HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use METAXOLONE TABLETS safely and effectively. See full prescribing information for METAXOLONE TABLETS

Metaxalone tablets, for oral use
Initial U.S. Approval: 1962

RECENT MAJOR CHANGES

Contraindications (4)	02/2022
Warnings and Precautions (5.1)	02/2022

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

The recommended dose for adults and pediatric patients 13 years of age and older is one 640 mg tablet three to four times a day. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 640 mg. (3)

CONTRAINDICATIONS

- Known hypersensitivity to any components of this product. (4)
- Known tendency to drug induced, hemolytic, or other anemias. (4)
- Patients with severely impaired renal or hepatic functions. (4)

WARNINGS AND PRECAUTIONS

- 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 and with metaxalone as a single agent taken at doses higher than the recommended dose. (5.1)
- Central Nervous System (CNS) Depression: Metaxalone Tablets may impair mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a motor vehicle, and may enhance the effects of alcohol and other CNS depressants. (5.2)
- Hepatic and Renal Impairment: Metaxalone Tablets should be administered with caution to patients with mild to moderate hepatic and renal impairment. (5.3)

ADVERSE REACTIONS

The most common adverse reactions to Metaxalone Tablets include drowsiness, dizziness, headache, and nervousness or "irritability", nausea, vomiting, gastrointestinal upset. (6)

Serotonin Syndrome: a potentially life-threatening condition, has 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. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Primus Pharmaceuticals, Inc. at 1-877-526-4040 and www.primusrx.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

CNS depressants: Use with caution. The sedative effects of Metaxalone Tablets and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) may be additive. (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

The recommended dose for adults and pediatric patients 13 years of age and older is one 640 mg tablet three to four times a day.

3 DOSAGE FORMS AND STRENGTHS

Metaxalone Tablet is available as a 640 mg oval, peach-colored tablet, debossed on one side with **M640** and plain on the other side.

4 CONTRAINDICATIONS

The use of Metaxalone Tablets is contraindicated in the following conditions:

- Known hypersensitivity to any components of this product.
- Known tendency to drug-induced, hemolytic, or other anemias.
- Patients with severely impaired renal or hepatic function.

5 WARNINGS AND PRECAUTIONS

5.1 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 Drug Interactions (7)]* and with metaxalone as a single agent taken at doses higher than the recommended dose *[See Overdosage (10)]*. 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) *[See Drug Interactions (7)]*.

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 Tablets if serotonin syndrome is suspected.

5.2 Central Nervous System (CNS) Depression

Metaxalone Tablets may enhance the effects of alcohol and other CNS depressants (e.g., benzodiazepines,

opioids, tricyclic antidepressants) and 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. Therefore, Metaxalone Tablets should be used with caution in patients who take one or more of these CNS depressants. *[See Drug Interactions (7)]* Elderly patients may be especially susceptible to CNS effects.

5.3 Hepatic and Renal Impairment Patients

Metaxalone Tablets are metabolized by the liver and excreted in the urine. Use caution when administering Metaxalone Tablets in patients with mild to moderate hepatic or renal impairment. Consider monitoring of liver and renal function in these patients. Metaxalone Tablets are contraindicated in patients with severe hepatic or renal impairment *[See Contraindications (4) and Use in Specific Populations (8.6, 8.7)]*.

6 ADVERSE REACTIONS

The most frequent reactions to Metaxalone Tablets 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: leucopenia; 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 and Precautions (5.1), Drug Interactions (7), and Overdosage (10)]*.
Anaphylactoid reactions have been reported with metaxalone.

7 DRUG INTERACTIONS

CNS Depressants

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.

Serotonergic Drugs

Serotonin syndrome has resulted from concomitant use of serotonergic drugs with metaxalone used within the recommended dosage range *[See Warnings and Precautions (5.3)]*. If concomitant use is warranted, carefully observe the patient, particularly during treatment initiation and dose adjustment. Discontinue Metaxalone Tablets 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-HT3 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).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on metaxalone use in pregnant women 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 evidence of impaired fertility or harm to 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 on 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

Safety and effectiveness in children 12 years of age and below have not been established.

8.5 Geriatric Use

The effects of age on the pharmacokinetics of Metaxalone Tablets have not been evaluated.

8.6 Hepatic Impairment

Formal pharmacokinetic studies using Metaxalone Tablets have not been conducted in patients with hepatic impairment. Since metaxalone undergoes hepatic metabolism, Metaxalone Tablets should be used with caution in patients with mild to moderate hepatic impairment. Metaxalone Tablets are contraindicated in patients with severe hepatic impairment. *[See Contraindications (4) and Warnings and Precautions (5.3)]*

8.7 Renal Impairment

Formal pharmacokinetic studies using Metaxalone Tablets have not been conducted in patients with renal impairment. Since metaxalone is excreted in the urine as unidentified metabolites, Metaxalone Tablets should be used with caution in patients with mild to moderate renal impairment. Metaxalone Tablets are contraindicated in patients with severe renal impairment. *[See Contraindications (4) and Warnings and Precautions (5.3)]*

10 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.

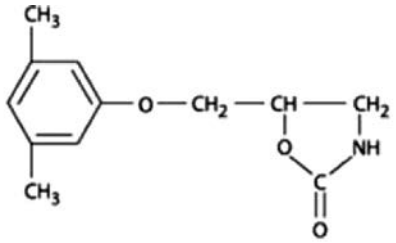
Serotonin syndrome has been reported when metaxalone was used at doses higher than the recommended dose *[See Warnings and Precautions (5.1) and Adverse Reactions (6)]*.

Treatment – Gastric lavage and supportive therapy. Consultation with a regional poison control center is recommended.

11 DESCRIPTION

Metaxalone Tablet is a muscle relaxant available as a 640 mg oval, peach-colored tablet, debossed on one side with **M640** and plain on the other side. The tablets are for oral administration. Each tablet contains 640 mg metaxalone and the following inactive ingredients: alginic acid, FD&C yellow #6, lactose monohydrate, magnesium stearate, propylene glycol alginate and povidone.

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.

12. CLINICAL PHARMACOLOGY

12.1 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.

12.3 Pharmacokinetics

Absorption

In a relative bioavailability study in healthy adult volunteers, the C_{max} (peak plasma concentration) and AUC (extent of absorption) values of metaxalone from Metaxalone Tablets, 640 mg were found to be similar to those from Skelaxin® 800 mg tablets. After a single dose of Metaxalone Tablets, 640 mg, under fasted conditions, mean C_{max} and AUC values were 2 mcg/mL and 16 mcg.h/mL, respectively. The time-to-peak plasma concentration (T_{max}) occurred at 3 h (range 1.5-12h). The plasma half-life in adult healthy subjects was about 5 hours after administration of Metaxalone Tablets.

Effect of Food: Compared to fasted condition, the presence of a high fat meal resulted in 23% increase in C_{max} with no change in AUC, and a T_{max} of 8h (range 3.5-24h).

Distribution

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.

Elimination

Metabolism
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*.

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

Specific Populations

Age: The effects of age on the pharmacokinetics of Metaxalone Tablets have not been evaluated.

Gender: Females exhibited higher systemic exposure compared to males following administration of Metaxalone Tablets under fasted state in healthy volunteers. The C_{max} and AUC were both found to be about 40% greater in females compared to males.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Mutagenesis
Studies to evaluate the mutagenic potential of metaxalone have not been conducted.

Impairment of Fertility
Reproduction studies in rats have not revealed evidence of impaired fertility or harm to the fetus due to metaxalone.

14 CLINICAL STUDIES

Efficacy studies were not conducted with Metaxalone Tablets. The efficacy of Metaxalone Tablets, 640 mg is based on demonstration of similar systemic exposures to the reference drug, Skelaxin® 800 mg tablets [see *Clinical Pharmacology (12.3)]*.

16 HOW SUPPLIED/STORAGE AND HANDLING

Metaxalone Tablets, 640 mg are available as oval, peach-colored tablets, debossed on one side with **M640** and plain on the other side. It is packaged as:

Bottle of 100 tablets, NDC 68040-712-38

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

17 PATIENT COUNSELING INFORMATION

Driving or Operating Heavy Machinery
Advise patients that 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 and other CNS depressants. Elderly patients may be especially susceptible to CNS effects.

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.

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