and older. (1)

DOSAGE AND ADMINISTRATION

- Recommended dosage of metaxalone in adults and pediatric patients 13 years of age and older is two 400 mg tablets (800 mg) orally three to four times a day. (2)
- Metaxalone tablets two 400 mg or one 800 mg are not substitutable on a mg to mg basis with metaxalone tablets, 640 mg. When it is appropriate to switch, see the Full Prescribing Information on switching instructions. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 400 mg peach, round, compressed tablets, debossed “cor” over “126” on one side and the other side is plain. (3)

CONTRAINDICATIONS

- Known hypersensitivity to any components of this product. (4)
- Known tendency to drug induced, hemolytic, or other anemias. (4)
- Severe renal or hepatic impairment. (4)

WARNINGS AND PRECAUTIONS

- Serotonin Syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of metaxalone (within the recommended dosage range) and other serotonergic drugs and with the use of metaxalone as the only serotonergic drug taken at a dosage higher than the recommended dosage. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dosage increases. Discontinue metaxalone if serotonin syndrome is suspected or it occurs. (5.1,7.1)
- Central Nervous System (CNS) Depression: Metaxalone may impair mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a motor vehicle, especially when used with other CNS depressants including alcohol. Follow patients closely for signs and symptoms of respiratory depression and sedation. If concomitant use is warranted, closely monitor for signs of respiratory depression and sedation, particularly during treatment initiation and dosage increases. (5.2, 7.2)

ADVERSE REACTIONS

Most common adverse reactions (incidence > 5%) are nausea and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Geriatric Use: Metaxalone-treated geriatric patients may be especially susceptible to CNS depression. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 8/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Metaxalone tablets are indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults and pediatric patients 13 years of age and older.

2 DOSAGE AND ADMINISTRATION

The recommended dosage of metaxalone in adults and pediatric patients 13 years of age and older is two 400 mg tablets (800 mg) orally three to four times a day [see *Use in Specific Populations (8)*].

Metaxalone tablets two 400 mg or one 800 mg are not substitutable on a mg to mg basis with metaxalone tablets, 640 mg [see *Clinical Pharmacology (12.3)*]. When it is appropriate to switch:

- Switch only in patients who have been taking metaxalone tablets, 640 mg on an empty stomach.
- Stop metaxalone tablets, 640 mg three times a day and start metaxalone tablets two 400 mg or one 800 mg three times a day on an empty stomach, OR stop metaxalone tablets 640 mg four times a day and start metaxalone tablets two 400 mg or one 800 mg four times a day on an empty stomach.

Do not switch from metaxalone tablets, 640 mg to metaxalone tablets two 400 mg or one 800 mg when the patient is taking food during administration.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 400 mg peach, round, compressed tablets, debossed “cor” over “126” on one side and the other side is plain.

4 CONTRAINDICATIONS

Metaxalone is contraindicated in patients with:

- Known hypersensitivity to any component of metaxalone.
- Known tendency to drug induced, hemolytic, or other anemias.
- Severe renal or hepatic impairment.

5 WARNINGS AND PRECAUTIONS

5.1 Serotonin Syndrome

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of metaxalone (within the recommended dosage range) and other serotonergic drugs [see *Drug Interactions (7)*] and with the use of metaxalone as the only serotonergic drug taken at a dosage higher than the recommended dosage [see *Overdosage (10)*].

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 after initiation of a serotonergic drug, but may occur later than that.

If concomitant use of metaxalone and another serotonergic drug is warranted, reassess the patient, particularly during treatment initiation and dosage increases. Discontinue metaxalone if serotonin syndrome is suspected or it occurs.

5.2 Central Nervous System Depression

Because of its central nervous system (CNS) depressant effects, 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 other CNS depressants including alcohol. Geriatric patients may be especially susceptible to CNS depression associated with metaxalone use. When used concomitantly, the sedative effects of metaxalone and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) may be additive [see *Drug Interactions (7)*].

Follow metaxalone-treated patients closely for signs and symptoms of respiratory depression and sedation. If concomitant use of metaxalone and another CNS depressant is warranted, closely monitor for signs of respiratory depression and sedation, particularly during treatment initiation and dosage increases.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of metaxalone were identified in clinical studies or post-marketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The most frequent reactions to metaxalone were:

- CNS: drowsiness, dizziness, headache, and nervousness or "irritability".
- Digestive: nausea, vomiting, gastrointestinal upset.

Other adverse reactions were:

- CNS: cases of serotonin syndrome have been reported during concomitant use of metaxalone (within the recommended dosage range) and other serotonergic drugs and with the use of metaxalone as the only serotonergic drug at a dosage higher than the recommended dosage [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.1)* and *Overdosage (10)*].
- Hematologic: leukopenia; hemolytic anemia;
- Hepatobiliary: jaundice;
- Immune System: anaphylaxis, hypersensitivity reaction, rash with or without pruritus.

7 DRUG INTERACTIONS

7.1 Serotonergic Drugs

If concomitant use of metaxalone and another serotonergic drug is warranted, carefully observe the patient, particularly during treatment initiation and dosage modification. Discontinue metaxalone if serotonin syndrome is suspected or if it occurs.

Serotonin syndrome has resulted from concomitant use of metaxalone (within the recommended dosage range) with other serotonergic drugs [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6)*].

Serotonergic drugs include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT₃ 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).

7.2 CNS Depressants

If concomitant use of metaxalone and another CNS depressant is warranted, closely monitor for signs of respiratory depression and sedation, particularly during treatment initiation and dosage increases.

Due to the additive pharmacologic effect, concomitant use of metaxalone with other CNS depressants may increase the risk of sedation and respiratory depression [see *Warnings and Precautions (5.2)*].

7.3 Interaction of Metaxalone with Benedict's Tests

False-positive Benedict's tests, due to an unknown reducing substance, have been noted in metaxalone-treated patients. A glucose-specific test will differentiate findings.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on metaxalone use in pregnant patients to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes despite decades of metaxalone use. Reproduction studies in rats have not revealed effects on the fetus due to metaxalone.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

8.2 Lactation

Risk Summary

There are no data available to evaluate the presence of metaxalone or its metabolite in either human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for metaxalone and any potential adverse effects on the breastfed infant from metaxalone or from the underlying maternal condition.

8.4 Pediatric Use

Metaxalone is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions in pediatric patients 13 years of age and older. The safety and effectiveness of metaxalone in pediatric patients 12 years of age or younger have not been established.

8.5 Geriatric Use

Clinical studies of metaxalone did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger adult patients.

Geriatric patients may be especially susceptible to CNS depression associated with metaxalone use [see *Warnings and Precautions (5.2)*].

The recommended metaxalone dosage in patients 65 years of age and older is the same as in younger adult patients. Metaxalone peak plasma concentrations (C_{max}) and area under the curve (AUC) were higher in patients 65 years of age and older in the fasted state; however, a clinically significant difference was not observed when metaxalone was administered in the fed state [see *Clinical Pharmacology (12.3)*].

8.6 Hepatic Impairment

Metaxalone is contraindicated in patients with severe hepatic impairment. Metaxalone should be used with caution and additional follow-up should be considered in patients with mild to moderate hepatic impairment. The effect of hepatic impairment on metaxalone pharmacokinetics is unknown; however, metaxalone undergoes extensive hepatic metabolism [see *Clinical Pharmacology (12.3)*].

8.7 Renal Impairment

Metaxalone is contraindicated in patients with severe renal impairment. Metaxalone should be used with caution and additional follow-up should be considered in patients with mild to moderate renal impairment. The effect of renal impairment on metaxalone pharmacokinetics is unknown; however, metaxalone undergoes renal excretion as unidentified metabolites [see *Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

Clinical Presentation of Metaxalone Overdose

Deaths by deliberate or accidental overdose have occurred with metaxalone, particularly in combination with other CNS depressants (including alcohol). CNS manifestations may include CNS depression, agitation, hallucinations, delusions, seizures, respiratory depression, and coma. Cardiovascular effects may include tachycardia and hypertension; hypotension has also been reported. Serotonin syndrome, leading to muscle rigidity, tremor, and hyperthermia, has been reported [see *Warnings and Precautions (5.1)*, *Drug Interactions (7.1, 7.2)*].

Treatment of Metaxalone Overdose

The standard of treatment is supportive care. Monitor for CNS and respiratory depression and manage airway with oxygen as needed. Gastrointestinal decontamination procedures (including emesis) should generally be avoided because aspiration may result from CNS depression and seizures. Extracorporeal elimination such as hemodialysis or plasmapheresis have no proven clinical benefit.

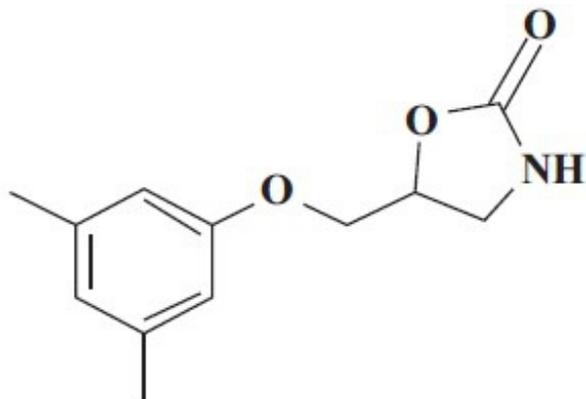
Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

Metaxalone tablets, USP contain 400 mg of metaxalone and the following inactive ingredients: alginic acid, FD&C Yellow No. 06 Aluminum Lake, lactose monohydrate, magnesium stearate, povidone and propylene glycol alginate.

Metaxalone is a muscle relaxant for oral administration.

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 g/mol. The structural formula is:



Metaxalone, USP is a white to almost white, crystalline powder freely soluble in chloroform, soluble in methanol and in alcohol, but practically insoluble in ether and in water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Metaxalone's mechanism of action has not been fully characterized, but may be related to its sedative properties. Metaxalone has no direct action on the contractile mechanism of striated muscle, the motor end plate, or the nerve fiber.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of metaxalone not been fully characterized.

12.3 Pharmacokinetics

Metaxalone pharmacokinetics were evaluated in two groups of healthy volunteers that received a single oral dose of 800 mg of metaxalone or 400 mg of metaxalone (0.5 times the approved recommended dose). Metaxalone pharmacokinetic parameters are presented below as mean (% CV) unless otherwise specified. Observed metaxalone peak plasma concentrations (C_{max}) and area under the curve (AUC) are shown in Table 1. Doubling the dose of metaxalone from 400 mg (0.5 times the approved recommended dose) to 800 mg resulted in a proportional increase in metaxalone C_{max} and AUC.

Table 1: Metaxalone Exposure after a Single-Dose of Metaxalone Under Fasting Conditions

Dose	C _{max} ²	AUC _∞ ²
400 mg ¹	983 (53) ng/mL	7,479 (51) ng•h/mL
800 mg	1,816 (43) ng/mL	15,044 (46) ng•h/mL

¹ 0.5 times the approved recommended dose
² Mean (% CV)

Absorption

The absolute bioavailability of metaxalone is not known. Peak plasma metaxalone concentrations occurred at a mean T_{max} of 3.3 hours (1.5 – 5 hours) of metaxalone under fasted conditions.

The single-dose pharmacokinetic parameters of metaxalone in two groups of healthy volunteers who received 400 mg or 800 mg of metaxalone are shown in Table 1.

Effect of Food: Peak plasma metaxalone concentrations were noted at a mean T_{max} of 4.3 hours (1.5 to 12 hours) under fed conditions. The mean T_{max} under fasting and fed conditions was 3.3 and 4.3 hours, respectively. Metaxalone exposure was increased and the half-life (t_{1/2}) was decreased following metaxalone administration with a high fat meal as shown in Table 2. 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.

Table 2: Relative Changes in Metaxalone Exposure, T_{max}, and t_{1/2} Following Metaxalone Administration with a High Fat Meal Compared to Fasting

Dose	C _{max} (ng/mL)	AUC _{0-t} (ng•h/mL)	AUC _{0-INF} (ng•h/mL)	T _{max} (hrs)	t _{1/2} (hrs)
400 mg*	↑ 78%	↑ 24%	↑ 15%	↑ 30%	↓ 73%
800 mg	↑ 94%	↑ 46%	↑ 42%	↑ 63%	↓ 48%

*0.5 times the approved recommended dose.

Distribution

Metaxalone apparent volume of distribution is approximately 800 Liters; however, plasma protein binding is unknown.

Elimination

Metaxalone mean ± SD terminal t_{1/2} is 9 ± 4.8 hours and apparent clearance is approximately 67 ± 34 L/h under fasted conditions.

Metabolism: Metaxalone is primarily metabolized by CYP1A2, CYP2D6, CYP2E1, and CYP3A4 and, to a lesser extent, CYP2C8, CYP2C9, and CYP2C19.

Excretion: Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites.

Specific Populations

The effect of renal impairment and hepatic impairment on metaxalone pharmacokinetics is unknown [see *Use in Specific Populations (8.6, 8.7)*].

Geriatric Patients: The effects of age on the pharmacokinetics of metaxalone were determined following administration of 800 mg of metaxalone under fasted and fed conditions. Age had a significantly greater effect on metaxalone pharmacokinetics under fasted conditions than under fed conditions. Bioavailability under fasted conditions increased with age. Metaxalone bioavailability under fasted and fed conditions in the three groups of healthy volunteers of varying age is shown in Table 3.

Table 3: Metaxalone Pharmacokinetic Parameters under Fasted and Fed Conditions in Three Age Groups Following Oral Administration of 800 mg of Metaxalone

Mean Age in Years (\pm SD)	26 \pm 9 Years Old		39 \pm 11 Years Old		72 \pm 5 Years Old	
	Fasted	Fed	Fasted	Fed	Fasted	Fed
C_{max} (ng/mL) ¹	1,816 (43)	3,510 (41)	2,719 (46)	2,915 (55)	3,168 (43)	3,680 (59)
T_{max} (hours) ¹	3 (39)	4.9 (4.8)	3 (40)	8.7 (91)	2.6 (30)	6.5 (67)
AUC_{0-t} (ng•h/mL) ¹	14,531 (47)	20,683 (41)	19,836 (40)	20,482 (37)	23,797 (45)	24,340 (48)
AUC_{∞} (ng•h/mL) ¹	15,045 (46)	20,833 (41)	20,490 (39)	20,815 (37)	24,194 (44)	24,704 (47)

¹ Mean values (% CV)

Male and Female Patients: The exposure of metaxalone was significantly higher in females compared to males as evidenced by C_{max} (2,115 ng/mL versus 1,335 ng/mL) and AUC_{∞} (17,884 ng•h/mL versus 10,328 ng•h/mL) following administration of 800 mg of metaxalone under fasted conditions. 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.

Drug Interaction Studies

In Vitro Studies: Metaxalone does not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Metaxalone does not induce CYP1A2, CYP2B6, and CYP3A4.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of metaxalone have not been

conducted. Studies to evaluate the mutagenic potential of metaxalone have not been conducted. No effects on fertility were observed in rats administered metaxalone.

16 HOW SUPPLIED/STORAGE AND HANDLING

Metaxalone Tablets USP, **400 mg** are supplied as peach, round, compressed tablets, debossed “**cor**” over “**126**” on one side and the other side is plain.

They are available as follows:

Bottles of 100: NDC 0115-1745-01

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

17 PATIENT COUNSELING INFORMATION

Serotonin Syndrome

Inform patients that metaxalone could cause a rare but potentially life-threatening condition called serotonin syndrome. 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 drugs [see *Warnings and Precautions (5.1)* and *Drugs Interactions (7.1)*].

Central Nervous System Depression

Advise patients that 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 and other CNS depressants [see *Drug Interactions (7.2)*].

Manufactured by:

Amneal Pharmaceuticals Pvt. Ltd.

Ahmedabad 382220, INDIA

Distributed by:

Amneal Pharmaceuticals LLC

Bridgewater, NJ 08807

Rev. 08-2024-01

PRINCIPAL DISPLAY PANEL

NDC 0115-1745-01

Metaxalone Tablets, USP 400 mg

100's count

Amneal Pharmaceuticals LLC

NDC 0115-1745-01

Metaxalone Tablets, USP

400 mg

SEALED FOR YOUR PROTECTION



Rx only
100 Tablets



Each Tablet Contains:

Metaxalone, USP 400 mg

USUAL DOSAGE: The recommended dose for adults and children over 12 years of age is two 400 mg tablets (800 mg) three to four times a day. See package insert for prescribing information.

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

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

Manufactured by: **Amneal Pharmaceuticals Pvt. Ltd.**
Ahmedabad 382220, INDIA

Distributed by: **Amneal Pharmaceuticals LLC**
Bridgewater, NJ 08807

Mfg. Lic. No. G/25/1941

Rev. 07-2021-00



Non-Varnish Area
(For Lot And Exp. Date)
(22 X 45 mm)

METAXALONE

metaxalone tablet

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:0115-1745
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
METAXALONE (UNII: 1NMA9J598Y) (METAXALONE - UNII:1NMA9J598Y)	METAXALONE	400 mg

Inactive Ingredients

Ingredient Name	Strength
ALGINIC ACID (UNII: 8C3Z4148WZ)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE K30 (UNII: U725QWY32X)	
PROPYLENE GLYCOL ALGINATE (UNII: 26CD3J2R0C)	

Product Characteristics

Color	orange (Peach)	Score	no score
Shape	ROUND	Size	11mm
Flavor		Imprint Code	cor;126
Contains			

Packaging

		Marketing Start	Marketing End
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#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0115-1745-01	100 in 1 BOTTLE; Type 0: Not a Combination Product	05/26/2016	
Marketing Information				
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date	
ANDA	ANDA040486	05/26/2016		

Labeler - Amneal Pharmaceuticals of New York LLC (123797875)

Revised: 8/2024

Amneal Pharmaceuticals of New York LLC