

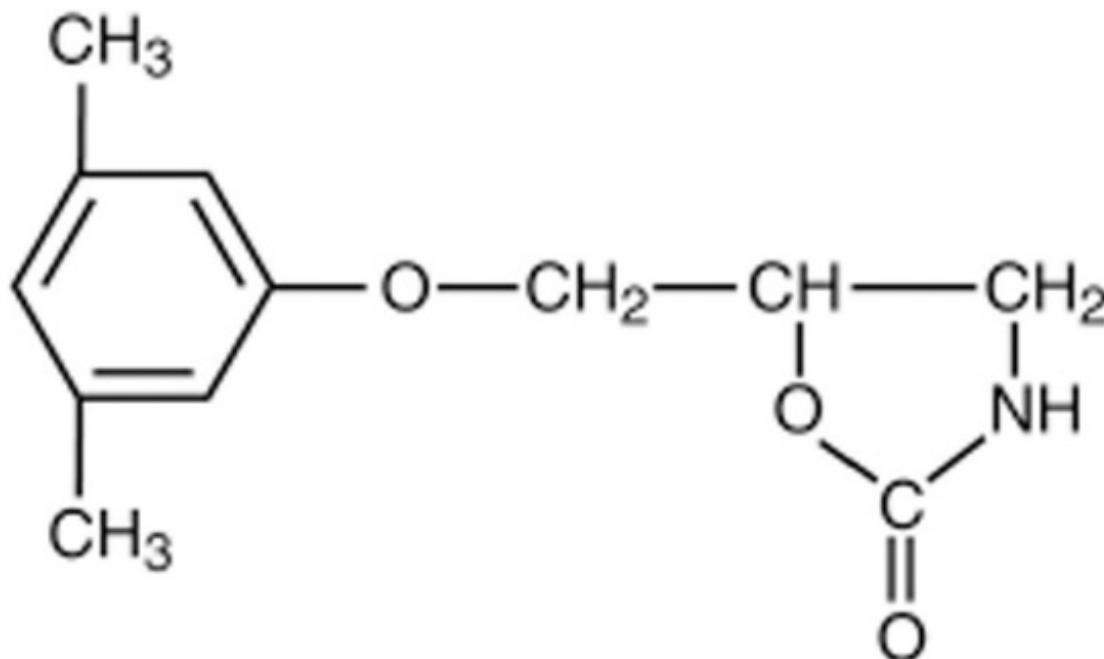
**METAXALONE- metaxalone tablet**  
**American Health Packaging**

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**Metaxalone Tablets, USP**  
**8213521/0419**  
**Rx only**

**DESCRIPTION**

Metaxalone tablets, USP is available as an 800 mg, light pink to pink, capsule shaped, scored uncoated 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, 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: calcium carbonate, FD&C Red #40, hypromellose, lactose monohydrate, microcrystalline cellulose, povidone, silicone dioxide, sodium starch glycolate and sodium stearyl fumarate.

**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  $9.0 \pm 4.8$  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)	$AUC_{\infty}$ (ng•h/mL)	$t_{1/2}$ (h)	CL/F (L/h)
400 *	983 (53)	3.3 (35)	7,479 (51)	9.0 (53)	68 (50)
800 †	1,816 (43)	3.0 (39)	15,044 (46)	8.0 (58)	66 (51)

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

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

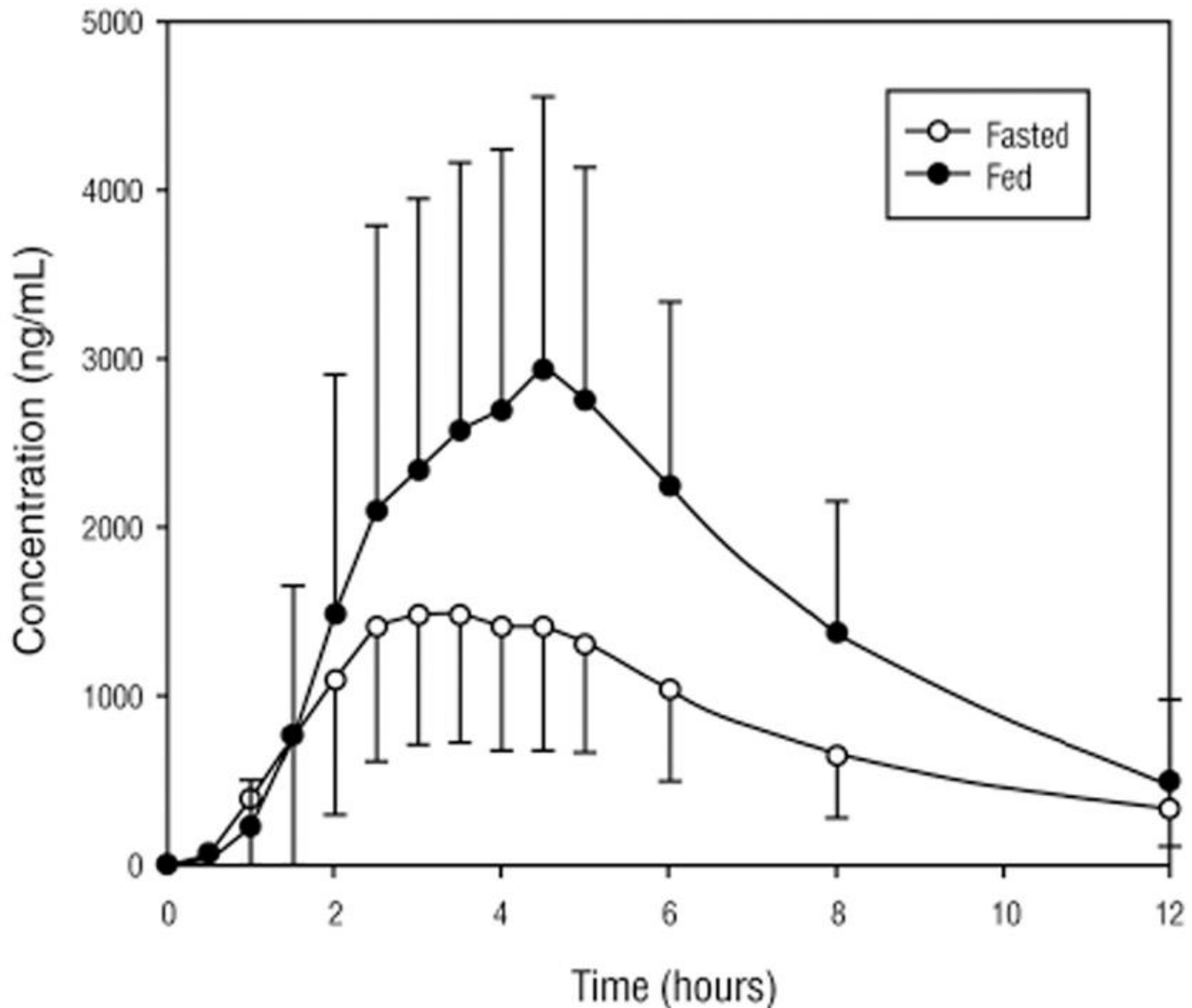
### Food Effects

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 =  $23.5 \pm 5.7$  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 ( $AUC_{0-t}$ ,  $AUC_{\infty}$ ) 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 =  $25.6 \pm 8.7$  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 ( $AUC_{0-t}$ ,  $AUC_{\infty}$ ) 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 ( $V/F \sim 800$  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) Pharmacokinetic Parameters Following Single Administration of Two 400 mg Metaxalone Tablets (800 mg) under Fasted and Fed Conditions**

	<b>Younger Volunteers</b>		<b>Older Volunteers</b>			
<b>Age</b> (years)	25.6 ± 8.7		39.3 ± 10.8		71.5 ± 5.0	
<b>N</b>	59		21		23	
<b>Food</b>	Fasted	Fed	Fasted	Fed	Fasted	Fed
<b>C<sub>max</sub></b> (ng/mL)	1,816 (43)	3,510 (41)	2,719 (46)	2,915 (55)	3,168 (43)	3,680 (59)
<b>T<sub>max</sub></b> (h)	3.0 (39)	4.9 (48)	3.0 (40)	8.7 (91)	2.6 (30)	6.5 (67)
<b>AUC<sub>0-t</sub></b> (ng·h/mL)	14,531 (47)	20,683 (41)	19,836 (40)	20,482 (37)	23,797 (45)	24,340 (48)
<b>AUC<sub>∞</sub></b> (ng·h/mL)	15,045 (46)	20,833 (41)	20,490 (39)	20,815 (37)	24,194 (44)	24,704 (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<sub>max</sub> (2,115 ng/mL *versus* 1,335 ng/mL) and AUC<sub>∞</sub> (17,884 ng·h/mL *versus* 10,328 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 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

### 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<sub>3</sub> 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 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 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<sub>3</sub> 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 Amneal Pharmaceuticals at 1-877-835-5472 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://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<sub>50</sub> in rats and mice, progressive sedation, hypnosis and finally

respiratory failure were noted as the dosage increased. In dogs, no LD<sub>50</sub> 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 is available as **800 mg**, light pink to pink, capsule shaped, scored uncoated tablet with debossing 'AN' on the left side of the scoring and '553' on the right side of the scoring. Other side of the tablet is plain.

They are available as follows:

Unit dose packages of 30 (3 x 10) NDC 68084-135-21

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

**FOR YOUR PROTECTION:** Do not use if blister is torn or broken.

## **PACKAGING INFORMATION**

American Health Packaging unit dose blisters (see How Supplied section) contain drug product from BluePoint Laboratories as follows:

(800 mg / 30 UD) NDC 68084-135-21 packaged from NDC 68001-004

Distributed by:

**American Health Packaging**

Columbus, OH 43217

**8213521/0419**

**Package/Label Display Panel - Carton - 800 mg**



NDC 68084-135-21

# Metaxalone

Tablets, USP

**800 mg**

30 Tablets (3 x 10)

Rx Only



NDC 68084-135-21

# Metaxalone

Tablets, USP

**800 mg**

30 Tablets (3 x 10)

Rx Only

**Each Tablet Contains:**

Metaxalone, USP.....800 mg

**Usual Dosage:** The recommended dose for adults and children over 12 years of age is one tablet (800 mg) three to four times a day. See package insert for full prescribing information.

**Store** at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

**Keep this and all drugs out of reach of children.**

**FOR YOUR PROTECTION:** Do not use if blister is torn or broken.

The drug product contained in this package is from NDC # 68001-004, BluePoint Laboratories.

Packaged and Distributed by:  
American Health Packaging  
Columbus, Ohio 43217

013521  
0213521/0419

NDC 68084- 135-21

## Metaxalone

Tablets, USP

**800 mg**

**30 Tablets (3 x 10)**

**Rx Only**

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Metaxalone, USP ..... 800 mg

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The drug product contained in this package is from

NDC # 68001-004, BluePoint Laboratories.

Packaged and Distributed by:  
American Health Packaging  
Columbus, Ohio 43217

013521  
0213521/0419

### Package/Label Display Panel - Blister - 800 mg

Metaxalone  
Tablet, USP  
800 mg  
  
(01) 003 68084 135 11 8  
American Health Packaging, Columbus, Ohio 43217

Expiry: xx/xx  
Lot: xxxxxxx

Expiry: xx/xx  
Lot: xxxxxxx


Metaxalone  
Tablet, USP  
800 mg  
  
(01) 003 68084 135 11 8  
American Health Packaging, Columbus, Ohio 43217

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Expiry: xx/xx  
Lot: xxxxxxx

Metaxalone  
Tablet, USP  
800 mg  
  
(01) 003 68084 135 11 8  
American Health Packaging, Columbus, Ohio 43217

Metaxalone  
Tablet, USP

**800 mg**

## METAXALONE

metaxalone tablet

### Product Information

#### Product Type

HUMAN PRESCRIPTION  
DRUG

#### Item Code (Source)

NDC:68084-135(NDC:68001-  
004)

#### Route of Administration

ORAL

**Active Ingredient/Active Moiety**

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

**Inactive Ingredients**

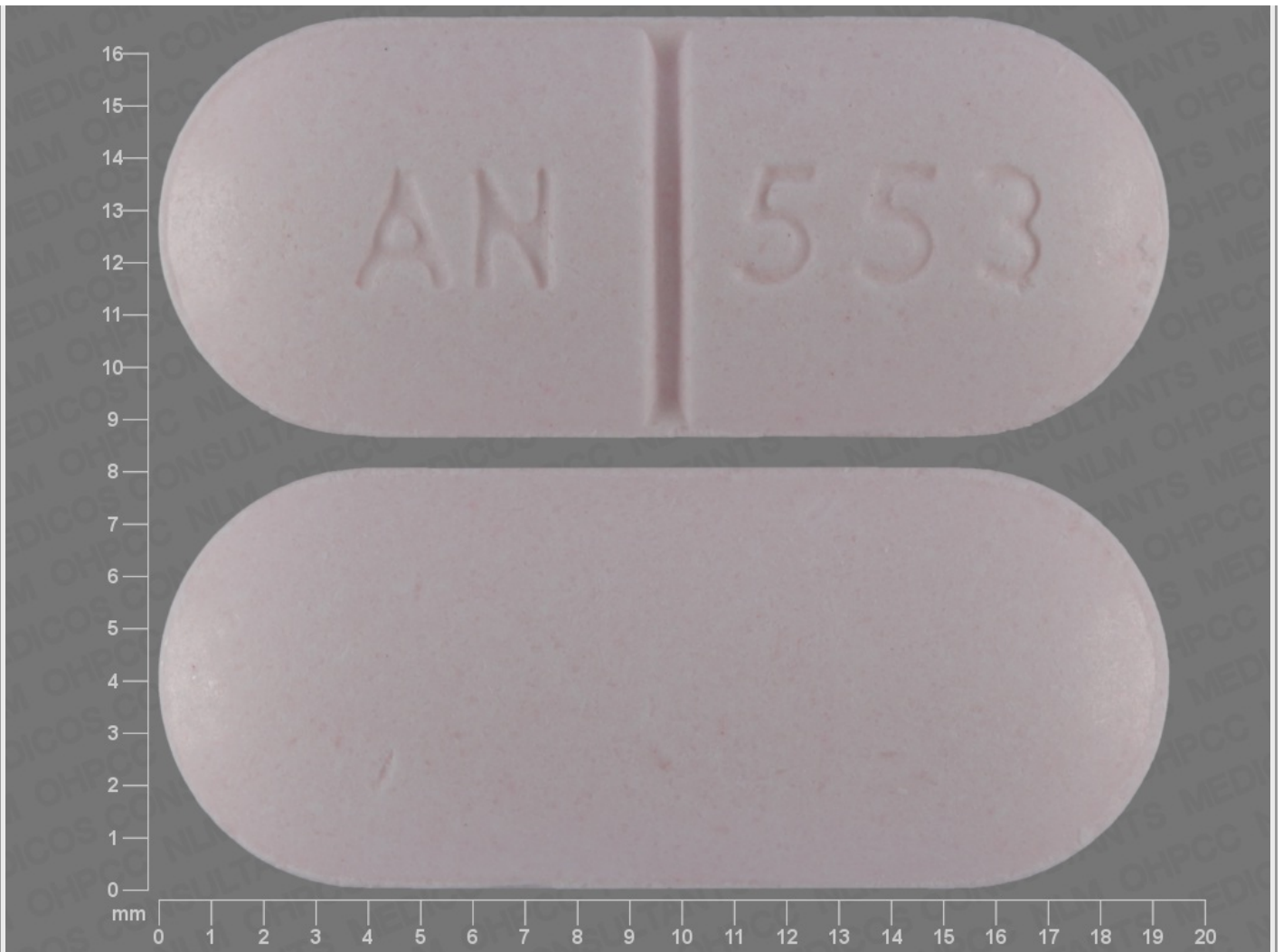
Ingredient Name	Strength
<b>CALCIUM CARBONATE</b> (UNII: H0G9379FGK)	
<b>FD&amp;C RED NO. 40</b> (UNII: WZB9127XOA)	
<b>HYPROMELLOSE, UNSPECIFIED</b> (UNII: 3NXW29V3WO)	
<b>LACTOSE MONOHYDRATE</b> (UNII: EWQ57Q8I5X)	
<b>MICROCRYSTALLINE CELLULOSE</b> (UNII: OP1R32D61U)	
<b>POVIDONE, UNSPECIFIED</b> (UNII: FZ989GH94E)	
<b>SILICON DIOXIDE</b> (UNII: ETJ7Z6XBU4)	
<b>SODIUM STARCH GLYCOLATE TYPE A POTATO</b> (UNII: 5856J3G2A2)	
<b>SODIUM STEARYL FUMARATE</b> (UNII: 7CV7WJK4UI)	

**Product Characteristics**

<b>Color</b>	pink (light pink to pink)	<b>Score</b>	2 pieces
<b>Shape</b>	CAPSULE	<b>Size</b>	19mm
<b>Flavor</b>		<b>Imprint Code</b>	AN;553
<b>Contains</b>			

**Packaging**

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68084-135-21	30 in 1 BOX, UNIT-DOSE	12/09/2013	07/31/2023
1	NDC:68084-135-11	1 in 1 BLISTER PACK; Type 0: Not a Combination Product		



### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA203399	12/09/2013	07/31/2023

**Labeler** - American Health Packaging (929561009)

### Establishment

Name	Address	ID/FEI	Business Operations
American Health Packaging		929561009	repack(68084-135)

Revised: 10/2022

American Health Packaging