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

SOMA (carisoprodol) Tablets for Oral use
Initial U.S. Approval: 1959

----------**RECENT MAJOR CHANGES**----------
Indications and Usage (1) 9/2007
Dosage and Administration (2) 9/2007

----------**INDICATIONS AND USAGE**----------
SOMA is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions. (1)

Important Limitations:
• Should only be used for acute treatment periods up to two or three weeks (1)
• Not recommended in pediatric patients less than 16 years of age (8.4)
----------**DOSAGE AND ADMINISTRATION**---------
• Recommended dose is 250 mg to 350 mg three times a day and at bedtime. (2)
----------**DOSAGE FORMS AND STRENGTHS**-------
Tablets: 250 mg, 350 mg (3)

----------**CONTRAINDICATIONS**----------
•Acute intermittent porphyria (4)
•Hypersensitivity reactions to a carbamate such as meprobamate (4)
----------**WARNINGS AND PRECAUTIONS**----------
• Due to sedative properties, may impair ability to perform hazardous tasks such as driving or operating machinery (5.1)
• Additive sedative effects when used with other CNS depressants including alcohol (5.1)
• Cases of Drug Dependence, Withdrawal, and Abuse (5.2)
• Seizures (5.3)
----------**ADVERSE REACTIONS**----------
Most common adverse reactions (incidence > 2%) are drowsiness, dizziness, and headache (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MedPointe Pharmaceuticals at 1-800-526-3840 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.
----------**DRUG INTERACTIONS**----------
• CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) - additive sedative effects (5.1 and 7.1)

See 17 for PATIENT COUNSELING INFORMATION
revised 9/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SOMA is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions in adults.

SOMA should only be used for short periods (up to two or three weeks) because adequate evidence of effectiveness for more prolonged use has not been established and because acute, painful musculoskeletal conditions are generally of short duration. [*see Dosage and Administration (2)*].

2 DOSAGE AND ADMINISTRATION

The recommended dose of SOMA is 250 mg to 350 mg three times a day and at bedtime. The recommended maximum duration of SOMA use is up to two or three weeks.

3 DOSAGE FORMS AND STRENGTHS

250 mg Tablets: round, convex, white tablets, inscribed with SOMA 250

350 mg Tablets: round, convex, white tablets, inscribed with SOMA 350

4 CONTRAINDICATIONS

SOMA is contraindicated in patients with a history of acute intermittent porphyria or a hypersensitivity reaction to a carbamate such as meprobamate.

5 WARNINGS AND PRECAUTIONS

5.1 Sedation

SOMA may have sedative properties (in the low back pain trials, 13% to 17% of patients who received SOMA experienced sedation compared to 6% of patients who received placebo) [*see ADVERSE REACTIONS (6.1)*] and may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a motor vehicle or operating machinery.

Since the sedative effects of SOMA and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) may be additive, appropriate caution should be exercised with patients who take more than one of these CNS depressants simultaneously.

5.2 Drug Dependence, Withdrawal, and Abuse

In the postmarketing experience with SOMA, cases of dependence, withdrawal, and abuse have been reported with prolonged use. Most cases of dependence, withdrawal, and abuse occurred in patients who have had a history of addiction or who used SOMA in combination with other drugs with abuse potential. Withdrawal symptoms have been reported following abrupt cessation after prolonged use. To reduce the chance of SOMA dependence, withdrawal, or abuse, SOMA should be used with caution in addiction-prone patients and in patients taking other CNS depressants including alcohol, and SOMA should be not be used more than two to three weeks for the relief of acute musculoskeletal discomfort.

One of the metabolites of SOMA, meprobamate (a controlled substance), may cause dependence [*see Clinical Pharmacology (12.3)]*.

5.3 Seizures

There have been postmarketing reports of seizures in patients who received SOMA. Most of these cases have occurred in the setting of multiple drug overdoses (including drugs of abuse, illegal drugs, and alcohol*) [see Overdosage (10)]*.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect rates observed in practice.

The data described below are based on 1387 patients pooled from two double blind, randomized, multicenter, placebo controlled, one-week trials in adult patients with acute, mechanical, lower back pain [*see Clinical Studies (14)*]. In these studies, patients were treated with 250 mg of SOMA, 350 mg of SOMA, or placebo three times a day and at bedtime for seven days. The mean age was about 41 years old with 54% females and 46% males and 74 % Caucasian, 16 % Black, 9% Asian, and 2% other.

There were no deaths and there were no serious adverse reactions in these two trials. In these two studies, 2.7%, 2%, and 5.4%, of patients treated with placebo, 250 mg of SOMA, and 350 mg of SOMA, respectively, discontinued due to adverse events; and 0.5%, 0.5%, and 1.8% of patients treated with placebo, 250 mg of SOMA, and 350 mg of SOMA, respectively, discontinued due to central nervous system adverse reactions.

Table 1 displays adverse reactions reported with frequencies greater than 2% and more frequently than placebo in patients treated with SOMA in the two trials described above.

Table 1: Patients with Adverse Reactions in Controlled Studies

Adverse Reaction	Placebo (n=560) n (%)	SOMA 250 mg (n=548) n (%)	SOMA 350 mg (n=279) n (%)
Drowsiness	31 (6)	73 (13)	47 (17)
Dizziness	11 (2)	43 (8)	19 (7)
Headache	11 (2)	26 (5)	9 (3)

6.2 Postmarketing Experience

The following events have been reported during postapproval use of SOMA. Because these reactions are 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.

Cardiovascular Tachycardia, postural hypotension, and facial flushing [*see Overdosage (10)*].

Central Nervous System Drowsiness, dizziness, vertigo, ataxia, tremor, agitation, irritability, headache, depressive reactions, syncope, insomnia, and seizures [*see Overdosage (10)*].

Gastrointestinal Nausea, vomiting, and epigastric discomfort.

Hematologic Leukopenia, pancytopenia

7 DRUG INTERACTIONS

7.1 CNS Depressants

The sedative effects of SOMA 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. Concomitant use of SOMA and meprobamate, a metabolite of SOMA, is not recommended [*see Warnings and Precautions (5.1)*].

7.2 CYP2C19 Inhibitors and Inducers

Carisoprodol is metabolized in the liver by CYP2C19 to form meprobamate [*see Clinical Pharmacology (12.3)*]. Co-administration of CYP2C19 inhibitors, such as omeprazole or fluvoxamine, with SOMA could result in increased exposure of carisoprodol and decreased exposure of meprobamate. Co-administration of CYP2C19 inducers, such as rifampin or St. John's Wort, with SOMA could result in decreased exposure of carisoprodol and increased exposure of meprobamate. Low dose aspirin also showed an induction effect on CYP2C19. The full pharmacological impact of these potential alterations of exposures in terms of either efficacy or safety of SOMA is unknown.

8 USE IN SPECIFIC POPULATION

8.1 Pregnancy: Pregnancy Category C.

There are no data on the use of SOMA during human pregnancy. Animal studies indicate that carisoprodol crosses the placenta and results in adverse effects on fetal growth and postnatal survival. The primary metabolite of carisoprodol, meprobamate, is an approved anxiolytic. Retrospective, post-marketing studies do not show a consistent association between maternal use of meprobamate and an increased risk for particular congenital malformations.

Teratogenic effects Animal studies have not adequately evaluated the teratogenic effects of carisoprodol. There was no increase in the incidence of congenital malformations noted in reproductive studies in rats, rabbits, and mice treated with meprobamate. Retrospective, post-marketing studies of meprobamate during human pregnancy were equivocal for demonstrating an increased risk of congenital malformations following first trimester exposure. Across studies that indicated an increased risk, the types of malformations were inconsistent.

Nonteratogenic effects In animal studies, carisoprodol reduced fetal weights, postnatal weight gain, and postnatal survival at maternal doses equivalent to 1-1.5 times the human dose (based on a ~~mg/m2~~ body surface area comparison). Rats exposed to meprobamate in-utero showed behavioral alterations that persisted into adulthood. For children exposed to meprobamate in-utero, one study found no adverse effects on mental or motor development or IQ scores. SOMA should be used during pregnancy only if the potential benefit justifies the risk to the fetus.

8.2 Labor and Delivery

There is no information about the effects of SOMA on the mother and the fetus during labor and delivery.

8.3 Nursing Mothers

Very limited data in humans show that SOMA is present in breast milk and may reach concentrations two to four times the maternal plasma concentrations. In one case report, a breast-fed infant received about 4-6% of the maternal daily dose through breast milk and experienced no adverse effects. However, milk production was inadequate and the baby was supplemented with formula. In lactation studies in mice, female pup survival and pup weight at weaning were decreased. This information suggests that maternal use of SOMA may lead to reduced or less effective infant feeding (due to sedation) and/or decreased milk production. Caution should be exercised when SOMA is administered to a nursing woman.

8.4 Pediatric Use

The efficacy, safety, and pharmacokinetics of SOMA in pediatric patients less than 16 years of age have not been established.

8.5 Geriatric Use

The efficacy, safety, and pharmacokinetics of SOMA in patients over 65 years old have not been established.

8.6 Renal Impairment

The safety and pharmacokinetics of SOMA in patients with renal impairment ~~has~~ have not been evaluated. Since SOMA is excreted by the kidney, caution should be exercised if SOMA is administered to patients with impaired renal function. Carisoprodol is dialyzable by hemodialysis and peritoneal dialysis.

8.7 Hepatic Impairment

The safety and pharmacokinetics of SOMA in patients with hepatic impairment ~~has~~ have not been evaluated. Since SOMA is metabolized in the liver, caution should be exercised if SOMA is administered to patients with impaired hepatic function.

8.8 Patients with Reduced CYP2C19 Activity

Patients with reduced CYP2C19 activity have higher exposure to carisoprodol. Therefore, caution should be exercised in administration of SOMA to these patients [*see Clinical Pharmacology (12.3)*].

9 DRUG ABUSE AND DEPENDENCE

[*see Warnings and Precautions (5.2)*]

10 OVERDOSAGE

Overdosage of SOMA commonly produces CNS depression. Death, coma, respiratory depression, hypotension, seizures, delirium, hallucinations, dystonic reactions, nystagmus, blurred vision, mydriasis, euphoria, muscular incoordination, rigidity, and/or headache have been reported with SOMA overdosage. Many of the SOMA overdoses have occurred in the setting of multiple drug overdoses (including drugs of abuse, illegal drugs, and alcohol). The effects of an overdose of SOMA and other CNS depressants (e.g., alcohol, benzodiazepines, opioids, tricyclic antidepressants) can be additive even when one of the drugs has been taken in the

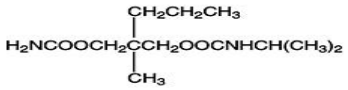
recommended dosage. Fatal accidental and non-accidental overdoses of SOMA have been reported alone or in combination with CNS depressants.

Treatment of Overdosage: Basic life support measures should be instituted as dictated by the clinical presentation of the SOMA overdose. Induced emesis is not recommended due to the risk of CNS and respiratory depression, which may increase the risk of aspiration pneumonia. Gastric lavage should be considered soon after ingestion (within one hour). Circulatory support should be administered with volume infusion and vasopressor agents if needed. Seizures should be treated with intravenous benzodiazepines and the reoccurrence of seizures may be treated with phenobarbital. In cases of severe CNS depression, airway protective reflexes may be compromised and tracheal intubation should be considered for airway protection and respiratory support.

The following types of treatment have been used successfully with an overdose of meprobamate, a metabolite of SOMA: activated charcoal (oral or via nasogastric tube), forced diuresis, peritoneal dialysis, and hemodialysis (carisoprodol is also dialyzable). Careful monitoring of urinary output is necessary and overhydration should be avoided. Observe for possible relapse due to incomplete gastric emptying and delayed absorption. For more information on the management of an overdose of SOMA, **contact a Poison Control Center.**

11 DESCRIPTION

SOMA (carisoprodol) Tablets are available as 250 mg and 350 mg round, white tablets. Carisoprodol is a white, crystalline powder, having a mild, characteristic odor and a bitter taste. It is slightly soluble in water; freely soluble in alcohol, in chloroform, and in acetone; and its solubility is practically independent of pH. Carisoprodol is present as a racemic mixture. Chemically, carisoprodol is N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate and the molecular formula is $C_{12}H_{24}N_2O_4$, with a molecular weight of 260.33. The structural formula is:



Other ingredients in the SOMA drug product include alginic acid, magnesium stearate, potassium sorbate, starch, and tribasic calcium phosphate.

12 CLINCIAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of carisoprodol in relieving discomfort associated with acute painful musculoskeletal conditions has not been clearly identified.

In animal studies, muscle relaxation induced by carisoprodol is associated with altered interneuronal activity in the spinal cord and in the descending reticular formation of the brain.

12.2 Pharmacodynamics

Carisoprodol is a centrally acting skeletal muscle relaxant that does not directly relax skeletal muscles.

A metabolite of carisoprodol, meprobamate, has anxiolytic and sedative properties. The degree to which these properties of meprobamate contribute to the safety and efficacy of SOMA is unknown.

12.3 Pharmacokinetics

The pharmacokinetics of carisoprodol and its metabolite meprobamate were studied in a crossover study of 24 healthy subjects (12 male and 12 female) who received single doses of 250 mg and 350 mg SOMA (see Table 2). The exposure of carisoprodol and meprobamate was dose proportional between the 250 mg and 350 mg doses. The Cmax of meprobamate was 2.5 ± 0.5 µg/mL (mean ± SD) after administration of a single 350 mg dose of SOMA, which is approximately 30% of the Cmax of meprobamate (approximately 8 µg/mL) after administration of a single 400 mg dose of meprobamate.

Table 2. Pharmacokinetic Parameters of Carisoprodol and Meprobamate (Mean ± SD, n=24)

	250 mg SOMA	350 mg SOMA
Carisoprodol		
Cmax (µg/mL)	1.2 ± 0.5	1.8 ± 1.0
AUC_{inf} (µg*hr/mL)	4.5 ± 3.1	7.0 ± 5.0
Tmax (hr)	1.5 ± 0.8	1.7 ± 0.8
$T_{1/2}$ (hr)	1.7 ± 0.5	2.0 ± 0.5
Meprobamate		
Cmax (µg/mL)	1.8 ± 0.3	2.5 ± 0.5
AUC_{inf} (µg*hr/mL)	32 ± 6.2	46 ± 9.0
Tmax (hr)	3.6 ± 1.7	4.5 ± 1.9
$T_{1/2}$ (hr)	9.7 ± 1.7	9.6 ± 1.5

Absorption: Absolute bioavailability of carisoprodol has not been determined. The mean time to peak plasma concentrations (Tmax) of carisoprodol was approximately 1.5 to 2 hours. Co-administration of a high-fat meal with SOMA (350 mg tablet) had no effect on the pharmacokinetics of carisoprodol. Therefore, SOMA may be administered with or without food.

Metabolism: The major pathway of carisoprodol metabolism is via the liver by cytochrome enzyme CYP2C19 to form meprobamate. This enzyme exhibits genetic polymorphism (see Patients with Reduced CYP2C19 Activity below).

Elimination: Carisoprodol is eliminated by both renal and non-renal routes with a terminal elimination half-life of approximately 2 hours. The half-life of meprobamate is approximately 10 hours.

Gender Exposure of carisoprodol is higher in female than in male subjects (approximately 30-50% on a weight adjusted basis). Overall exposure of meprobamate is comparable between female and male subjects.

Patients with Reduced CYP2C19 Activity SOMA should be used with caution in patients with reduced CYP2C19 activity. Published studies indicate that patients who are poor CYP2C19 metabolizers have a 4-fold increase in exposure to carisoprodol, and concomitant 50% reduced exposure to meprobamate compared to normal CYP2C19 metabolizers. The prevalence of poor metabolizers in Caucasians and African Americans is approximately 3-5% and in Asians is approximately 15-20%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term studies in animals have not been performed to evaluate the carcinogenic potential of carisoprodol.

SOMA was not formally evaluated for genotoxicity. In published studies, carisoprodol was mutagenic in the *in vitro* mouse lymphoma cell assay in the absence of metabolizing enzymes, but was not mutagenic in the presence of metabolizing enzymes. Carisoprodol was clastogenic in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells with or without the presence of metabolizing enzymes. Other types of genotoxic tests resulted in negative findings. Carisoprodol was not mutagenic in the Ames reverse mutation assay using *S. typhimurium* strains with or without metabolizing enzymes, and was not clastogenic in an *in vivo* mouse micronucleus assay of circulating blood cells.

SOMA was not formally evaluated for effects on fertility. Published reproductive studies of carisoprodol in mice found no alteration in fertility although an alteration in reproductive cycles characterized by a greater time spent in estrus was observed at a carisoprodol dose of 1200 mg/kg/day. In a 13-week toxicology study that did not determine fertility, mouse testes weight and sperm motility were reduced at a dose of 1200 mg/kg/day. In both studies, the no effect level was 750 mg/kg/day, corresponding to approximately 2.6 times the human equivalent dosage of 350 mg four times a day, based on ~~mg/m^2~~a body surface area comparison. The significance of these findings for human fertility is not known.

14 CLINICAL STUDIES

The safety and efficacy of SOMA for the relief of acute, idiopathic mechanical low back pain was evaluated in two, 7-day, double blind, randomized, multicenter, placebo controlled, U.S. trials (Studies 1 and 2). Patients had to be 18 to 65 years old and had to have acute back pain (≤ 3 days of duration) to be included in the trials. Patients with chronic back pain; at increased risk for vertebral fracture (e.g., history of osteoporosis); with a history of spinal pathology (e.g., herniated nucleus pulposis, spondylolisthesis or spinal stenosis); with inflammatory back pain, or with evidence of a neurologic deficit were excluded from participation. Concomitant use of analgesics (e.g., acetaminophen, NSAIDs, tramadol, opioid agonists), other muscle relaxants, botulinum toxin, sedatives (e.g., barbiturates, benzodiazepines, promethazine hydrochloride), and anti-epileptic drugs was prohibited.

In Study 1, patients were randomized to one of three treatment groups (i.e., SOMA 250 mg, SOMA 350 mg, or placebo) and in Study 2 patients were randomized to two treatment groups (i.e., SOMA 250 mg or placebo). In both studies, patients received study medication three times a day and at bedtime for seven days.

The primary endpoints were the relief from starting backache and the global impression of change, as reported by patients, on ~~study~~ Study ~~day~~ Day #3. Both endpoints were scored on a 5-point rating scale from 0 (worst outcome) to 4 (best outcome) in both studies. The primary statistical comparison was between the SOMA 250 mg and placebo groups in both studies.

The proportion of patients who used concomitant acetaminophen, NSAIDs, tramadol, opioid agonists, other muscle relaxants, and benzodiazepines was similar in the treatment groups.

The results for the primary efficacy evaluations in the acute, low back pain studies are presented in Table 3.

Table 3~~:~~. Results of the Primary Efficacy Endpoints[a] in Studies 1 and 2

Study	Parameter	Placebo	SOMA 250 mg	SOMA 350 mg
1	**Number of Patients**	n=269	n=264	n=273
	Relief from Starting Backache, Mean (SE)[b]	1.4 (0.1)	1.8 (0.1)	1.8 (0.1)
	Difference between SOMA and Placebo, Mean (SE)[b] (95% CI)		0.4 (0.2, 0.5)	0.4 (0.2, 0.6)
	Global Impression of Change, Mean (SE)[b]	1.9 (0.1)	2.2 (0.1)	2.2 (0.1)
	Difference between SOMA and Placebo, Mean (SE)[b] (95% CI)		0.2 (0.1, 0.4)	0.3 (0.1, 0.4)
2	**Number of Patients**	n=278	n=269	
	Relief from Starting Backache, Mean (SE)[b]	1.1 (0.1)	1.8 (0.1)	
	Difference between SOMA and Placebo, Mean (SE)[b] (95% CI)		0.7 (0.5, 0.9)	
	Global Impression of Change, Mean (SE)[b]	1.7 (0.1)	2.2 (0.1)	
	Difference between SOMA and Placebo, Mean (SE)[b] (95% CI)		0.5 (0.4, 0.7)	

a The primary efficacy endpoints (Relief from Starting Backache and Global Impression of Change) were assessed by the patients on Study Day #3. These endpoints were scored on a 5-point rating scale from 0 (worst outcome) to 4 (best outcome).

b Mean is the least squared mean and SE is the standard error of the mean. The ANOVA model was used for the primary statistical comparison between the SOMA 250 mg and placebo groups.

Patients treated with SOMA experienced improvement in function as measured by the Roland-Morris Disability Questionnaire (RMDQ) score on Days 3 and 7.

16 HOW SUPPLIED/STORAGE AND HANDLING

250mg Tablets: round, convex, white tablets, inscribed with SOMA 250; available in bottles of 100 (NDC 0037-2250-10).
350mg Tablets: round, convex, white tablets, inscribed with SOMA 350; available in bottles of 100 (NDC 0037-2001-01).

Storage:

Store at 25 C (77 F); excursions permitted between 15 and 30 C (59 and 86 F) (see USP Controlled Room Temperature).

17 PATIENT COUNSELING INFORMATION

Patients should be advised to contact their physician if they experience any adverse reactions to SOMA.

17.1 Sedation

Since SOMA may cause drowsiness and/or dizziness, patients should be advised to assess their individual response to SOMA before engaging in potentially hazardous activities such as driving a motor vehicle or operating machinery [*see Warnings and Precautions (5.1)*].

17.2 Avoidance of Alcohol and Other CNS Depressants

Patients should be advised to avoid alcoholic beverages while taking SOMA and to check with their doctor before taking other CNS depressants such as benzodiazepines, opioids, tricyclic antidepressants, sedating antihistamines, or other sedatives [*see Warnings and Precautions (5.1)*].

17.3 SOMA Should Only ~~be~~ Be Used for Short-Term Treatment

Patients should be advised that treatment with SOMA should be limited to acute use (up to two or three weeks) for the relief of acute, musculoskeletal discomfort. If symptoms still persist, patients should contact their healthcare provider for further evaluation.

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