CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

11-792/S041

Trade Name: SOMA

Generic Name: carisoprodol

Sponsor: Meda Pharmaceuticals, Inc

Approval Date: 09/13/2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 11-792/s-041

MedPointe Pharmaceutical
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Attention: Michael Bernhard, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Bernhard:

Please refer to your supplemental new drug application dated November 10, 2006, received November 13, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SOMA (carisoprodol), 250 mg Tablets.

We acknowledge receipt of your submissions dated January 9, February 1 and 8, March 2 and 27, April 3, 12, 13, and 24, May 10, June 6 and 14, July 10 and 17, August 8 and 16 and September 4 and 6, 2007.

This supplemental new drug application provides for the use of SOMA (carisoprodol), 250 mg Tablets for the relief of discomfort associated with acute, painful musculoskeletal conditions.

We have completed our review of this application, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with minor editorial revisions indicated in the enclosed labeling.

Content of Labeling

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling text for the package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 11-792/s-041."

Carton and Immediate Container Labels

We acknowledge your July 10, 2007, submission containing final printed carton and container labels.

Marketing this product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Pediatric Research Equity Act (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for this application.

Promotional Materials

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Letters to Health Care Professionals

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

Stability/Shelf Life

An expiration dating period of 36 months is granted for SOMA, 250 tablets.

Reporting Requirements

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Sharon Turner-Rinehardt, Regulatory Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Rigoberto Roca, M.D.
Deputy Director
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosures: Package Insert
Immediate Container Label
Carton Label

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rigoberto Roca

9/13/2007 05:17:47 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

LABELING

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

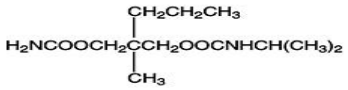
recommended dosage. Fatal accidental and non-accidental overdoses of SOMA have been reported alone or in combination with CNS depressants.

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.

MedPointe Pharmaceuticals
MedPointe Healthcare Inc.
Somerset, NJ 08873

(b) (4)

1/2" Non-varnish Area

0037-2250-10

NDC 0037-2250-10

SOMA® 250 MG

Carisoprodol Tablets

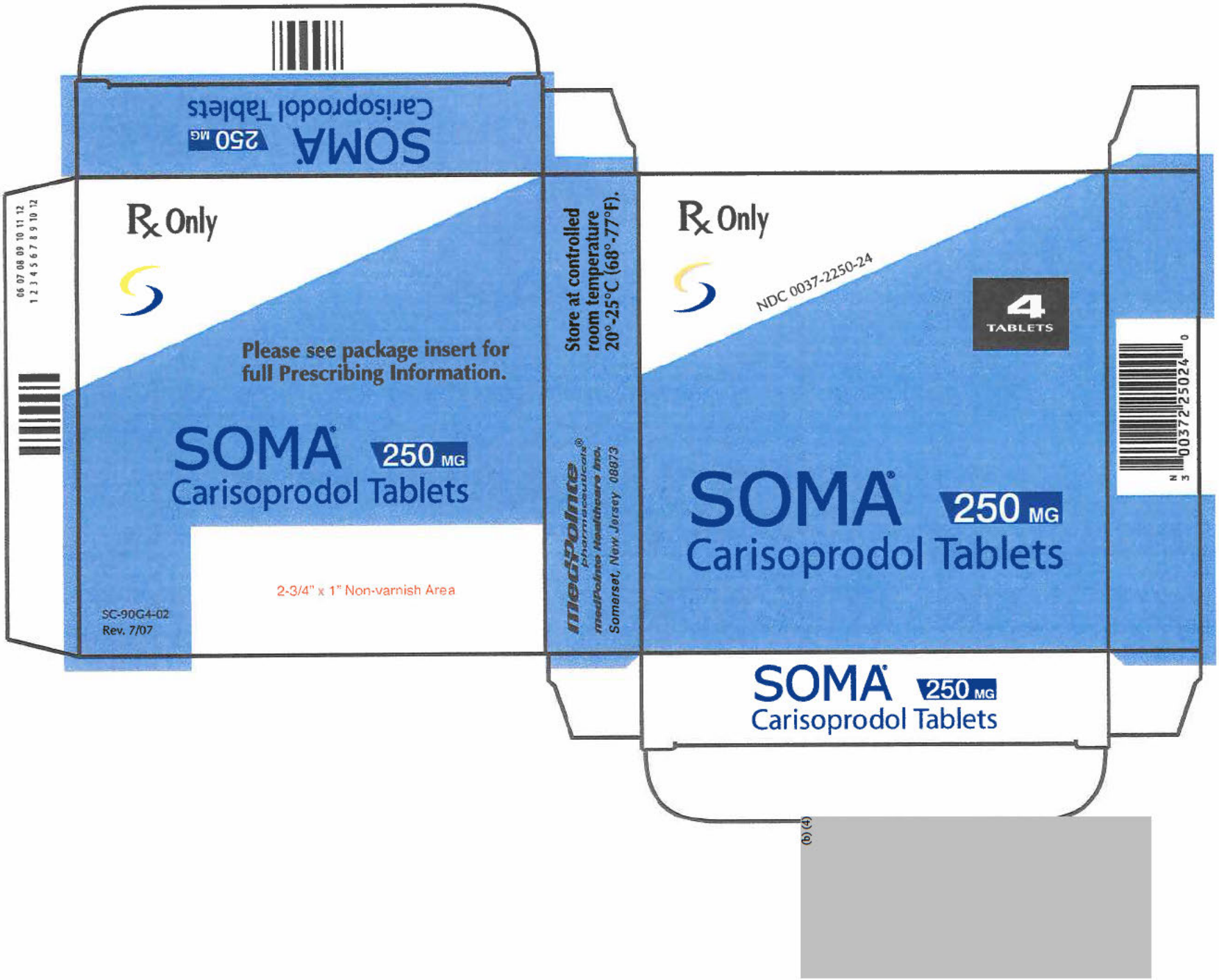
100 Tablets

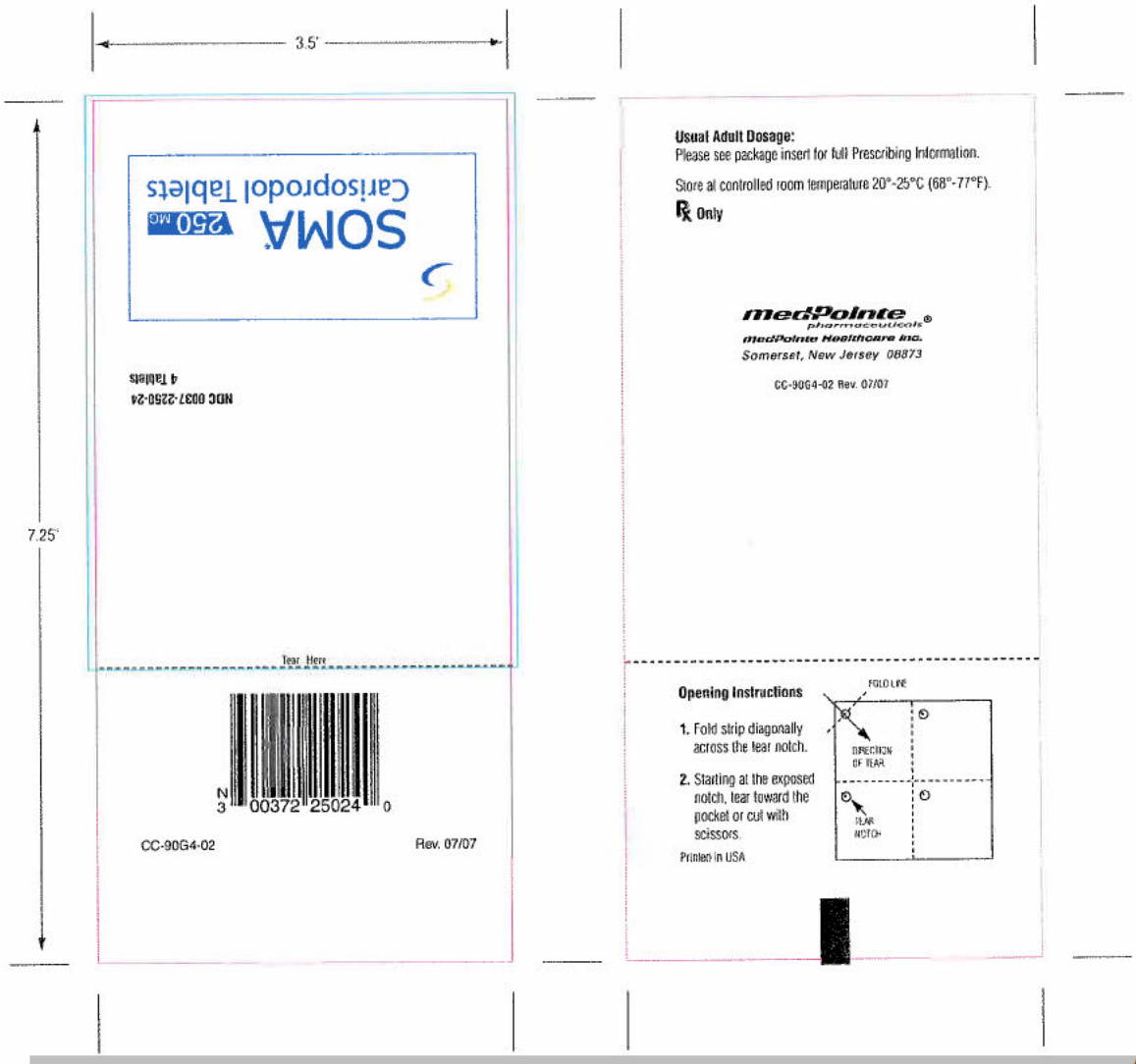
℞ Only

Dispense in tight container.
Store at controlled room temperature
20°-25°C (68°-77°F).

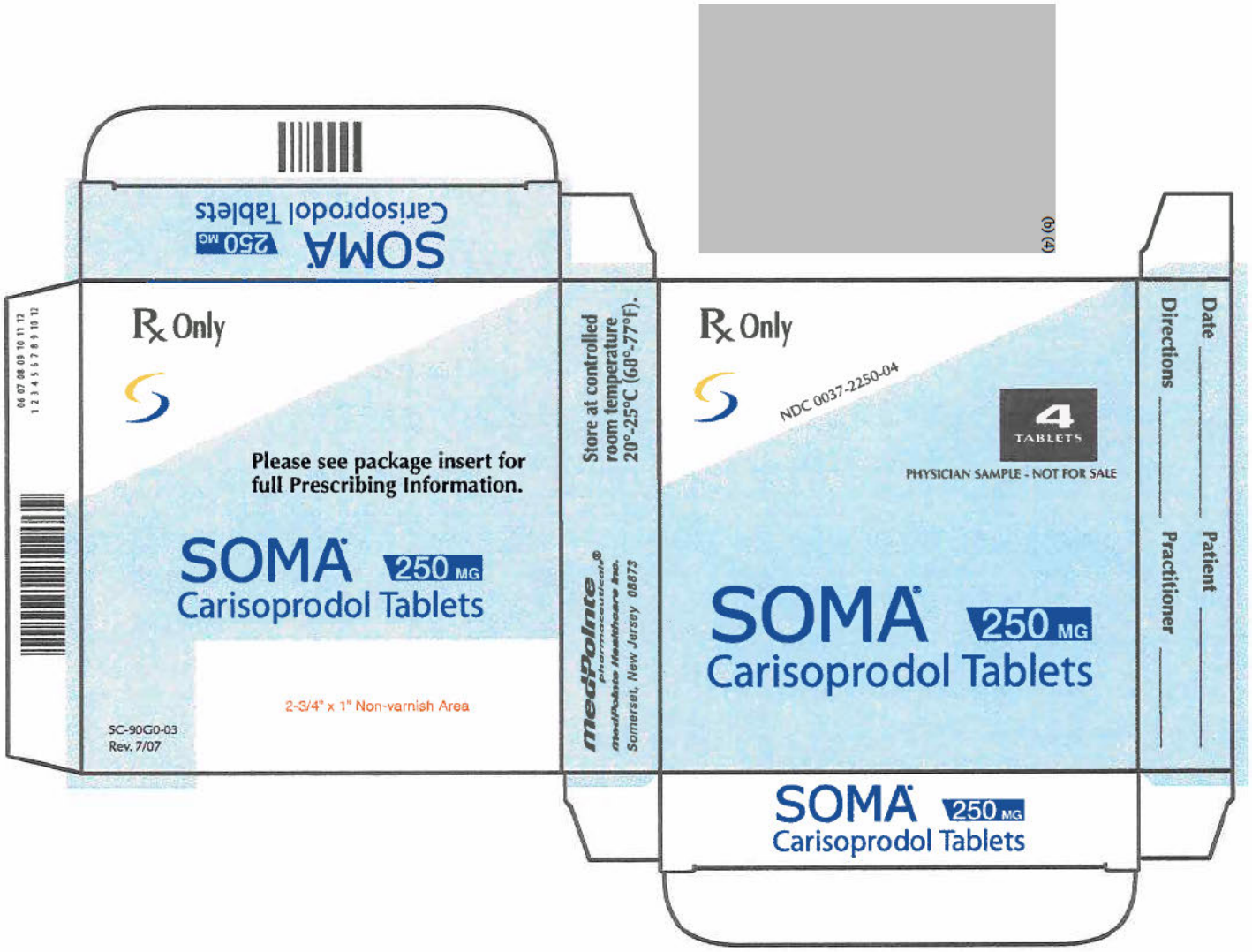
Please see enclosed full Prescribing Information

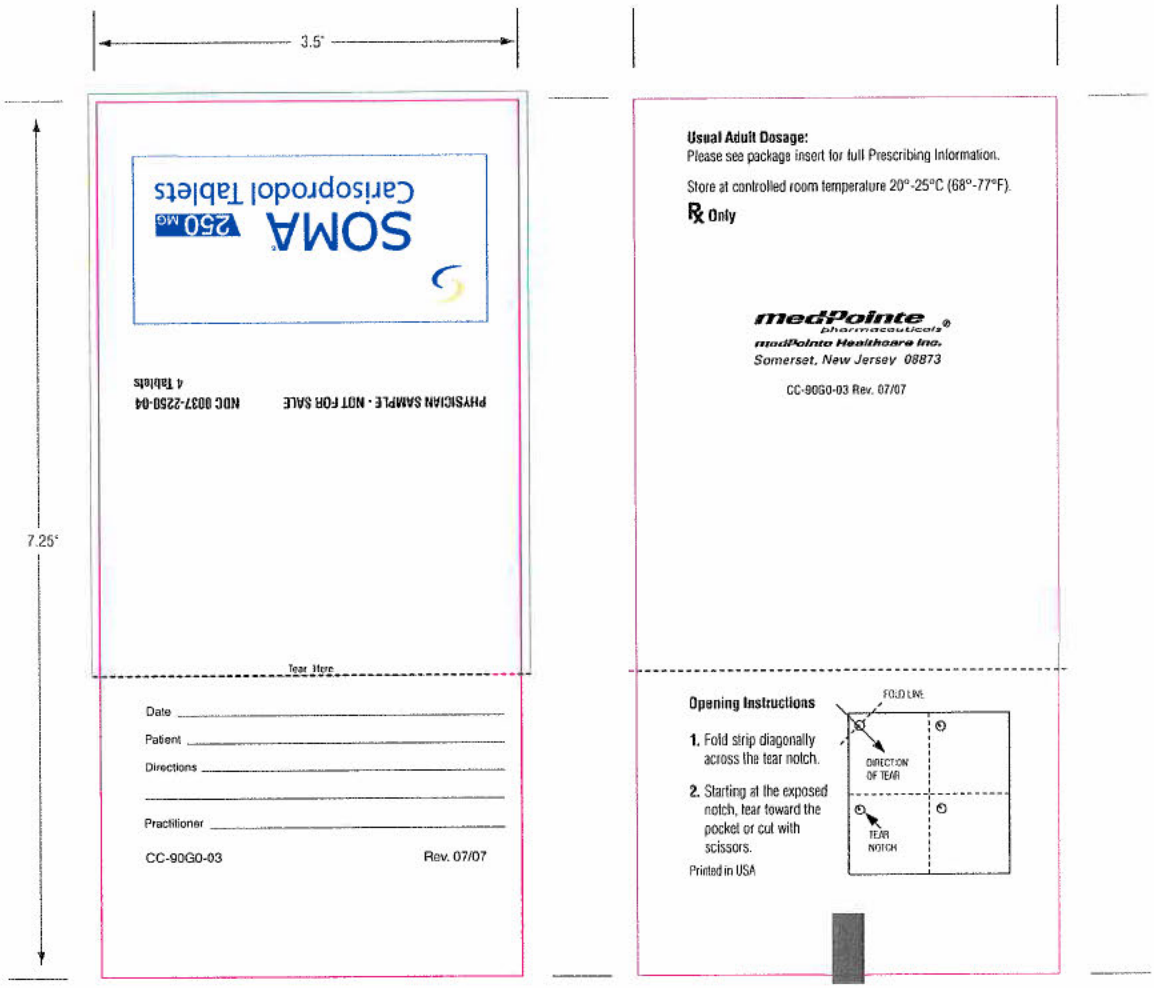
LB-9062-03 Rev. 7/07


SOMA 250 MG
Carisoprodol Tablets
℞ Only
Please see package insert for full Prescribing Information.
SOMA 250 MG
Carisoprodol Tablets
2-3/4" x 1" Non-varnish Area
SC-90G4-02
Rev. 7/07
06 07 08 09 10 11 12
1 2 3 4 5 6 7 8 9 10 12
Store at controlled room temperature 20°-25°C (68°-77°F).
medPointe Pharmaceuticals
medPointe Healthcare Inc.
Somerset, New Jersey 08873
℞ Only
NDC 0037-2250-24
4 TABLETS
N 3 00372 25024 0
SOMA 250 MG
Carisoprodol Tablets
(b) (4)

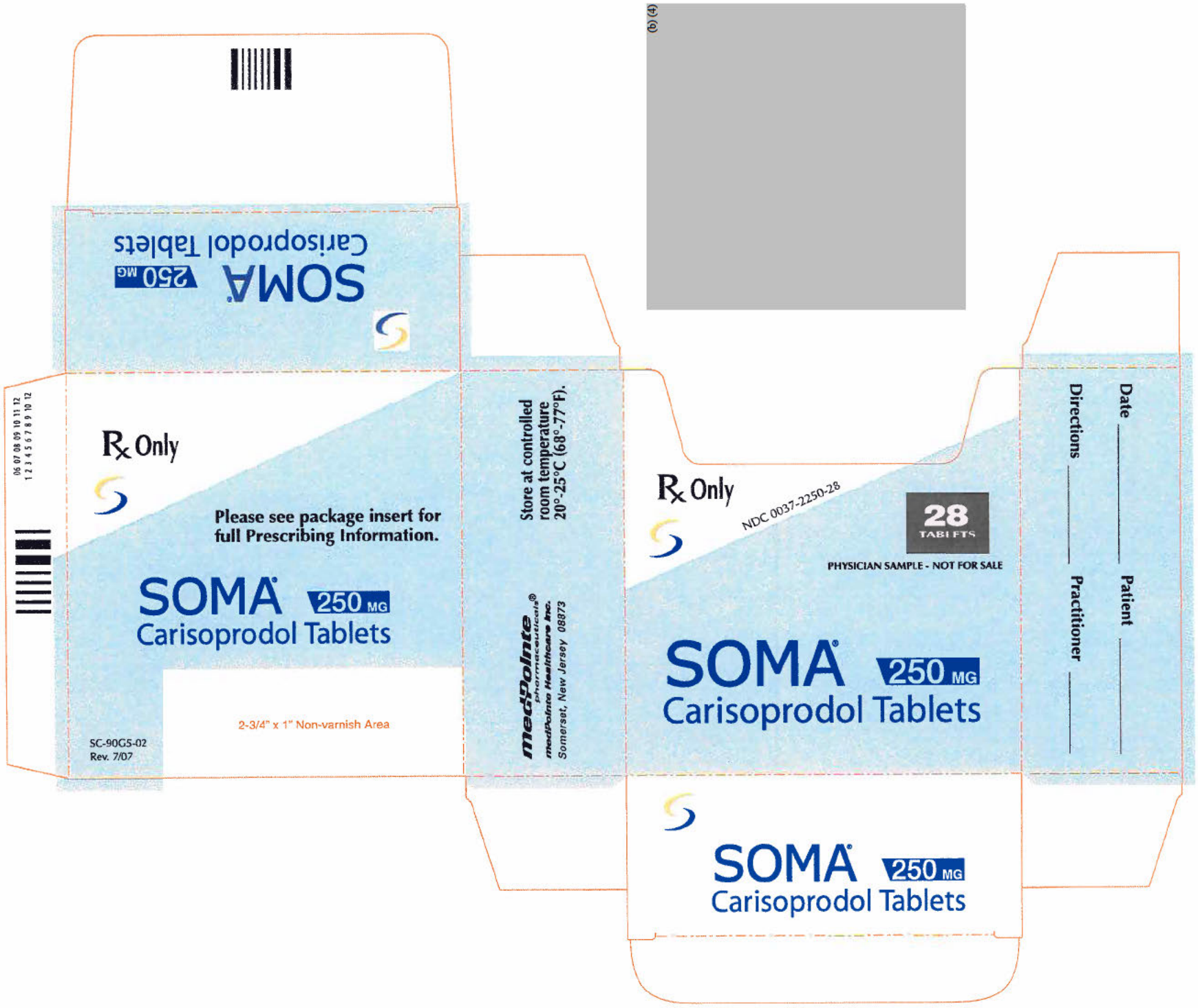

3.5"
7.25"
SOMA 250 MG
Carisoprodol Tablets
NDC 0037-2250-24
4 Tablets
Tear Here
N 3 00372 25024 0
CC-90G4-02
Rev. 07/07
Usual Adult Dosage:
Please see package insert for full Prescribing Information.
Store at controlled room temperature 20°-25°C (68°-77°F).
℞ Only
medPointe pharmaceuticals
medPointe Healthcare Inc.
Somerset, New Jersey 08873
CC-90G4-02 Rev. 07/07
Opening Instructions
1. Fold strip diagonally across the tear notch.
2. Starting at the exposed notch, tear toward the pocket or cut with scissors.
Printed in USA
FOLD LINE
DIRECTION OF TEAR
TEAR NOTCH

(b) (4)


SOMA 250 MG
Carisoprodol Tablets
℞ Only
Please see package insert for full Prescribing Information.
SOMA 250 MG
Carisoprodol Tablets
2-3/4" x 1" Non-varnish Area
SC-90G0-03
Rev. 7/07
Store at controlled room temperature 20°-25°C (68°-77°F).
medPointe Pharmaceuticals
medPointe Healthcare Inc.
Somerset, New Jersey 08873
℞ Only
NDC 0037-2250-04
4 TABLETS
PHYSICIAN SAMPLE - NOT FOR SALE
SOMA 250 MG
Carisoprodol Tablets
Date
Patient
Directions
Practitioner
SOMA 250 MG
Carisoprodol Tablets


3.5"
7.25"
SOMA 250 mg
Carisoprodol Tablets
PHYSICIAN SAMPLE - NOT FOR SALE
NDC 0037-2250-04
4 Tablets
Tear Here
Date
Patient
Directions
Practitioner
CC-90G0-03
Rev. 07/07
Usual Adult Dosage:
Please see package insert for full Prescribing Information.
Store at controlled room temperature 20°-25°C (68°-77°F).
℞ Only
medPointe pharmaceuticals
medPointe Healthcare Inc.
Somerset, New Jersey 08873
CC-90G0-03 Rev. 07/07
Opening Instructions
1. Fold strip diagonally across the tear notch.
2. Starting at the exposed notch, tear toward the pocket or cut with scissors.
Printed in USA
FOLD LINE
DIRECTION OF TEAR
TEAR NOTCH

(b) (4)


SOMA 250 MG
Carisoprodol Tablets
Rx Only
Please see package insert for full Prescribing Information.
SOMA 250 MG
Carisoprodol Tablets
2-3/4" x 1" Non-varnish Area
SC-90G5-02
Rev. 7/07
06 07 08 09 10 11 12
1 2 3 4 5 6 7 8 9 10 12
Store at controlled room temperature 20°-25°C (68°-77°F).
medpointe pharmaceuticals®
medPointe Healthcare Inc.
Somerset, New Jersey 08873
Rx Only
NDC 0037-2250-28
28 TABLETS
PHYSICIAN SAMPLE - NOT FOR SALE
SOMA 250 MG
Carisoprodol Tablets
Date
Patient
Directions
Practitioner
SOMA 250 MG
Carisoprodol Tablets

SOMA®
Carisoprodol Tablets
250 mg
Pouch Labeling

SOMA® Carisoprodol Tablets, 250mg Lot XXXXXXXXXX Exp MM/YYYY	SOMA® Carisoprodol Tablets, 250mg Lot XXXXXXXXXX Exp MM/YYYY
SOMA® Carisoprodol Tablets, 250mg Lot XXXXXXXXXX Exp MM/YYYY	SOMA® Carisoprodol Tablets, 250mg Lot XXXXXXXXX Exp MM/YYYY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

OFFICE DIRECTOR MEMO

Food and Drug Administration
CENTER FOR DRUG EVALUATION AND RESEARCH
Division of Anesthesia, Analgesia, and Rheumatology Products
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Deputy Division Director Review and Basis for Approval

Date:	September 13, 2007
Drug:	Carisoprodol (Soma®) 250-mg tablet
NDA Number	11-792/S-041
Type of Submission:	SE-2
Sponsor:	MedPointe Pharmaceuticals
Indication:	For the relief of discomfort associated with acute painful musculoskeletal conditions.

Carisoprodol is classified as a centrally acting skeletal muscle relaxant although its mechanism of action has not been fully elucidated. Nonclinical data suggests that it may produce muscle relaxation by blocking interneuronal activity in the descending reticular formation and spinal cord, but that it lacks direct action on the muscles or the neuromuscular junction. Carisoprodol was originally approved in May 1959 for the treatment of a variety of musculoskeletal conditions. (b) (4) However, carisoprodol was evaluated as part of the Drug Efficacy Study Implementation (DESI) process, and a review in 1974 determined that although the 350-mg dosage regimen was found to be effective, (b) (4) The NDA holder at that time, Carter-Wallace, (b) (4).

Carter-Wallace sought, and received, approval to market Soma® Compound (aspirin 325 mg/carisoprodol 200 mg), and Soma® Compound with Codeine (aspirin 325 mg/carisoprodol 200 mg/codeine 16 mg), and even though there was another DESI determination in 1979 that supported reclassifying the 250-mg dosage form of SOMA as

effective, the company never sought to re-introduce this dosage regimen. Carter-Wallace was purchased by MedPointe Pharmaceutical in 2001. MedPointe's position is that the finding of effectiveness for the 250-mg capsules in 1979 was not supported by the data because most of the trial participants received two tablet of the Soma® compound (and therefore 400 mg of carisoprodol) per dose.

MedPointe Pharmaceutical is now seeking marketing approval for a 250-mg tablet, submitting a 505(b)2 application containing the data from two clinical trials in patients with mechanical low-back pain and two single-dose pharmacokinetic studies. The company has not conducted any new non-clinical studies but has submitted data from published literature. Based on the data from this application, the company is seeking the following language in the Indication section:

> "SOMA is indicated for the relief of discomfort associated with acute painful musculoskeletal conditions. (b) (4)
>
> (b) (4)

The clinical reviewer for this supplement was Eric Brodsky, M.D., with Sarah Okada, M.D., as the secondary reviewer; the statistical review was performed by Ted Guo, Ph.D., with Dionne Price, Ph.D., performing the secondary review. The clinical pharmacology reviewer was Lei Zhang, Ph.D., and Suresh Doddapaneni, Ph.D., was the secondary clinical pharmacology reviewer; the pharmacology/toxicology review was performed by Steven Leshin, D.V.M., Ph.D., with Adam Wasserman, Ph.D., as the secondary reviewer. The chemistry, manufacturing and controls evaluation was performed by Donald Klein, Ph.D., with Jim Vidra, Ph.D as the secondary reviewer.

Consultations were obtained from the Division of Drug Marketing, Advertising, and Communications (DDMAC); the Division of Scientific Investigations (DSI); the Office of Surveillance and Epidemiology (OSE); the Study Endpoints and Labeling Development (SEALD) Team; and the Pediatric and Maternal Health Team.

This memorandum will briefly review the effectiveness and safety data summarized in the primary and secondary clinical reviews, as well as any relevant information found in the reviews by the other disciplines, and document my recommendations for action on this NDA supplement.

Efficacy:
The applicant submitted data from two clinical trials conducted in patients with acute mechanical back pain, Study MP502 and Study MP505. Both studies were of a randomized, double-blind, multi-center, parallel-group, placebo-controlled design, and of a similar duration; they differed in that Study MP502 contained two carisoprodol treatment groups:

Study MP502
- Placebo (276 patients)
- Carisoprodol, 250 mg (271 patients)
- Carisoprodol, 350 mg (279 patients)

Study MP505
- Placebo (284 patients)
- Carisoprodol, 250 mg (277 patients)

The treatment regimen for both studies was noted as being dosed three times a day and at bedtime, for no longer than 7 days.

There were two co-primary endpoints based on an assessment of the change in the mean score on study Day 3 from baseline for the 250-mg tablet compared to placebo: "relief from starting backache" (RSB) and patient "global impression of change" (GIC). Both endpoints needed to be significant at the 0.025 alpha level (Bonferroni adjustment) and the comparison of the 250-mg and 350-mg tablet treatment groups were considered only as supportive.

The RSB endpoint consisted of the patients being asked how they felt on Day 3 compared to baseline, using the following 5-point categorical responses: complete relief (4), a lot of relief (3), some relief (2), a little relief (1), and no relief (0). The data point analyzed was the mean value of the patient's morning assessment (between 0600 and 0900 hours) and the evening assessment (between 1800 and 2100 hours) on Day 3.

The GIC endpoint was similar to the RSB endpoint in that it was the mean value of an assessment, compared to baseline, performed by the patient on Day 3 (similar time windows as the RSB). The 5-point categorical assessment in this endpoint was: marked improvement (4), moderate improvement (3), mild improvement (2), no change (1), or worsening (0).

There were also seven secondary endpoints:
- Roland-Morris Disability Questionnaire (RMDQ, Day 7 score compared to baseline
  - a 24-item tool assessing the amount of disability, with a score ranging from 0 (no disability) to 24 (maximum disability);
- RMDQ score on Day 3 compared to baseline;
- Amount of flexion in lower back (measured in centimeters) on Day 7 compared to baseline;
- Amount of flexion in lower back (measured in centimeters) on Day 3 compared to baseline;
- Patient-rated Medication Helpfulness assessment on Day 7

  - consisted of a multiple-choice response (Excellent, Very Good, Good, Fair, or Poor) to the following question: "How would you rate this study medication in improving your condition?";
- Patient-rated Medication Helpfulness assessment on Day 3; and
- Time (in days) to the first patient-reported assessment of moderate improvement (3) or marked improvement (4) on the GIC scale.

Results

Patients in Study MP502 were randomized the following number of patients into the three treatment groups: placebo, 276 patients; Soma® 250 mg, 271 patients; and Soma® 350 mg, 281 patients.

Patients in Study MP505 were randomized the following number of patients into the two treatment groups: placebo, 285 patients; and Soma® 250 mg, 277 patients.

Since the design and conduct of the two studies were similar, it is possible to discuss the breakdown of the demographics and the disposition of the patients in the two studies together. The table below, adapted from Dr. Brodsky's review, summarizes the patient disposition and their totals in the different patient populations used in the statistical analyses.

	Placebo N (n%)	**Soma® 250 mg N (n%)**	**Soma® 350 mg N (n%)**
Randomized	561 (100)	548 (100)	281 (100)
Completed	470 (83.8)	491 (89.6)	239 (85.1)
Discontinued	91 (16.2)	57 (10.4)	42 (14.9)
Populations for statistical analysis			
Safety	560 (99.8)	548 (100)	279 (99.3)
Intent-to-treat (ITT)	547 (96.5)	533 (97.3)	273 (97.2)
Per-protocol	467 (83.2)	478 (87.2)	232 (82.6)

The definitions of the different patient populations were as follows:

- *safety population*: patients who received at least one dose of medication.
- *intent-to-treat population*: patients who received at least one dose of medication and who had at least one post-baseline efficacy assessment. This was the primary population utilized in the statistical analyses of the primary efficacy endpoints.
- *per-protocol population*: patients in the ITT population who took at least 70% of the required study medication and completed the study with complete diary data.

The baseline demographics of the patients enrolled were similar across the treatment groups, with respect to age, gender, race, ethnicity, height and weight, duration of back pain, and severity of back pain.

The following table summarizes the reason for discontinuation for the patients within the safety population.

Reason for Discontinuation	Placebo N = 560 (n%)	Soma® 250 mg N = 548 (n%)	Soma® 350 N = 279 (n%)
Total discontinuations	91 (16.3)	57 (10.4)	42 (15.1)
Unsatisfactory therapeutic effect	39 (7)	10 (1.8)	7 (2.5)
Lost to follow-up	16 (2.9)	17 (13.1)	11 (3.9)
Adverse event	15 (2.7)	11 (2)	15 (5.4)
Patient withdrew consent	9 (1.6)	11 (2)	6 (2.2)
Other	9 (1.6)	5 (0.9)	1 (0.4)
Protocol violation	2 (0.4)	2 (0.4)	1 (0.4)
Abnormal test procedure	1 (0.2)	1 (0.2)	1 (0.4)

The proportion of patients who discontinued due to an adverse event was higher in the 350-mg treatment group, and comparable between the 250-mg treatment group and placebo. This will be further discussed later, including the reasons for discontinuations in the safety section of this document.

The following table, reproduced from Dr. Okada's review, summarizes the results from the two co-primary efficacy endpoints, global impression of change (GIC) and relief from starting backache (RSB) on Day 3.

Study	Parameter	Placebo	Soma® 250 mg	Soma® 350 mg
MP502	N	269	264	273
	GIC on Day 3, LS mean (SE)*	1.9 (0.1)	2.2 (0.1)	2.2 (0.1)
	Difference between Soma® and placebo (95% CI)	-	0.2 (0.1, 0.4)	0.3 (0.1, 0.4)
	p-value†	-	0.0046‡	0.0011
	RSB on Day 3, LS mean (SE)*	1.4 (0.1)	1.8 (0.1)	1.8 (0.1)
	Difference between Soma® and placebo (95% CI)	-	0.4 (0.2, 0.5)	0.4 (0.2, 0.6)
	p-value†	-	0.0001‡	<0.0001
MP505	N	278	269	-
	GIC on Day 3, LS mean (SE)*	1.7 (0.1)	2.3 (0.1)	-
	Difference between Soma® and placebo (95% CI)	-	0.5 (0.4, 0.7)	-
	p-value†	-	<0.0001	-
	RSB on Day 3, LS mean (SE)*	1.1 (0.1)	1.8 (0.1)	-
	Difference between Soma® and placebo (95% CI)	-	0.7 (0.5, 0.9)	-
	p-value†	-	<0.0001	-

*LS Mean is the least squared mean and SE is the standard error of the mean

†The p-values were calculated using an ANOVA model with treatment and pooled center as terms; the primary statistical population was the ITT population (defined as patients who received at least one dose of study medication and who had at least one post-baseline efficacy assessment).

‡In Study MP502, the primary comparison was between the 250 mg Soma® and placebo groups; the other comparisons were exploratory.

With respect to the secondary endpoints, most of them did not showed any evidence of efficacy (b) (4), either because of poor design, reliance upon a non-validated tool for assessment, or a marginally clinically significant response. The RMDQ is a validated instrument for the evaluation of physical functioning due to back pain; the data demonstrated that the groups treated with Soma® showed a greater improvement in the RMDQ scores at Day 3 and Day 7 that was statistically significant, and therefore will be included in the label.

Safety:

The safety profile of Soma® has been well-characterized over the years since its approval in 1959. Furthermore, since the applicant is seeking a dosage regimen that will most likely have a lower exposure than the currently approved regimen, there is the expectation that the safety profile would be the same, if not better, for the new dosage regimen. Therefore, the applicant's submission safety database of 1435 subject/patients, the majority of which (875, or 61%) were exposed to Soma, seemed to be sufficient to support the application. However, since 48 of the 875 individuals exposed to Soma® were participants in the single-dose pharmacokinetic studies, and the safety information obtained from those studies is of minimal utility, the primary assessment by the review team of the new dosage regimen was performed on the safety database from Studies MP502 and MP505.

There were no deaths reported in either of the studies, and only one serious adverse events (SAE) was reported. The SAE consisted of a patient in the 350-mg treatment group of Study MP502 who was hospitalized for lumbar surgery after being diagnosed with a herniated disc; it was not attributed to the study treatment.

There was a smaller proportion of treatment discontinuations due to adverse events in the 250-mg treatment group compared to the 350-mg treatment group, and the proportions in the 250-mg treatment group and placebo group were comparable. The actual numbers in each category were low, i.e., there were no observable clustering, making it difficult to conclude that a particular category was treatment-specific or dose-specific. The table below, adapted from Dr. Brodsky's review, illustrates this observation.

Adverse Event	**Placebo** **N = 560** **n (%)**	**Soma® 250 mg** **N = 548** **n (%)**	**Soma® 350 mg** **N = 279** **n (%)**
Number of patients with ≥ 1 adverse event leading to treatment discontinuation	15 (2.7)	11 (2.0)	15 (5.4)
Dizziness	1 (0.2)	3 (0.5)	2 (0.7)
Headache	1 (0.2)	3 (0.5)	1 (0.4)
Diarrhea	1 (0.2)	1 (0.2)	-
Stomach discomfort or upper abdominal pain	-	1 (0.2)	2 (0.7)
Somnolence	2 (0.4)	-	2 (0.7)
Nausea	2 (0.4)	-	1 (0.4)
Rash	1 (0.2)	-	1 (0.4)
Nephrolithiasis	1 (0.2)	-	1 (0.4)

Adverse Event	**Placebo** **N = 560** **n (%)**	**Soma® 250 mg** **N = 548** **n (%)**	**Soma® 350 mg** **N = 279** **n (%)**
Intervertebral disc protrusion	-	1 (0.2)	1 (0.4)
Pain in extremity	-	1 (0.2)	-
Abdominal distension	-	1 (0.2)	-
Fatigue	-	-	1 (0.4)
Disorientation	-	-	1 (0.4)
Paraesthesia	-	-	1 (0.4)
Skin papilloma	-	-	1 (0.4)
Food poisoning	1 (0.2)	-	-
Back pain	1 (0.2)	-	-
Gastrointestinal viral	1 (0.2)	-	-
Muscle spasms	1 (0.2)	-	-
Spinal fracture	1 (0.2)	-	-
Irritability	1 (0.2)	-	-

The most common adverse events reported were related to the central nervous system effects, such as sedation, headache, and dizziness. Both Soma® treatment groups had higher incidence rates than placebo, and the incidence of the most common adverse events was similar between the two Soma treatment groups. This is summarized in the table below, reproduced from Dr. Brodsky's review, which identifies the events that were reported at a rate of >0.5% in any treatment group in the safety population (patients who received at least one dose of medication).

Preferred term	**Placebo** **N = 560** **n (%)**	**Soma® 250 mg** **N = 548** **n (%)**	**Soma® 350 mg** **N = 279** **n (%)**
Patients with ≥ 1 adverse event	111 (20.3)	166 (30.3)	95 (34.1)
Somnolence or sedation	31 (5.5)	73 (13.4)	4 (16.9)
Dizziness	11 (2.0)	43 (7.8)	19 (6.8)
Headache	11 (2.0)	26 (4.7)	9 (3.2)
Nausea	15 (2.7)	6 (1.1)	12 (4.3)
Stomach discomfort, abdominal discomfort, or upper abdominal pain	7 (1.3)	10 (1.8)	5 (1.8)
Fatigue or lethargy	2 (0.4)	8 (1.5)	3 (1.1)
Diarrhea	6 (1.1)	5 (0.9)	1 (0.4)
Dry mouth	4 (0.7)	3 (0.5)	2 (0.7)
Irritability	0	3 (0.5)	0
Blood CPK increased	3 (0.5)	2 (0.4)	2 (0.7)

With respect to laboratory abnormalities, there were no clinically meaningful shifts in laboratory values in any of the treatment groups.

There were insufficient numbers of patients who were older than 65 years of age, had renal insufficiency, or hepatic insufficiency, to permit subgroup analyses with respect to the safety profile of the dosage regimen. As for gender, there appeared to be a higher incidence of adverse events reported by women for the most common adverse events, which would correlate with the pharmacokinetic data that indicates a higher exposure of carisoprodol and meprobamate in women. However, it was not a consistent finding, and this hypothesis was not supported by the incidences of adverse events observed in women when stratified by the dosage regimen (250 mg vs. 350 mg); definitive conclusions could not be drawn based on Study MP502 alone. The table below, adapted from Dr. Brodsky's review, summarizes the most common adverse events (>2%) reported in both studies.

	Gender	**Placebo n (%)***	**Soma® 250 mg n (%)***	**Soma® 350 mg n (%)***
Total number in safety population	Women	325	275	154
	Men	235	273	125
Patients with ≥ 1 adverse event	Women	72 (22.2)	109 (39.6)	54 (35.1)
	Men	41 (17.4)	57 (20.9)	41 (32.8)
Somnolence or sedation	Women	17 (5.2)	52 (18.9)	25 (16.2)
	Men	14 (6)	21 (7.7)	22 (17.6)
Dizziness	Women	7 (2.2)	30 (10.9)	12 (7.8)
	Men	4 (1.7)	13 (4.8)	7 (5.6)
Headache	Women	8 (2.5)	19 (6.9)	6 (3.9)
	Men	3 (1.3)	7 (2.6)	3 (2.4)
Nausea	Women	7 (2.2)	2 (0.7)	6 (3.9)
	Men	8 (3.4)	4 (1.5)	6 (4.8)
Stomach distention, abdominal discomfort, or upper abdominal pain	Women	7 (2.2)	8 (2.9)	3 (2.4)
	Men	-	1 (0.4)	2 (1.6)
Fatigue, lethargy, or asthenia	Women	2 (0.6)	7 (2.5)	3 (1.9)
	Men	1 (0.4)	1 (0.4)	1 (0.8)

*Patients were counted once within each preferred term, and may have had more than one adverse event.

Clinical Pharmacology and Biopharmaceutics:

Data from two pharmacokinetic studies performed with health volunteers were submitted with this application. Study MP500 was a food effect study and Study MP501 was a relative bioavailability study comparing the 250-mg and 350-mg tablets. Each study enrolled 12 male and 12 female subjects.

The data indicate that there is dose proportionality between the 250-mg and the 350-mg dosages, and there is no apparent food effect. There does appear to be higher exposures of carisoprodol and meprobamate in females compared to males, but based on the data in the clinical trials, it is not possible at this time to conclude that it is to a degree that imparts a clinical significance.

No formal drug-drug interactions studies were performed by the applicant, however, there is evidence that carisoprodol is metabolized by CYP2C19. The implication is that drugs that inhibit CYP2C19 could result in higher levels of carisoprodol and lower levels of its metabolite, meprobamate. It is also possible that co-administration with a CYP2C19 inducer might result in lower levels of carisoprodol and lower levels of meprobamate.

Since CYP2C19 is a polymorphic enzyme, with 15-20% of Asians being considered poor metabolizers compared to 3-5% of the caucasian or black populations, it is possible that there may be ethnic variability with respect to efficacy and, potentially, adverse events. However, genotyping was not performed in the pharmacokinetic studies that would help confirm these hypotheses, and the clinical trials were not powered to evaluate a difference in safety or efficacy based on ethnic group.

The pharmacokinetic studies were able to demonstrate a difference in exposure to carisoprodol and meprobamate between males and females, but it was not possible to reach a definitive conclusion as to whether there is a difference in safety and efficacy based on gender using the clinical data submitted.

Non-clinical Pharmacology and Toxicology:
Although non-clinical studies were not performed by the applicant, the review team used the literature information submitted by the applicant to update the label with available non-clinical toxicology findings. Additionally, the pregnancy and nursing mothers section of the label will be updated.

Chemistry, Manufacturing, and Controls:
There were several requests for additional information sent to the applicant during the course of the review, and all issues have been resolved to the review team's satisfaction. There are no outstanding issues from a CMC perspective.

Abuse Liability:
Meprobamate, a Schedule IV substance, is a major metabolite of carisoprodol. The abuse potential of carisoprodol was the topic of discussion at a Drug Abuse Advisory Committee meeting in February, 1997. After presentations by the DEA, the FDA, academia, and the NDA holder (Carter-Wallace at that time), no definitive conclusions were drawn at the meeting and carisoprodol remained unscheduled under the Controlled Substances Act of 1970.

It is expected that the lower dosage form proposed by this application is not likely to increase the risk for abuse or diversion compared to the currently marketed 350-mg tablet. Furthermore, the currently approved label for Soma® has adequate descriptions of the potential for drug dependence, withdrawal, and abuse which will be retained in the new label.

Data integrity:
The Division of Scientific Investigation (DSI) performed a routine inspection of one of the sites in Study MP502 and found no significant regulatory violations. The conclusion was that the site complied with applicable statutory requirements and FDA regulations.

Discussion:
MedPointe Pharmaceutical has submitted data from two adequate and well-controlled trials in support of their application for marketing approval of a 250-mg tablet. Based on these two trials, there is substantial evidence of safety and efficacy for the dosage regimen, and the data from the pharmacokinetic studies also provide information supporting the new tablet.

An argument could be made that the data submitted do not support all of the proposed language requested by the company. Drs. Brodsky and Okada have articulated in their reviews how the design of the studies does not permit inclusion of some of language proposed by the applicant, for example, in the Indication, Dosage and Administration, and Clinical Studies sections of the label. Their concerns range from the wording advising a recommended starting dose and duration of treatment, (b) (4) to wording that is similar, if not identical, to wording found in the label of another product approved for the same indication (cyclobenzaprine) but which is not supported by the data in the submission.

It is understood that drug development and clinical study trial design is a constantly evolving process. Different opinions can arise over a short time over the most appropriate endpoints that should be studied, what assessment tools should be used, what the design of the trial should be, and what type of statistical analyses should be performed on the data. It is very possible that if a pharmaceutical company were to approach the Division today, different advice could be given with respect as to what would be required to obtain marketing approval.

It is also important to be cognizant of the previous discussion they have had with the Agency with respect to the study endpoints and clinical trial design and analyses, and the previous agreements reached.

For example, Dr. Brodsky makes several points to support why the Dosage and Administration section should not indicate the recommended dosing period be (b) (4) He noted that there are no data on the efficacy of the 250-mg dosing regimen beyond 7 days, that there were multiple interactions with the company where the division strongly recommended that the trials' duration be of at least two weeks, and that there have been post-marketing reports of carisoprodol dependence, withdrawal, and abuse associated with prolonged use of carisoprodol.

However, as documented in the meeting minutes from a meeting in June 2005, that was held to discuss the issue of the study trial duration, the Division agreed in a post-meeting note that a 7-day trial would be acceptable for evaluation of the efficacy of the 250-mg

tablet. Since this meeting occurred in the context that the applicant was seeking an indication that was similar to what they already had for the 350-mg dosing regimen, it is interpreted that the post-meeting note applied to the proposed wording in the label regarding the recommended duration of treatment. Furthermore, the design of the studies was very similar to the design that supported the approval of the 5 mg cyclobenzaprine immediate- release regimen in 2003 for acute painful musculoskeletal conditions, and the approval of the cyclobenzaprine extended-release formulation earlier this year.

Ultimately, the decision as to what information should be included in the new label should take into account that this is a drug that has been approved for almost 50 years, with a well-characterized efficacy and safety profile, and that the applicant is seeking the marketing approval for a dosage strength that is less that what is currently being marketed under an existing NDA. Against this backdrop, the goals are to include wording that accurately describes the data that were in the submission, to make sure that any labeling does not inadvertently place one pharmaceutical company at an unfair marketing advantage, while also conforming to the new Physician's Labeling Rule (PLR) format.

With respect to requirements to do pediatric studies as mandated under the Pediatric Research Equity Act (PREA) of 2003, I agree with Dr. Okada's assessment that although back pain may not be uncommon in children and adolescents, it is rarely of sufficient intensity or duration to cause significant disability. When this is coupled with the relatively modest treatment effect demonstrated by the clinical trial data, the benefit:risk ratio would not favor the use of this product to treat acute mechanical back pain in the pediatric population. I concur with her recommendation that pediatric studies be waived for pediatric patients less than 16 years of age, and that the label indicate that efficacy and safety has not been established.

Recommended Action:
Approval of supplement.

Rigoberto Roca, M.D.
Deputy Division Director
Division of Anesthesia, Analgesia, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rigoberto Roca
9/13/2007 01:16:13 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

MEDICAL REVIEW(S)

CLINICAL REVIEW of a SOMA® (carisoprodol) EFFICACY SUPPLEMENT

Application Type	NDA
Submission Number	11-792
Submission Code	41
Letter Date	November 10, 2006
Stamp Date	November 10, 2006
PDUFA Goal Date	September 13, 2007
Reviewer Name	Eric Brodsky, M.D.
Review Completion Date	September 7, 2007
Established Name	Carisoprodol
Trade Name	Soma®
Therapeutic Class	Skeletal muscle relaxant
Applicant	MedPointe Pharmaceuticals
Priority Designation	S
Formulation	Oral tablets
Proposed Dosing Regimen	250 mg TID and qhs and may increase to 350 mg TID and qhs
Proposed Indication	relief of discomfort associated with acute, painful musculoskeletal conditions (b) (4)
Intended Population	Adults and (b) (4) with acute, painful musculoskeletal conditions

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

From a clinical perspective, an **approval** action is recommended for the 250 mg Soma® (carisoprodol) tablets for the **short-term treatment of discomfort associated with acute, painful musculoskeletal conditions in adults** with labeling revisions.

Two adequate and well-controlled (i.e., randomized, double-blind, multi-center, placebo-controlled) U.S. trials demonstrated substantial evidence of effectiveness and safety of the 250 mg carisoprodol regimen for the short-term treatment of discomfort in patients with acute, idiopathic, mechanical low back pain. Although the important carisoprodol studies were performed in patients with acute, idiopathic, mechanical low back pain, the broader indication in patients with acute, painful musculoskeletal conditions is acceptable because acute mechanical low back pain has been the model historically utilized to grant this indication for skeletal muscle relaxants, including carisoprodol; treatment of acute mechanical low back pain is the primary condition for which skeletal muscle relaxants are prescribed; and this has been the wording of the indication for which carisoprodol has been approved for use for almost 50 years.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Additional risk assessment and risk minimization activities are not indicated.

1.2.2 Required Phase 4 Commitments

Phase 4 commitments are not indicated.

1.2.3 Other Phase 4 Requests

Other phase 4 requests are not indicated.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Medpointe Pharmaceuticals (Medpointe) submitted an efficacy supplement, NDA 11-792/S-041, on November 10, 2006 [under 505(b)(2) of the Federal Food, Drug, and Cosmetic Act] to support the approval of a new dose and new dosage regimen of oral Soma® (carisoprodol) tablets, a skeletal muscle

relaxant, for "the relief of discomfort associated with acute, painful musculoskeletal conditions" for (b) (4) Carisoprodol has been approved in the United States since May 1959. The currently approved carisoprodol dosing regimen is 350 mg tablets three times a day and at bedtime. In their efficacy supplement application, Medpointe proposes a new 250 mg carisoprodol tablet to be dosed three times a day and at bedtime. Medpointe argues that the new lower-dose carisoprodol regimen is beneficial because the lower-dose regimen has similar efficacy to the approved higher-dose regimen and has a lower incidence of central nervous system (CNS) adverse drug reactions (ADRs) compared to the approved higher-dose regimen.

Medpointe submitted the results of four, new, short-term (≤ 7 days duration) clinical studies of 250 mg carisoprodol tablets (i.e., two single-dose pharmacokinetic studies in healthy subjects and two seven-day efficacy/safety studies in patients with acute, idiopathic, mechanical, low back pain) to support approval of their efficacy supplement. The entire safety database in the four studies consisted of 1435 subjects/patients [of which 875 (61.0%) and 560 (39.0%) subjects/patients received carisoprodol and placebo, respectively].

1.3.2 Efficacy

The most important efficacy studies (i.e., Studies MP502 and MP505) in this efficacy supplement were two randomized, double-blind, placebo-controlled, parallel-group, multiple-center, U.S. studies of carisoprodol in adult patients between 18 and 65 years of age with acute, idiopathic, mechanical low back pain. Patients with evidence of non-mechanical back pain (e.g., from inflammatory arthritis, malignancy) or patients with evidence of serious complications of mechanical back pain (e.g., nerve root compression, cauda equida syndrome, osteoporotic fracture) were excluded from participation. In Study MP502, patients were randomized 1:1:1 to one of the following three treatments given four times a day for seven days: 250 mg of carisoprodol tablets, 350 mg of carisoprodol tablets (the currently approved carisoprodol regimen), and placebo; and in Study MP505, patients were randomized 1:1 to the 250 mg carisoprodol regimen or placebo four times a day for seven days. In both low back pain studies, the pre-specified, **co-primary efficacy endpoints** were the following patient-reported outcomes (PROs):

1) Mean value of the morning and the evening assessments of the **"Global Impression of Change" (GIC)** on Study Day #3. The GIC score was obtained from responses to the following question, "compared with how you felt prior to starting study medication, and regardless of whether you think the change was due to the medicine, please indicate if you have experienced" one of the following: marked improvement (4), moderate improvement (3), mild improvement (2), no change (1), or worsening (0); and
2) Mean value of the morning and the evening assessments of **"Relief from Starting Backache" (RSB)** on Study Day #3. RSB was obtained from responses to the following question, "compared with how you felt prior to starting study medication, and regardless of whether you think the change was due to medicine, please indicate if you have experienced" one the following: complete relief (4), a lot of relief (3), some relief (2), a little relief (1), or no relief (0).

In both studies, the primary statistical comparison for the co-primary efficacy endpoints was between the 250 mg carisoprodol group and the placebo group.

Although, the co-primary efficacy endpoints in the low back pain studies are not the most optimal measures of efficacy of products intended for the treatment of acute, low back pain; these primary efficacy endpoints were acceptable for the low back pain studies because:

1) These endpoints have been used as the primary efficacy endpoints or important secondary efficacy endpoints in the recent approval of other muscle relaxants [i.e., cyclobenzaprine (Flexeril®); cyclobenzaprine extended-release capsules (Amrix®)] for the identical proposed indication;
2) Deficiencies in endpoints in pain trials designed to demonstrate superiority are likely to adversely affect the efficacy of the investigational product more than the placebo control; and
3) In multiple meetings with Medpointe; the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) accepted the adequacy of the primary efficacy endpoints for the proposed low back pain studies.

Of the seven, pre-specified, **secondary efficacy endpoints** in the two low back pain studies; the following PRO endpoints were the most important:

1) Roland-Morris Disability Questionnaire (RMDQ) score of function [ranging from 0 (no disability) to 24 (maximum disability)] on Study Day #7 minus the RMDQ baseline; and
2) RMDQ score on Study Day #3 minus the RMDQ baseline score.

The two RMDQ endpoints were the most important secondary endpoints in the low back pain studies because:

1) The RMDQ is a validated, functional instrument in low back pain;
2) A minimal clinical meaningful change in the RMDQ has been identified;
3) Unlike most of the other pre-specified endpoints, the RMDQ reduces recall bias; and
4) Multiple members of the July 1999 Joint Over-the-Counter (OTC) and Arthritis Advisory Committee Meeting ─ who advised the FDA regarding the approvability of low dose Flexeril for OTC use ─ recommended the use of instruments that measure disability/function in low back pain trials.

Efficacy Results

Table I delineates the **efficacy results of the co-primary efficacy endpoints** (i.e., GIC and RSB on Day #3) in the low back pain studies. The 250 mg carisoprodol group demonstrated statistical significance, compared to the placebo group, for both primary efficacy endpoints in both low back pain studies. For the 5-point GIC on Day #3, the treatment differences between the 250 mg carisoprodol and placebo groups were 0.2 and 0.5 in Studies MP502 and MP505, respectively. For the 5-point RSB on Day #3, the treatment differences between the 250 mg carisoprodol and placebo groups were 0.4 and 0.7 in Studies MP502 and MP505, respectively.

Although the comparisons of the 250 mg and 350 mg carisoprodol groups for the primary efficacy endpoints were exploratory in Study MP502, the treatment effect sizes of both carisoprodol groups appeared similar.

Table I: Results of the co-primary efficacy endpoints (i.e., GIC and RSB) in the low back pain studies

Study	Parameter	Placebo	Carisoprodol 250 mg	Carisoprodol 350 mg
MP502	n	269	264	273
	GIC on Day #3, LS Mean (SE)[1]	1.9 (0.1)	2.2 (0.1)	2.2 (0.1)
	Difference between carisoprodol and placebo (95% CI)	-	0.2 (0.1,0.4)	0.3 (0.1,0.4)
	p-value[2]	-	0.0046[3]	0.0011
	RSB on Day #3, LS Mean (SE)[1]	1.4 (0.1)	1.8 (0.1)	1.8 (0.1)
	Difference between carisoprodol and placebo (95% CI)	-	0.4 (0.2,0.5)	0.4 (0.2,0.6)
	p-value[2]		0.0001[3]	<0.0001
MP505	n	278	269	-
	GIC on Day #3, LS Mean (SE)[1]	1.7 (0.1)	2.2 (0.1)	-
	Difference between carisoprodol and placebo (95% CI)	-	0.5 (0.4,0.7)	-
	p-value[2]	-	<0.0001	-
	RSB on Day #3, LS Mean (SE)[1]	1.1 (0.1)	1.8 (0.1)	-
	Difference between carisoprodol and placebo (95% CI)	-	0.7 (0.5,0.9)	-
	p-value[2]	-	<0.0001	-

1 LS Mean is the least squared mean and SE is the standard error of the mean
2 p-values were calculated using an ANOVA model with treatment and pooled center as terms. The primary statistical population was the ITT population.
3 In Study MP502, the primary comparison was between the 250 mg carisoprodol and placebo groups and the other comparisons were exploratory.
Reference: Adapted from Volume 1, Table 3.6.2.1-1, Page 49 (See Tables 12 and 13 in Section 6.1.4 for more details)

Table II displays the **efficacy results of the most important secondary efficacy endpoints** (i.e., change in RMDQ) in the low back pain studies. The 250 mg carisoprodol group demonstrated a greater treatment effect, compared to the placebo group, for both RMDQ endpoints in both low back pain studies. In Study MP502, the treatment effect size in the 24-point RMDQ was 1.0 and 1.1 on Days #3 and #7, respectively; and in Study MP505, the treatment effect size was 1.9 and 2.3 on Days #3 and #7, respectively. In both studies, the effect size was maintained after seven days of therapy.

Although the comparisons of the 250 mg and 350 mg carisoprodol groups for the RMDQ endpoints were exploratory in Study MP502, the treatment effect sizes of the two carisoprodol groups appeared similar.

Table II: Results of the important secondary endpoints (i.e., change in RMDQ) in the low back pain studies

Study	Parameter	Placebo	Carisoprodol 250 mg	Carisoprodol 350 mg
MP502	n	269	264	273
	Change from baseline in RMDQ on Day #3, LS Mean (SE)[1]	-2.0 (0.3)	-3.0 (0.3)	-2.9 (0.3)
	LS Mean Difference (placebo minus carisoprodol), 95% CI	-	1.0 (0.3,1.7)	1.0 (0.3,1.7)
	p-value[2]	-	0.0057[3]	0.0067
	Change from baseline in RMDQ on Day #7, LS Mean (SE)[1]	-4.4 (0.3)	-5.4 (0.3)	-5.7 (0.3)
	LS Mean Difference (placebo minus carisoprodol), 95% CI	-	1.1 (0.3,1.9)	1.3 (0.5,2.1)
	p-value[2,3]	-	0.0112[3]	0.0017
MP505	n	278	269	-
	Change from baseline in RMDQ on Day #3, LS Mean (SE)[1]	-1.4 (0.3)	-3.2 (0.3)	-
	LS Mean Difference (placebo minus carisoprodol), 95% CI	-	1.9 (1.2,2.5)	-
	p-value[2]	-	<0.0001	-
	Change from baseline in RMDQ on Day #7, LS Mean (SE)[1]	-3.1 (0.3)	-5.4 (0.3)	-
	LS Mean Difference (placebo minus carisoprodol), 95% CI	-	2.3 (1.6,3.0)	-
	p-value[2]	-	<0.0001	-

1 LS Mean is the least squared mean and SE is the standard error of the mean
2 No pre-specified multiplicity adjustments were made for the seven pre-specified secondary efficacy endpoints in the low back pain studies. The ANCOVA model was used with treatment, pooled center, and baseline value as covariates. The primary statistical population was the ITT population.
3 In Study MP502, the primary statistical comparison was between the 250 mg carisoprodol and placebo groups.
Reference: Adapted from Volume 18, Table 11-11, Page 68; Volume 18, Table 11-12, Page 69; Volume 53, Table 11-10, Page 63; and Volume 53, Table 11-11, Page 64. For more details see Tables 14 and 15 in Section 6.1.4 of this review.

The efficacy of the 250 mg carisoprodol regimen in the treatment of acute low back pain was established because the 250 mg regimen, compared to the placebo group, demonstrated:

1) Statistical significance for the co-primary efficacy endpoints;
2) Numerical improvement for the two RMDQ secondary endpoints;
3) Replicability for the two primary and the two important secondary endpoints in two studies; and
4) Similar effect size compared to the effect size of recently approved muscle relaxants for identical efficacy endpoints in analogous acute, low back pain studies.

Although the comparison between the carisoprodol groups in Study MP502 was exploratory, the similar efficacy results between the 250 mg carisoprodol regimen and the approved 350 mg carisoprodol regimen for the co-primary efficacy and the RMDQ endpoints also supports the efficacy of the 250 mg carisoprodol regimen.

In summary, the clinical data from the two studies of patients with acute, idiopathic, mechanical low back pain **support the efficacy** of the new 250 mg carisoprodol regimen in the short-term treatment of discomfort associated with acute, painful musculoskeletal conditions in adults.

1.3.3 Safety

The entire safety database in the four studies submitted in this efficacy supplement consisted of 1435 subjects/patients [of which 875 (61.0%) and 560 (39.0%) subjects/patients received carisoprodol and placebo, respectively]. Of the 875 subjects/patients who received carisoprodol in the safety population, 827 (94.5%) subjects/patients received a daily carisoprodol dose that was equal or greater than the new proposed carisoprodol daily dose (i.e., one gram per day) in this efficacy supplement. The safety database of the most important clinical studies (i.e., Studies MP502 and MP505) to support the efficacy and safety of the 250 mg carisoprodol regimen consisted of 1387 patients with acute low back pain [of which 560 (40.4%), 548 (39.5%), and 279 (20.1%) patients received placebo, the 250 mg carisoprodol regimen, and the 350 mg carisoprodol regimen, respectively]. In Studies MP502 and MP505, the mean duration of exposures for the placebo, the 250 mg carisoprodol, and the 350 mg carisoprodol groups were 6.4, 6.5, and 6.6 days, respectively. In these studies, the mean daily carisoprodol doses in the placebo, 250 mg carisoprodol, and the 350 mg carisoprodol groups were 0, 0.9, and 1.2 grams, respectively.

There were no deaths and there were no carisoprodol-related, non-fatal serious adverse events (SAEs) in the four carisoprodol studies. A single SAE (i.e., herniated lumber disc with neurologic deficit that required hospitalization and decompression surgery) occurred in one patient who received the 350 mg carisoprodol regimen in Study MP502; however, this SAE was likely related to complications of the patient's underlying disease. In the two low back pain studies, 15 (2.7%), 11 (2.0%), and 15 (5.4%) of patients had adverse events leading to discontinuation (DAEs) in the placebo, 250 mg carisoprodol, and the 350 mg carisoprodol groups, respectively. Furthermore, 3 (0.5%), 3 (0.5%), and 5 (1.8%) of patients had central nervous system (CNS)-related DAEs in the placebo, 250 mg carisoprodol, and the 350 mg carisoprodol groups, respectively. In the low back pain studies, the most common adverse events (AEs) and the most common adverse drug reactions (ADRs) in the carisoprodol groups were CNS AEs (e.g., somnolence, sedation, dizziness) ─ 41 (7.3%), 117 (21.4%), and 68 (24.4%) of patients had CNS ADRs in the placebo, 250 mg carisoprodol, and the 350 mg carisoprodol groups, respectively.

The lack of a follow-up safety visit to assess withdrawal symptoms off treatment is a limitation of the safety monitoring program since there have been post-marketing reports of withdrawal symptoms after cessation of carisoprodol dosing. Despite this limitation of safety monitoring, the safety database was adequate to support the safety of the 250 mg carisoprodol regimen for the short-term treatment of acute, musculoskeletal conditions because:

- The carisoprodol label conveys the above limitation (there are WARNINGS regarding the possible withdrawal symptoms after abrupt cessation of carisoprodol dosing);
- The lower-dose carisoprodol regimen (250 mg QID or 1 gram per day) is less likely to contribute to withdrawal symptoms compared to the approved higher-dose carisoprodol regimen (350 mg QID or 1.4 grams per day);

- The higher-dose carisoprodol regimen has been approved and marketed in the United States for almost 50 years;
- The 250 mg regimen demonstrated a slightly improved safety profile compared to the 350 mg dose regimen in the low back pain studies (i.e., a lower incidence of CNS DAEs and CNS ADRs); and
- The safety database from the low back pain studies is adequate to support the safety of carisoprodol for short-term use.

In summary, the submitted carisoprodol studies **support the safety** of the 250 mg carisoprodol regimen for the short-term treatment of acute, painful musculoskeletal conditions.

1.3.4 Dosing Regimen and Administration

Medpointe proposed the following language for carisoprodol dosing (b) (4) However, there is no data on the efficacy of the 350 mg carisoprodol regimen in patients who do not respond to the 250 mg regimen. Additionally, there is no significant data on the durability of response of either carisoprodol regimen after seven days of therapy. Finally, four times a day (QID) dosing is more appropriate than three times a day and at bedtime dosing because the QID dosing is simpler and was more consistent with the actual dosing in the low back pain studies.

Therefore, the following dosing language is recommended:

> "The recommended dose of SOMA is one 250 mg or 350 mg tablet four times a day and the recommended maximum duration of SOMA use is up to seven days."

1.3.5 Drug-Drug Interactions

There are no new identified drug-drug interactions.

1.3.6 Special Populations

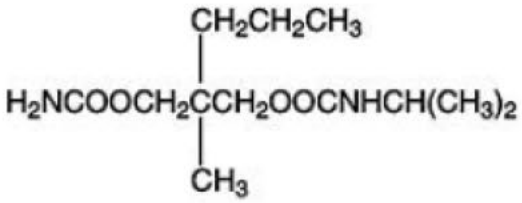
There are no new special carisoprodol dosing considerations for gender, race, or for patients with hepatic or renal insufficiency. There are no new dosing considerations for geriatric patients.

Since there are no data from efficacy/safety studies, literature reports, pharmacokinetic studies, or other data on the use of carisoprodol in pediatric patients aged 0 to 16 years old; **the use of carisoprodol is not recommended in pediatric patients less than 16 years old**. A full waiver is recommended for pediatric studies that are required under the 2003 Pediatric Research Equity Act because the "drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients."

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Trade Name (established name): SOMA® (carisoprodol) has the following structural formula:



Currently Approved Indication: "Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions."

Proposed Indication: "SOMA is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions [redacted (b) (4)]

SOMA [redacted (b) (4)] used for short periods [redacted (b) (4)] because adequate evidence of effectiveness for more prolonged use is not available and because acute, painful musculoskeletal conditions are generally of short duration.

[redacted (b) (4)]

Proposed Age Group: Adults

Medical Reviewer's Comments: The proposed Pediatric Use subsection of the USE IN SPECIFIC POPULATIONS section of the proposed carisoprodol label states that the "efficacy and safety of SOMA in patients less than 12 years of age has not been determined." However, the proposed INDICATIONS AND USAGE section of the proposed carisoprodol label is silent regarding the use of carisoprodol in pediatric patients 12 to 18 years old. The sponsor must address the use of carisoprodol in all age groups including pediatric patients 12 to 16 years old.

The proposed Geriatric Use subsection of the USE IN SPECIFIC POPULATIONS section of the proposed carisoprodol label states that the [redacted (b) (4)] "

Pharmacologic Class: Skeletal muscle relaxant

Route of Administration, Description, and Formulation: The proposed oral 250 mg tablets are round, convex, and white. The approved oral 350 mg tablets are round, convex, and white.

Efficacy Supplement Code: SE2 (e.g., a new dosage regimen, a decrease in daily dosage).

Approved Treatment Regimen: One 350 mg tablet three times a day and at bedtime

Proposed Treatment Regimen: (b) (4) (b) (4)

Molecular Formula: $C_{12}H_{24}N_2O_4$

Chemical Name: N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate

2.2 Currently Available Treatment for Indications

Table 1 displays 10 monotherapy products (7 products with different active ingredients) that are approved for the treatment of discomfort associated with acute, painful musculoskeletal conditions. The seven products are a heterogeneous group of drugs including muscle relaxants and a benzodiazepene.

Table 1: Currently approved products for the relief of discomfort associated with acute, painful musculoskeletal conditions (in order of year of approval)

	Product	Approval Year	NDA# (Sponsor)	Approved Dosing Regimen	Formulation
1	**AMRIX®** (cyclobenzaprine HCl extended-release capsules)	2007	21-777 (ECR Pharmaceuticals)	15 mg once daily (maximum dose is 30 mg/day)	Oral capsules
2	**FLEXERIL®** (cyclobenzaprine HCl)	1977	17-821 (McNeil Pharmaceuticals)	5 mg TID (may be increased to 10 mg TID)	Oral tablets
3	**VALIUM®** (diazepam)[1]	1963	13-263 (Roche)	2 to 10 mg TID or QID	Oral tablets
4	**SKELAXIN®** (metaxalone)	1962	13-217 (Jones Pharma Inc.)	800 mg three to four times a day	Oral tablets
5	**NORFLEX** (orphenadrine citrate) Injection	1960	13-055 (3M)	60 mg IV or IM every 12 hours	IV or IM
6	**SOMA®** (carisoprodol)	1959	11-792 (Medpointe Pharm HLC)	350 mg three times daily and at bedtime[2]	Oral tablets
7	**NORFLEX** (orphenadrine citrate) Tablets[3]	1959	12-157[3] (3M)	100 mg BID	Oral tablets
8	**ROBAXIN® Injectable** (methocarbamol injection)	1959	11-790 (Baxter Healthcare)	1 gram IV q 8 hours TID up to 3 days or 0.5 grams IM q 8 hours	IV and IM
9	**PARAFON FORTE® DSC** (chlorzoxazone)	1958	11-529 (Ortho McNeil Pharmaceuticals)	500 mg TID or QID (may increase to 750 mg TID or QID)	Oral tablets
10	**ROBAXIN®** (methocarbamol tablets) and **ROBAXIN®-750** (methocarbamol) tablets)	1957	11-011 (Schwarz Pharma)	Initial dose: 1500 mg QID Maintenance dose: 1000 mg QID, 750 mg q 4 hours, or 1500 mg TID	Oral tablets

1 According to the **INDICATIONS** section of the valium label, "Valium is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma)." Valium is also indicated for the treatment of anxiety disorders, treatment of acute alcohol withdrawal, spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia), adjunctively in convulsive disorders.

2 Proposed new dosing regimen is (b) (4) (b) (4)

3 Norflex tablets (under NDA 12-157) were discontinued. However, there are several generics (under different ANDAs) that are currently active.

Reference: The approved labels at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

Table 2 displays four combination products that are approved for the treatment of discomfort associated with acute, painful musculoskeletal conditions.

Table 2: Currently approved fixed dose combination products for the relief of discomfort associated with acute, painful musculoskeletal conditions[1]

	Product	Approval Year	NDA# (Sponsor)	Approved Dosing Regimen	Formulation
1	**NORGESIC® and NORGESIC® FORTE** (orphenadrine citrate; aspirin; caffeine)	1964	13-416 (3M)	Norgesic 1 to 2 tablets TID or QID (25/385/30 mg) Norgesic Forte 0.5 to 1 tablets TID or QID (50/770/60 mg)	Fixed dose combination oral tablets
2	**SOMA® COMPOUND** (carisoprodol and aspirin tablets)	1960	12-365 (Medpointe Pharm HLC)	1 to 2 tablets QID (200/325 mg)	Fixed dose combination oral tablets
3	**SOMA® COMPOUND with CODEINE** (carisoprodol, aspirin, and codeine phosphate tablets)	1960	12-366 (Medpointe Pharm HLC)	1 to 2 tablets QID (200/325/16 mg)	Fixed dose combination oral tablets
4	**ROBAXISAL®** (methocarbamol and aspirin)	1960	12-281 (Wyeth)	2 tablets QID Maximum dose: 3 tablets QID for severe conditions up to 3 days (400/325 mg)	Fixed dose combination oral tablets

1 In order of year of approval
Reference: The approved labels at http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm

2.3 Availability of Proposed Active Ingredient in the United States

The carisoprodol moiety is available in three approved products in the United States (see Table 3).

Table 3: Approved products with carisoprodol as an active moiety in the United States[1]

	Product	Approval Year	NDA# (Sponsor)	Approved Dosing Regimen	Formulation
1	**SOMA®** (carisoprodol)	1959	11-792 (Medpointe Pharm HLC)	350 mg three times daily and at bedtime	Oral tablets
2	**SOMA® COMPOUND** (carisoprodol and aspirin tablets)	1960	12-365 (Medpointe Pharm HLC)	1 to 2 tablets QID (200/325 mg)	Fixed dose combination oral tablets
3	**SOMA® COMPOUND with CODEINE** (carisoprodol, aspirin, and codeine phosphate tablets)	1960	12-366 (Medpointe Pharm HLC)	1 to 2 tablets QID (200/325/16 mg)	Fixed dose combination oral tablets

1 SOMA, SOMA COMPOUND, and SOMA COMPOUND with CODEINE all have approved generics on the market in the United States.
Reference: The approved labels at http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm

SOMA (carisoprodol) was approved on April 9, 1959

2.4 Important Issues With Pharmacologically Related Products

The following skeletal muscle relaxants are approved for the treatment of discomfort associated with acute, musculoskeletal conditions: SOMA (carisoprodol), FLEXERIL (cyclobenzaprine hydrochloride), SKELAXIN (metaxalone), NORFLEX (orphenadrine citrate), ROBAXIN (methocarbamol tablets), and PARAFON FORTE DSC (chlorzoxazone). See Table 1 in Section 2.2 for more details. LIORESAL (baclofen) and DANTRIUM (Dantrolene) are skeletal muscle relaxants that are approved for the treatment of spasticity.

The skeletal muscle relaxants have not had recent major labeling changes.

2.5 Presubmission Regulatory Activity

The following paragraphs present the pre-submission regulatory history of the proposed carisoprodol dosing regimen (250 mg three times a day (b) (4)

2.5.1 Pre-IND Meeting

In June 2004, the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP) ─ formerly known as the Division of Analgesic, Anti-Inflammatory and Ophthalmic Drug Products ─ and MedPointe Pharmaceuticals (Medpointe) had a pre-IND meeting regarding Medpointe's proposed development program for a lower carisoprodol dosing regimen for the adjunctive relief of discomfort associated with acute, painful musculoskeletal conditions (with rest, physical therapy, and other measures). The highlights of this meeting include:

- DAARP stated that analysis "of post-marketing reports and review of the literature" of the "potential for drug dependence and abuse" of carisoprodol will need to be submitted;
- DAARP stated that Medpointe's proposed bioavailability study of 150, 250 mg, and 350 mg of carisoprodol tablets should "enroll roughly equal numbers of males and females to allow for a secondary analysis based on gender" and "the effect of a standardized high fat meal on the product" should be established;
- Medpointe stated that they intend to file a supplemental NDA (sNDA) for the new carisoprodol regimen. In addition, Medpointe asked DAARP if the new carisoprodol regimen would be entitled to a three year period of exclusivity under 21 CFR 314.108(b)(5) because this new dosing regimen is either not covered by the 1979 DESI upgrade or the upgrade was invalid because of lack of effectiveness. DAARP stated that "the possibility for granting exclusivity based on clinical trials of the 250 mg dose is uncertain. In order to determine if exclusivity could be granted the results of two DESI determinations must be reviewed and found to be incorrect and the findings withdrawn. The information underlying these DESI determinations is currently under review." In addition, the Office of Regulatory Policy that that they "will research the DESI, efficacy inquiry"; and
- Medpointe proposed to summarize the non-clinical pharmacology and toxicology data in the sNDA (without conducting new studies). DAARP recommended that the sNDA include "relevant historical and current information and literature pertaining to the

pharmacology, mechanism of action, absorption, distribution, metabolism, abuse potential, and safety of carisoprodol and its metabolite meprobamate." In addition, DAARP recommended that "information concerning mutagenesis, carcinogenicity, and reproductive toxicology" of carisoprodol and meprobamate be included in the sNDA because there is "minimal information on these critical topics in the current product label".

2.5.2 IND Submission

In November 2004, Medpointe submitted a carisoprodol IND application (i.e., IND# 71,218).

2.5.3 End of Phase II Meeting

In February 2005, DAARP and Medpointe had an end of phase II meeting to discuss Medpointe's proposed phase 3 clinical program for the new carisoprodol dosing regimen. The highlights of this meeting include:

- Medpointe agreed to change their proposed design of their phase 3 studies from open-labeled to double-blind;
- Medpointe proposed to conduct two 7-day clinical trials. However, DAARP recommended Medpointe conduct trials with at least 14 days in duration (primary efficacy outcomes should be measured on days 3 and 7). In addition, DAARP recommended that safety data and efficacy data for durability of response be collected over the entire 14 day study duration. Medpointe stated that 14 day trials (in contrast to 7 day trials) would suffer from noncompliance because of carisoprodol-associated sedation and resolution of the acute muscle lower back spasm. In addition, Medpointe stated that safety of the lower 250 mg carisoprodol dosing regimen could be supported with the 350 mg approved dosing regimen. DAARP stated that the study duration issue would be re-evaluated internally and asked Medpointe to provide additional support for their proposed 7 day studies;
- Medpointe proposed the following three co-primary efficacy endpoints for their phase 3 trials: patient rating of pain intensity, patient rated global impression of change, and range of motion. DAARP recommended that the range of motion be a secondary endpoint; not a primary endpoint because it is unlikely that the study population would have significant abnormal range of motion throughout the study duration. DAARP also recommended that the physician assessment of muscle spasm be a primary endpoint and the patient rating of pain intensity could be a secondary endpoint. DAARP agreed to evaluate the endpoints in context of the endpoints used in clinical trials of similar products; and
- Medpointe agreed to eliminate their (b) (4)

2.5.4 Special Protocol Assessment

In March 2005, Medpointe submitted a Special Protocol Assessment (SPA) for Protocol MP502 and in April 2005, DAARP provided the following comments to Medpointe:

- "We do not agree that the proposed approach to the primary efficacy endpoints is acceptable. If you choose 3 co-primary endpoints, successful results for all three are required, not the proposed two out of three."
- "We recommend that you consider modifying the primary efficacy endpoints. Rather than the proposed pain endpoint we recommend use of 'Relief from starting backache' to distinguish this from the pain outcome in an analgesic trial."
- "We agree with using a rating of patient helpfulness as one of the primary efficacy endpoints."
- "We suggest using a patient-rated global impression of change as the third co-primary endpoint."
- "There would be expectation of a dose response trending across the two active treatment arms."
- "We strongly recommend that you increase study duration to 14 days for efficacy and safety. As previously discussed, a study duration of 7 days is inadequate."
- "We agree that the primary efficacy outcomes may be analyzed on Day 4, but the clinical effect must be followed through Day 14. If there is evidence of ongoing muscle spasm symptoms through Day 14, there would also be expectation of ongoing clinical benefit maintained through Day 14."
- "The protocol lacks a description of how to address missing data due to dropouts. This must be addressed prospectively as a component of the statistical analysis plan."

2.5.5 Post SPA Communications

In June 2005, DAARP and Medpointe had a Type A meeting to discuss the unresolved issues regarding the SPA for Protocol MP502. During this meeting:

- DAARP recommended the following three co-primary endpoints: relief from initial backache, patient global impression of change, and a rating of medication helpfulness. However, DAARP stated that Medpointe could use relief from initial backache and patient global impression of change as co-primary efficacy endpoints and use medication helpfulness as an important secondary endpoint;
- Medpointe stated that muscle spasm studies of seven day duration is of sufficient length to document efficacy and additional exposure would be associated with ongoing AEs including fatigue and somnolence that would limit the return to full activity for patients. Medpointe had the following arguments to support their proposal to use a seven day duration for their phase 3 studies: the acute nature of low back muscle spasm, compliance issues with longer duration studies, and the preponderance of seven-day studies in the literature [including the seven day studies of Flexeril (cyclobenzaprine) that DAARP accepted], and the existing safety data on the approved higher 350 mg dosing regimen. Moreover, Medpointe stated that the labels of several products for the treatment of acute pain are approved for longer durations of use compared to the trial durations that supported their approvals. DAARP responded by citing literature describing eleven trials of 7 to 18 days of duration for similar products. Moreover, DAARP argued that there will be a proportion of low back pain patients that will require more than 7 days of therapy and it is important to document efficacy of the lower carisoprodol dosing regimen in these

> patients. DAARP stated that current sponsors of muscle relaxants were being asked to perform 14-day studies. DAARP acknowledged that this represented a difference from prior regulatory requirements. DAARP stated they would internally discuss Medpointe's proposal for 7 day low back pain trials and would provide the results of these discussions within 30 days.

In July 2005, in the official meeting minutes to the June 2005 Type A meeting regarding the SPA, DAARP stated the following: "a duration of 7 days would be acceptable for evaluation of the efficacy of the 250-mg dose of carisoprodol. Support for the 7-day duration includes that the product under study is a lower dose than currently approved products, so that safety is not a concern, and the lower, 5-mg dose of Flexeril was approved based on a 7-day duration of study."

In July 2006, DAARP sent a letter to Medpointe regarding Medpointe's proposed amendment to the statistical analysis plans for studies MP502 and MP505. DAARP stated that the "statistical aspect of the protocol is acceptable, in general. However, we recommend that you investigate the sensitivity of the results to the procedure for handling missing data using conservative approaches such as a continuous responder analysis and a baseline observation carried forward (BOCF) analysis."

2.6 Other Relevant Background Information

The following present the regulatory history of carisoprodol from 1959 (the year of carisoprodol's initial approval) to 2004 (see Section 2.5 for carisoprodol's regulatory history after 2004).

- On May 8, 1959, carisoprodol (SOMA) was approved under NDA 11-792 for the following indications:

  > "Soma relieves pain, spasm, and stiffness in a variety of inflammatory, traumatic and degenerative conditions affecting muscles and joints, including: arthritis, osteoarthritis, rheumatoid arthritis, periarthritis, spondylitis, lumbosacral and sacroiliac strain, sprains, whiplash injuries, intervertebral disc syndrome, bursitis, torticollis, fibrositis, fibromyositis, and tenosynovitis. In addition, Soma acts to normalize motor activity in certain neurologic disturbances, such as cerebral palsy, and other dyskinesias."

  The "Administration and Dosage" section of the original label stated that the "usual adult dose of Soma is one 350 mg tablet three times daily and at bedtime."

- A supplement to NDA 11-792 was approved on September 17, 1959 with a new adult indication, a new pediatric indication, a new dosing regimen, and a new dosing formulation. The "Indications and Uses" section was revised to the following (words **bolded and underlined** were additions to the originally approved carisoprodol label):

  > "Soma relieves pain, spasm, and stiffness in a variety of inflammatory, traumatic and degenerative conditions affecting muscles and joints, including: arthritis, osteoarthritis, rheumatoid arthritis, periarthritis, spondylitis, lumbosacral and sacroiliac strain, sprains,

whiplash injuries, intervertebral disc syndrome, bursitis, torticollis, fibrositis, fibromyositis, and tenosynovitis. **It is useful for the relief of postoperative myalgia.** In addition, Soma acts to normalize motor activity in certain neurologic disturbances, such as cerebral palsy, and other dyskinesias **characterized by abnormal reflex activity, increased muscle tonus, involuntary movements and incoordination. In children Soma is indicated in cerebral palsy and other conditions in which muscle spasm is a factor.**"

In addition, this supplement modified the "Administration and Dosage" section of the label to the following:

"The usual adult dose of Soma is one 350 mg tablet three times daily and at bedtime. **The usual dose of Soma for children, 5 years or over, is one 250 mg capsule two or three times a day. The contents of the capsule may be removed and mixed with such flavoring agents as jelly or chocolate syrup in order to facilitate administration to children and others unable to swallow capsules. A part of the contents of one capsule can be used for administration to children under 5 years of age.**"

- Since carisoprodol was approved before 1962, the National Academy of Science/National Research Council (NAS/NRC) evaluated the efficacy of 250 and 350 mg carisoprodol dosage regimens.*

* A 1962 amendment to the Federal Food, Drug and Cosmetic Act (called the Kefauver-Harris amendment) required the FDA to conduct a retrospective evaluation of the effectiveness of the drugs that FDA had approved between 1938 and 1962 (on the basis of safety without demonstration of efficacy). The FDA contracted with the NAS/NRC to make an initial evaluation of drugs that were approved between 1938 and 1962. The FDA's implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI).

- After NAS/NRC reported the results of their evaluations to the FDA, the FDA published a Federal Register (FR) Notice on September 1, 1970 (35 FR 13854) stating that the carisoprodol 350 mg regimen was "possibly effective for symptomatic relief in conditions characterized by skeletal muscle spasm and mild to moderate pain" and this regimen lacked "substantial evidence of effectiveness for all other labeled indications."

- After Carter-Wallace (the predecessor to MedPointe) submitted data to support the 350 mg dosage regimen (and after the FDA's review of this data), the FDA published an August 15, 1974 FR (39 FR 29399) which stated the 350 mg carisoprodol dosing regimen is "effective in the treatment of discomfort associated with acute, painful musculoskeletal conditions." In addition, this FR notice stated that no "studies were conducted with the 250 mg strength of carisoprodol" and the 250 mg dosing regimen "is regarded as an inappropriate dosage strength and accordingly lacks substantial evidence of effectiveness" for all indications. In addition, the FR notice provided Medpointe of the 250 mg carisoprodol capsules "an opportunity for a hearing to show why approval of the new drug applications should not be withdrawn".

- After publication of the August 1974 FR notice, Carter-Wallace did not request a hearing and did not provide supportive data for the 250 mg carisoprodol capsules. In August 1974, Carter-Wallace withdrew the 250 mg carisoprodol capsules from marketing.

- A May 4, 1979 FR notice (44 FR 16165) was published by the FDA in response to the carisoprodol's submission of data to support marketing of SOMA COMPOUND (under NDA 12-365) and SOMA COMPOUND with CODEINE (NDA 12-366). This May 1979 FR notice stated that "(a)lthough data were not submitted specifically concerning a 250 milligram strength of carisoprodol, the studies of the two combinations, each of which contains 200 milligrams carisoprodol justify reclassifying the 250-milligrams carisoprodol to effective."

- On June 29, 1979, Carter-Wallace informed the FDA that they discontinued the marketing of 250 mg carisoprodol capsules in August 1974.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

From a chemistry, manufacturing, and controls (CMC) standpoint, Dr. Don Klein (the CMC reviewer) recommends the approval of the 250 mg carisoprodol dose. According to Dr. Klein, the sponsor's updated specifications of the drug substance and drug product and adequate packaging materials support the approval of this supplement. Dr. Klein recommends a 36-month expiration shelf life period for the 250 mg carisoprodol dose. See Dr. Klein's review for more details.

3.2 Animal Pharmacology/Toxicology

No new animal pharmacology or animal toxicology studies were required for this efficacy supplement because carisoprodol has been approved and marketing in the United States for almost 50 years and the proposed carisoprodol dose is lower then the currently approved dose.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Four sponsor-conducted carisoprodol studies were evaluated in this review, including:

- Two randomized, double-blind, placebo-controlled trials of carisoprodol in adult patients with acute, idiopathic mechanical low back pain (i.e., Studies MP502 and MP505); and
- Two pharmacokinetic studies of carisoprodol in healthy subjects (i.e., Studies MP500 and MP501).

The four final study reports were submitted in paper.

Additionally, post-marketing Adverse Event Reporting System (AERS) reports of adverse events associated with the use of carisoprodol 350 mg tablets were evaluated in this review.

4.2 Tables of Clinical Studies

Table 4 lists the four clinical studies of carisoprodol submitted in this efficacy supplement. The most important studies for the efficacy and safety review of carisoprodol are Studies MP502 and MP505.

Table 4: The four carisoprodol studies submitted in the efficacy supplement

STUDY[1]	DESIGN	TREATMENT GROUPS	DURATION
MP500 (N=24) (12/10/04 to 12/20/04)	Randomized, open-label, single-dose, crossover, pharmacokinetic, single-center, U.S. trial on the effect of food on the absorption of carisoprodol from 350 mg carisoprodol tablets in **healthy subjects**	Two sequences: 1) A then B (n=12) 2) B then A (n=12) A is a single-dose of 350 mg of carisoprodol in fed state B is a single-dose of 350 mg of carisoprodol in fast state	Two single doses separated by 7 days of washout
MP501 (N=24) (2/28/05 to 3/21/05)	Randomized, open-label, single-dose, crossover, pharmacokinetic, single-center, U.S. trial on the absorption of carisoprodol from 150 mg and 250 mg carisoprodol tablets relative to that from 350 mg carisoprodol tablets in **healthy subjects**	Six sequences: (N=24) 1) A then B then C 2) A then C then B 3) B then A then C 4) B then C then A 5) C then A then B 6) C then B than A A is 150 mg of carisoprodol B is 250 mg of carisoprodol C is 350 mg of carisoprodol	Three single doses (each dose separated by a 7 day washout period)
MP502 (N=826) (8/15/05 to 7/18/06)	Randomized, double-blind, placebo-controlled, parallel-group, multi-center, U.S., one week trial of 250 mg and 350 mg carisoprodol tablets in adult **patients** aged 18 to 65 years old **with acute, idiopathic, mechanical low back pain**	1) Placebo (n=276) 2) Carisoprodol 250 mg (n=271) 3) Carisoprodol 350 mg (n=279) (all treatment groups dosed four times a day)	Up to 7 days
MP505 (N=561) (8/11/05 to 6/8/06)	Randomized, double-blind, placebo-controlled, parallel-group, multi-center, U.S., one-week trial of 250 mg carisoprodol tablets in adult **patients** aged 18 to 65 years old **with acute, idiopathic mechanical low back pain**	1) Placebo (n=284) 2) Carisoprodol 250 mg (n=277) (all treatment groups dosed four times daily)	Up to 7 days

1 Study columns includes the study initiation date to the study completion date
Reference: NDA 11-792 submission

4.3 Review Strategy

This medical officer was responsible for the entire efficacy and safety reviews of this carisoprodol efficacy supplement.

Studies MP502 and MP505 are the two important trials for the **efficacy review** because these two trials are adequate and well-controlled studies of the proposed 250 mg carisoprodol dose regimen in patients with acute, idiopathic mechanical low back pain. Studies MP500 and MP501 (single-dose PK studies in healthy subjects) were not used for the efficacy review because these PK studies did not include efficacy assessments and these studies were conducted in healthy subjects (not patients with acute, musculoskeletal conditions).

Studies MP502 and MP505 are the two most important trials for the **safety review** because these two trials are adequate and well-controlled studies of the proposed 250 mg carisoprodol dose regimen in patients with acute, idiopathic mechanical low back pain. Additionally, Studies

MP500 and MP501 were reviewed for significant adverse events (i.e., deaths, nonfatal SAEs, and adverse events leading to discontinuations).

4.4 Data Quality and Integrity

DAARP selected four clinical sites from the two low back pain studies (i.e., Studies MP502 and MP505) for inspection. These four sites were chosen because these sites enrolled a larger number of patients, compared to other sites. In addition, the proposed 250 mg carisoprodol dose regimen demonstrated larger treatment effect sizes for the co-primary efficacy endpoints (according to the efficacy by site analyses) for these four sites, compared to other sites (see Table 5). DAARP consulted the Division of Scientific Investigations (DSI) to audit one of these four clinical sites.

Table 5: Four possible clinical sites for DSI inspection and the treatment effect size for the co-primary efficacy endpoints by site for the 250 mg carisoprodol dose

Site #	Study	Location (Investigator)	N	Difference in efficacy of the 250 mg dose from PL in the first primary endpoint[1]	Difference in efficacy of the 250 mg dose from PL in the second primary endpoint[2]
241	MP502	Sun Research Institute 730 North Main Avenue, Suite 424 San Antonio, TX 78205 (Stephen C. Cohen, MD)	27	1.3	1.0
263[3]	**MP502**	**1745 Old Spring House Lane, Suite 420, Atlanta, GA 30338 (Ateeqahmed S. Patel, MD)**	**34**	**1.3**	**1.0**
283	MP502	Crest Clinical Trials, Inc. 3340 West Ball Road, Suite I Anaheim, CA 92804 (Simon Babazadeh, MD)	31	1.4	1.0
566	MP505	Quality of Life Medical Center, LLC 21520 South Pioneer Blvd., Suite 203, Hawaiian Gardens, CA 90716 (Vladimir Samonte, MD)	40	1.3	1.5

1 The first co-primary efficacy endpoint was patient-rated relief from starting backache (scale was graded from 0 to 4)
2 The second co-primary efficacy endpoint was patient-rated global impression of change (scale was graded from 0 to 4)
3 The DSI inspected Site #263.
Reference: Volume 19, Section 16.1.4, Pages 315-322 and Volume 54, Section 16.1.4, Pages 177-180.

DSI chose to inspect Site 263 in Atlanta, GA. DSI stated that 36 and 34 patients enrolled and completed the study at this site, respectively. DSI inspected 35 patient records and found "No significant regulatory violations" and they concluded that the site "adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects."

4.5 Compliance with Good Clinical Practices

According to Medpointe, both studies in the treatment of low back muscle spasm (i.e., Studies MP502 and MP505) were conducted in compliance with good clinical practice (GCP) guidelines,

as described in the 1996 International Committee on Harmonization (ICH) Harmonized Tripartite Guidelines for GCP; U.S. Code of Federal Regulations (CFR) dealing with clinical studies, informed consent, and institutional review board (IRB) regulations; and the Declaration of Helsinki concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects). A signed informed consent form was obtained for each patient prior to enrollment and IRB approval was obtained by the principle investigators according to 21 CFR 50 and 56. According to Medpointe, all of the studies were conducted in accordance with acceptable ethical standards.

4.6 Financial Disclosures

Medpointe submitted FDA Form 3454 certifying that the clinical investigators in Studies MP502 and MP505):

- Did not participate in any financial arrangement with the sponsor, whereby the value of compensation to the investigators for conducting the study could be affected by the outcome of the study [as defined in 21 CFR 54.2(a)]:
- Had no proprietary interest in this product or significant equity interest in the sponsor [as defined in 21 CFR 54.2(b)]: and
- Was not the recipient of significant payments of other sorts [as defined in 21 CFR 54.2(f)].

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The pharmacokinetics (PK) of carisoprodol and its metabolite, meprobamate, were studied in Study MP501 (a randomized, crossover, open-label, single-dose PK, single-center, U.S. study on the absorption of carisoprodol from 150 mg, 250 mg, and 350 mg carisoprodol tablets in healthy subjects). According to Dr. Lei Zhang, the clinical pharmacology reviewer, the following are the important PK results from Study MP501:

- The exposure of carisoprodol and its metabolite, meprobamate, were dose proportional between the 250 mg and 350 mg doses;
- After carisoprodol administration, the exposure of meprobamate was higher (i.e., about 6-fold higher for AUC and about 50% higher for Cmax) than carisoprodol;
- The half life of meprobamate (i.e., 10 hours) was longer than the half life of carisoprodol (i.e., 2 hours); and
- The exposure of carisoprodol and meprobamate were higher in females compared to males.

The PK of carisoprodol and meprobamate were studied in Study MP500 (a randomized, crossover, open-label, single-dose PK, single-center, U.S. study on the effect of food on the absorption of carisoprodol from 350 mg carisoprodol tablets in healthy subjects). According to Dr. Zhang, the following are the important PK results from Study MP500:

- The exposure of carisoprodol and meprobamate were similar after fasting and after eating a high fat meal;
- The absorption rate of carisoprodol was similar after fasting and after eating a high fat meal; and
- The exposure of carisoprodol and meprobamate were higher in females compared to males.

Dr. Zhang also had the following comments regarding the metabolism and clearance of carisoprodol:

- Carisoprodol is metabolized by CYP2C19 to form meprobamate, its major metabolite. To a smaller extent, carisoprodol is metabolized to hydroxyl-carisoprodol by an unknown enzyme. Subsequently, both meprobamate and hydroxyl-carisoprodol are metabolized to hydroxyl-meprobamate, conjugated, and then excreted in the urine.
- Carisoprodol is eliminated by renal and non-renal routes.

For more details about the PK of carisoprodol and meprobamate see Dr. Zhang's review.

5.2 Pharmacodynamics

Pharmacodynamic studies (including thorough QT/QTc studies) were not submitted in this efficacy supplement.

5.3 Exposure-Response Relationships

There was one dose-ranging clinical trial submitted in this efficacy supplement (i.e., Study MP502). See Sections 6 and 7 for the results of this study. However, Study MP502 did not include pharmacokinetic assessments.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Proposed Indication

Proposed Indication: "SOMA is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions [redacted (b) (4)]

SOMA [redacted (b) (4)] used for short periods [redacted (b) (4)] because adequate evidence of effectiveness for more prolonged use is not available and because acute, painful musculoskeletal conditions are generally of short duration.

[redacted (b) (4)]

6.1.1 Methods

Studies MP502 and MP505 are the two important trials for the **efficacy review** because these two trials are adequate and well-controlled studies of the proposed 250 mg carisoprodol regimen in patients with acute, idiopathic mechanical low back pain. Studies MP500 and MP501 (single-dose PK studies in healthy subjects) were not used for the efficacy review because these PK studies did not include efficacy assessments and these studies were conducted in healthy subjects (not patients with acute, musculoskeletal conditions).

6.1.2 General Discussion of Endpoints

In the low back pain studies, the **patient-reported** (using diary cards), 5-point categorical co-primary efficacy endpoints were the following:

1) "Relief from Starting Backache": Mean value [of the morning assessment (6:00 to 9:00 AM) and the evening assessment (6:00 to 9:00 PM)] of lower back pain relief on Study Day #3. Lower back pain relief was obtained from responses to the following question, "compared with how you felt prior to starting study medication, and regardless of whether you think the change was due to medicine, please indicate if you have experienced" (compared to baseline) one the following: complete relief (4), a lot of relief (3), some relief (2), a little relief (1), or no relief (0); and
2) "Global Impression of Change": Mean value [of the morning assessment (6:00 to 9:00 AM) and the evening assessment (6:00 to 9:00 PM)] of the "global impression of change" on Study Day #3. The "global impression of change" score was obtained from responses to the following question, "compared with how you felt prior to starting study medication, and regardless of whether you think the change was due to the medicine, please indicate if you have experienced" one of the following: marked improvement (4), moderate improvement (3), mild improvement (2), no change (1), or worsening (0).

Medical Reviewer's Comments: The two low back pain studies had two pre-specified co-primary efficacy endpoints that were one-item patient reported outcomes (PROs) with Likert responses. Both of these endpoints have limitations in the ability to assess pain relief in low back pain patients.

Limitations of the "Relief from Starting Backache" (RSB) PRO instrument include (see the 2006 *Patient Reported Outcome Measures* Draft Guidance):

- **Responses that did not offer a clear distinction between choices. Low back pain patients are not likely to differentiate between "some relief (2)" and "a little relief (1)";**
- **Recall bias: Patients had to compare their back pain in the morning and evening of Day #3 to their back pain at baseline (which had occurred about 48 to 60 hours earlier on the morning of Day #1). Ideally, it "is usually better to construct items that ask patients to describe their current state than to ask them to compare their current state with an earlier period".**
- **Lack of content validation: The protocol did not contain a description of the following: the generation, modification, and finalization of RSB; the reliability of RSB; the reproducibility of RSB; and the ability of RSB to detect change in acute, mechanical low back pain patients; and**
- **No minimally clinical important difference was identified.**

Limitations of the "Global Impression of Change" (GIC) PRO instrument include (see the 2006 *Patient Reported Outcome Measures* Draft Guidance):

- **Unbalanced response options: There were more positive responses [marked improvement (4), moderate improvement (3), and mild improvement (2)] then negative responses [worsening (0)] and this may bias the direction of the results.**
- **Recall bias: Patients had to compare their back pain in the morning and evening of Day #3 to their back pain at baseline (which had occurred about 48 to 60 hours earlier on the morning of Day #1). Ideally, it "is usually better to construct items that ask patients to describe their current state than to ask them to compare their current state with an earlier period."**
- **Lack of content validation: The protocol did not contain a description of the following: the generation, modification, and finalization of GIC; the reliability of GIC; the reproducibility of GIC; and the ability of GIC to detect change in acute, mechanical low back pain patients; and**
- **No minimally clinical important difference was identified.**

These co-primary efficacy endpoints are not the most optimal instruments for assessment of pain relief. However, these co-primary efficacy endpoints are acceptable for these two low back pain trials because:

- **Suboptimal endpoints in pain trials designed to demonstrate superiority may adversely affect the investigational product more than the control;**

- **In multiple meetings with Medpointe, DAARP did not question the adequacy of the primary efficacy endpoints; and**
- **These endpoints have been used in the recent approval of other products for the identical proposed indication [i.e., cyclobenzaprine (Flexeril); cyclobenzaprine extended-release capsules (AMRIX)].**

The seven pre-specified secondary efficacy endpoints for the low back pain studies were the following:

1) Roland-Morris Disability Questionnaire (RMDQ) score of function [ranging from 0 (no disability) to 24 (maximum disability)] on Study Day #7 minus the baseline score (see Table 6);
2) RMDQ score on Study Day #3 minus the baseline score;
3) Amount of forward flexion of the lower back in centimeters (the mean value of three measurements for forward bending minus the mean value for standing straight up) on Day #7 minus the forward flexion baseline score;
4) Amount of forward flexion of the lower back on Day #3 minus the baseline score;
5) Patient-rated Medication Helpfulness on Study Day # 7: Patients were asked, "How would you rate this study medication in improving your condition?" with the following responses: Excellent (4), Very good (3), Good (2), Fair (1), or Poor (0);
6) Patient-rated Medication Helpfulness on Study Day # 3; and
7) Time (in days) from the start study treatment to the first patient-reported moderate improvement (3) or marked improvement (4) on the GIC scale.

Table 6: Roland-Morris Disability Questionnaire (RMDQ)[1]

1)	I stay at home most of the time because of my back;
2)	I change position frequently to try and get my back comfortable;
3)	I walk more slowly than usual because of my back;
4)	Because of my back, I am not doing any of the jobs that I usually do around the house;
5)	Because of my back, I use a handrail to get upstairs;
6)	Because of my back, I lie down to rest more often;
7)	Because of my back, I have to hold on to something to get out of an easy chair;
8)	Because of my back, I try to get other people to do things for me;
9)	I get dressed more slowly than usual because of my back;
10)	I only stand for short periods of time because of my back;
11)	Because of my back, I try not to bend or kneel down;
12)	I find it difficult to get out of a chair because of my back;
13)	My back is painful almost all the time;
14)	I find it difficult to turn over in bed because of my back;
15)	My appetite is not very good because of my back pain;
16)	I have trouble putting on my socks (or stockings) because of the pain in my back;
17)	I only walk short distances because of my back;
18)	I sleep less well on my back;
19)	Because of my back pain, I get dressed with help from someone else;
20)	I sit down for most of the day because of my back;
21)	I avoid heavy jobs around the house because of my back;
22)	Because of my back pain, I am more irritable and bad tempered with people than usual;
23)	Because of my back pain, I go upstairs more slowly than usual;
24)	I stay in bed most of the time because of my back.

1 Patients were instructed to answer the question based upon their symptoms on the current day
Reference: Adapted from Volume 54, Page 161, Sample Case Report Form

<u>Medical Reviewer's Comments</u>: The two RMDQ endpoints (the change from baseline on Days #3 and #7) are the most important secondary efficacy endpoints because the RMDQ is a functional endpoint and the RMDQ has been validated. Multiple members of the July 1999 Joint Over-the-Counter and Arthritis Advisory Committee Meeting (advising the FDA regarding the approvability of low dose Flexeril for over-the-counter use) stated that they want to see instruments that measure disability in low back pain trials. In addition, multiple studies in the literature state that the RMDQ has been validated as a functional instrument in low back pain. Finally, the RMDQ endpoints do not reduce recall bias (patients are asked to assess their back pain on the current day at baseline and on Days #3 and #7 during the treatment period).

The Medication Helpfulness endpoints on Days #3 and #7 (secondary endpoints #5 and #6) are very similar to the co-primary efficacy endpoints (i.e., RSB and GIC) because all three endpoints:

- **Are based on a five-point Likert response;**
- **Are measured only during the treatment period (the baseline measurements are not computed in the instruments); and**
- **Measure improvement in low back pain.**

The two flexibility secondary endpoints (i.e., the change in forward flexion from baseline on Days #3 and #7) are not standard evaluations in low back pain studies and these flexibility endpoints have not be validated.

The pre-specified time to event endpoint (i.e., the number of days from the start study treatment to the first moderate or marked improvement on the GIC scale) is not an important secondary endpoint because this survival analysis has too few time points (the analysis is based on full day assessments; not on 12 hour assessments). The results of this secondary endpoint will not be presented given its deficiencies.

Table 7 presents a comparison of the primary efficacy endpoints used in the carisoprodol low back pain studies to the primary efficacy endpoints used in the cyclobenzaprine extended-release and the cyclobenzaprine studies in patients with back pain.

Table 7: Primary efficacy endpoints supporting this carisoprodol efficacy supplement and recently approved products for the relief of discomfort associated with acute, painful musculoskeletal conditions

	Product	Clinical trial Design	Comparators[1]	Primary efficacy endpoints[2]
1	**SOMA®** (carisoprodol) NDA 11-792/S-041	Study 502MP: R, DB, PC, **one-week trial** of 18-65 year old patients with acute, painful, lower back muscle spasm.	Placebo (n=269) Soma 250 mg QID (n=264) Soma 350 mg QID (n=273)	1) Global Impression of Change 2) Relief from Starting Backache
		Study 505MP: R, DB, PC, **one-week trial** of 18-65 year old patients with acute, painful, lower back muscle spasm.	Placebo (n=278) Soma 250 mg QID (n=269)	1) Global Impression of Change 2) Relief from Starting Backache
2	**AMRIX®** (cyclobenzaprine HCl extended-release capsules) NDA 21-777	Study 1105: R, DB, PC, **two-week** trial of patients 18 to 75 years old with acute, painful cervical or lumbar muscle spasm	Placebo (n=64) Flexeril IR 10 mg TID (n=62) Amrix 15 mg q day (n=64) Amrix 30 mg q day (n=64)	Two primary assessments[3] 1) Medication Helpfulness 2) Global Assessment
		Study 1106: R, DB, PC, **two-week** trial of patients 18 to 75 years old with acute, painful cervical or lumbar muscle spasm	Placebo (n=64) Flexeril IR 10 mg TID (n=61) Amrix 15 mg q day (n=63) Amrix 30 mg q day (n=62)	Two primary assessments[3] 1) Medication Helpfulness 2) Global Assessment
3	**FLEXERIL®** (cyclobenzaprine HCl) NDA 17-821/S-045	Study 006: R, DB, PC, **one-week** trial of patients ≥ 18 years old with acute, painful cervical or lumbar muscle spasm	Placebo (n=241) Flexeril 5 mg TID (n=238) Flexeril 10 mg TID (n=238)	Three primary assessments[4] 1) Global Impression of Change 2) Medication Helpfulness 3) Relief from Starting Backache
		Study 008: R, DB, PC, **one-week** trial of patients ≥ 18 years old with acute, painful cervical or lumbar muscle spasm	Placebo (n=217) Flexeril 2.5 mg TID (n=216) Flexeril 5 mg TID (n=215)	Three primary assessments[4] 1) Global Impression of Change 2) Medication Helpfulness 3) Relief from Starting Backache

1 n is the number of patients in the ITT population (the primary population for efficacy)

2 All primary efficacy endpoints were patient-reported outcomes (PROs) except the physician's global assessment (a physician-reported outcome) in the Amrix studies.

- Global Impression of Change was a 0-4 PRO scale with the following responses: marked improvement (4), moderate improvement (3), mild improvement (2), no change (1), or worsening (0).
- Relief from Starting Backache was a 0-4 PRO scale with the following responses: complete relief (4), a lot of relief (3), some relief (2), a little relief (1), or no relief (0).
- Medication Helpfulness was a 0-4 PRO scale with the following responses: Excellent (4), Very good (3), Good (2), Fair (1), or Poor (0).
- Physician's Global Assessment, an investigator outcome, was based on the physical exam, degree of muscle spasm, reaction to palpation, limitation of range of motion, and evaluation of patient's reported functional assessment and it had the following responses: Marked improvement (5), Moderate improvement (4), Slight change (3), No change (2), and Worse (1).

3 Amrix studies 1105 and 1106 had two co-primary efficacy endpoints: The PRO Medication Helpfulness and Physician's Global Assessment on Day #4. The primary statistical analysis was performed with the Wilcoxon Rank Sum Test comparing each Amrix group (i.e., 15 mg and 30 mg) with the placebo group.

4 Flexeril studies 006 and 008 had six primary comparisons between the Flexeril 5 mg TID and placebo treatment groups on Days #3 and #7. The GIC and Medication Helpfulness endpoints were performed in clinic on Day #3 (or Day #4) and Day #8. The RSB was performed at home (by patient diary) on Day #3 (or Day #4) and Day #7. Statistical significance in favor of Flexeril 5 mg TID was required for at least two of the three parameters for at least one of the two time points in order to conclude superiority of Flexeril 5 mg TID over placebo. Each of the six individual comparisons were made at the 0.03 level. The analysis of variance (ANOVA) was used for the primary efficacy endpoints.

R is randomized, DB is double-blind, and PC is placebo-controlled.

Reference: The approved labels at http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm and NDA 11-792/S-041

Medical Reviewer's Comments: The primary efficacy endpoints in the carisoprodol low back pain studies in this efficacy supplement were similar to the primary efficacy endpoints that supported the approval of cyclobenzaprine extended-release in 2007 and the 5 mg cyclobenzaprine immediate-release regimen in 2003 for the relief of acute, painful, musculoskeletal conditions. Both co-primary efficacy endpoints in the carisoprodol low back pain studies were used in the cyclobenzaprine immediate-release studies. One of the co-primaries in the cyclobenzaprine extended-release studies (i.e., Medication Helpfulness) was a secondary endpoint in the carisoprodol low back pain studies. All of the primary efficacy endpoints in these studies were PROs except the physician global assessment in the cyclobenzaprine extended-release studies.

6.1.3 Study Design

The sponsor submitted two important clinical trials (i.e., Studies MP502 and MP505) to support the efficacy of 250 mg of carisoprodol three times daily and once nightly for the relief of discomfort of acute, musculoskeletal conditions. The overview of the design of both trials is presented in this section and the complete study designs are presented in the Appendix (Studies MP502 and MP505 are presented in Sections 10.1.1 and 10.1.2, respectively).

Study MP502

Title: Study MP502 entitled "Randomized, Double-Blind Trial of Carisoprodol 250 mg Tablets Compared to Placebo and Carisoprodol 350 mg Tablets in Patients with Acute, Painful Musculoskeletal Spasm of the Lower Back"

Objective: The primary objective of this study, according to Medpointe, was to determine the efficacy and safety of 250 mg of carisoprodol dose regimen (three times daily and at bedtime) versus placebo in patients with acute musculoskeletal spasm of the lower back.

Overall Design: A randomized, double-blind, placebo-controlled parallel-group, multiple-center (57 sites), U.S. study of carisoprodol in adult patients 18-65 years of age with acute idiopathic, mechanical low back pain. Patients were randomized 1:1:1 to one of the following three treatments four times a day for seven days: 250 mg of carisoprodol tablets, 350 mg of carisoprodol tablets, and placebo.

Conduct Time: The first patient was enrolled on August 15, 2005 and the last patient completed the trial on July 18, 2006.

Study MP505

Title: Study MP505 entitled "Randomized, Double-Blind Trial of Carisoprodol 250 mg Tablets Compared to Placebo in Patients with Acute, Painful Musculoskeletal Spasm of the Lower Back"

Objective: The primary objective of this study, according to Medpointe, was to determine the efficacy and safety of 250 mg of carisoprodol dose regimen (three times daily and at bedtime) versus placebo in patients with acute musculoskeletal spasm of the lower back.

Overall Design: A randomized, double-blind, placebo-controlled parallel-group, multiple-center (47 sites), U.S. study of carisoprodol in patients 18-65 years of age with acute idiopathic, mechanical low back pain. Patients were randomized 1:1 to one of the following two treatments four times a day for seven days: 250 mg of carisoprodol tablets and placebo.

Conduct Time: The first patient was enrolled on August 11, 2005 and the last patient completed the trial on June 8, 2006.

A Comparison between Studies MP502 and MP505: Studies MP502 and MP505 had identical eligibility criteria, study durations (i.e., seven days), prohibited concomitant medication, procedures and evaluations, primary efficacy endpoints, secondary efficacy endpoints, safety monitoring, primary statistical population, and statistical methods (including imputation methods and primary multiplicity adjustments).

The major difference between the two studies was that Study MP505 only contained two arms (carisoprodol 250 mg QID and placebo); whereas, Study MP502 contained three arms (carisoprodol 250 mg QID, carisoprodol 350 mg QID, and placebo).

Medical Reviewer's Comments: The studies are well-designed and well-controlled. The studies only included patients between 18 and 65 years old. Optimally, geriatric patients should have been included in the low back pain studies because geriatric patients develop acute, mechanical, lower back pain. In addition, since geriatric patients are more likely to have sedative AEs with the use of CNS depressants like carisoprodol, it is important to evaluate if a lower carisoprodol dose reduces the incidence of sedative effects in the geriatric population. Since geriatric patients were not included in these studies, the sponsor's proposal (i.e., to include a statement in the Geriatric Use section of the label that the safety and efficacy of carisoprodol has not been evaluated in geriatric patients) is acceptable.

The carisoprodol low back pain trials were similar to the design of the cyclobenzaprine immediate-release and cyclobenzaprine extended-release trials in patients with back pain (see Table 7). All of the trials were short-term, randomized, double-blind, placebo-controlled trials in patients with back pain. Most of these trials had a dose-ranging control. The cyclobenzaprine immediate-release and cyclobenzaprine extended-release trials included patients with lumbar and cervical back pain; however, the carisoprodol clinical trials included only patients with low back pain. The cyclobenzaprine immediate-release and extended-release trials included geriatric patients; in contrast, the carisoprodol trials did not include geriatric patients. The duration of the cyclobenzaprine extended-release trials were two weeks; whereas, the duration of the cyclobenzaprine immediate-release and the carisoprodol trials were one week. See Section 6.1.4 for a review of the primary efficacy endpoints in these trials.

6.1.4 Efficacy Findings

Disposition: Table 8 shows the disposition of patients in the two low back pain studies.

Table 8: Disposition of patients in the low back pain studies[1]

	Placebo	Carisoprodol 250 mg	Carisoprodol 350 mg
Total randomized, N (%)	561 (100)	548 (100)	281 (100)
Safety population[2], n (%)	560 (99.8)	548 (100)	279 (99.3)
ITT population[3], n (%)	547 (96.5)	533 (97.3)	273 (97.2)
Per protocol population[4], n (%)	467 (83.2)	478 (87.2)	232 (82.6)
Total completed, n (%)	470 (83.8)	491 (89.6)	239 (85.1)
Total discontinuations[5], n (%)	91 (16.2)	57 (10.4)	42 (14.9)

1 The low back pain studies were Studies MP502 and MP505.
2 The safety population included randomized patients who received at least one dose of study medication.
3 The ITT population included patients who received at least one dose of study medication and who had at least one post-baseline efficacy assessment. The ITT population was the primary statistical population for the efficacy endpoints.
4 The per protocol population included ITT patients who took at least 70% of the required study medication and completed the study with complete diary data. The PP population was the confirmatory population for the efficacy endpoints.
5 See Table 21 for the reasons for discontinuations in the low back pain studies
Reference: Adapted from Volume 1, Table 3.6.3.1-1, Page 51; Volume 15, Table 8.1.2.4-1, Page 17; and Volume 15, Table 8.1.2.4-2, Page 17.

Baseline Characteristics: Table 9 displays the baseline characteristics of the patients in the two low back pain studies. In addition, Table 39 in Section 7.2.1.2 summarizes the demographics in Studies MP502 and MP505.

Table 9: Baseline characteristics of the patients in the low back pain studies[1]

Characteristic	Placebo n=560[2]	Carisoprodol 250 mg n=548[2]	Carisoprodol 350 mg n=279[2]
Duration of lower back pain in days, mean (SD)	1.7 (0.8)	1.6 (0.8)	1.6 (0.7)
Mild severity of low back pain, %	0.2	0.2	0
Moderate severity of low back pain, %	68.4	70.1	66.3
Severe severity of low back pain, %	31.4	29.7	33.7
Forward flexion of lower back in cm, mean (SD)	6.2 (3.0)	6.5 (3.2)	6.5 (3.1)

1 The low back pain studies were Studies MP502 and MP505.
2 The safety population (patients who received at least one dose of study medication).
Reference: Adapted from Volume 16, Table 8.2.1-2, Pages 72-74.

Medical Reviewer's Comments: The baseline patient characteristics (i.e., the duration of low back pain, the severity of low back pain, and the flexibility of the lower back) in the three treatment groups were similar in the low back pain studies. The patients had acute low back pain (i.e., the duration of low back pain was ≤ 3 days); not chronic low back pain.

Table 10 displays the baseline use of analgesics, muscle relaxants, and benzodiazepines in the low back pain studies.

Table 10: Baseline use[1] of analgesics, muscle relaxants, and benzodiazepines in the low back pain studies[2]

Product	Placebo n=560[3] n (%)	Carisoprodol 250 mg n=548[3] n (%)	Carisoprodol 350 mg n=279[3] n (%)
NSAIDs (including aspirin)	145 (25.9)	144 (26.3)	70 (25.1)
Acetaminophen and acetaminophen combinations	20 (3.6)	32 (5.8)	27 (9.7)
Opioid agonists and opioid agonist combinations	5 (0.9)	7 (1.3)	8 (2.9)
Benzodiazepines	3 (5.4)	7 (1.3)	2 (0.7)
Muscle relaxants	8 (1.4)	3 (0.6)	3 (1.1)
Tramadol and tramadol/acetaminophen	0 (0)	3 (0.6)	0 (0)
Gabapentin and pregabalin	0 (0)	1 (0.2)	1 (3.4)

1 Numbers and percentages are the number of uses of these products (patients may be counted twice in each listing if they received more than one product)
2 Studies MP502 and MP505 were low back pain studies.
3 The safety population (patients who received at least one dose of study medication).
Reference: Adapted from Volume 18, Table 14.1.7.1, Pages 132-143 and Volume 53, Table 14.1.7.1, Pages 117-123.

Medical Reviewer's Comments: The baseline use of analgesics, muscle relaxants, and benzodiazepines in the three treatment groups appeared to be balanced. Opioids were used at a greater frequency in the carisoprodol groups than the placebo group; however, benzodiazepines were used at a greater frequency in the placebo group than the carisoprodol groups.

Concomitant Medication Use: Table 11 displays the concomitant use of analgesics, muscle relaxants, and benzodiazepines during the one-week treatment period in the low back pain studies.

Table 11: Concomitant use of analgesics, muscle relaxants, and benzodiazepines during the treatment period in the low back pain studies[2]

Product	Placebo n=560[3] n (%)	Carisoprodol 250 mg n=548[3] n (%)	Carisoprodol 350 mg n=279[3] n (%)
NSAIDs (including aspirin)	99 (17.6)	110 (20.0)	49 (17.6)
Acetaminophen and acetaminophen combinations	47 (8.4)	48 (8.8)	24 (8.6)
Opioid agonists and opioid agonist combinations	13 (2.3)	11 (2.0)	6 (2.2)
Benzodiazepines	8 (1.4)	8 (1.5)	3 (1.1)
Muscle relaxants	10 (1.8)	5 (0.9)	2 (0.7)
Tramadol and tramadol/acetaminophen	0 (0)	2 (0.4)	2 (0.7)
Gabapentin and pregabalin	1 (0.2)	1 (0.2)	2 (0.7)

1 Numbers and percentages are the number of uses of these products (patients may be counted twice in each listing if they received more than one product)
2 Studies MP502 and MP505 were low back pain studies.
3 The safety population (patients who received at least one dose of study medication).
Reference: Adapted from Volume 18, Table 14.1.7.2, Pages 144-161 and Volume 53, Table 14.1.7.2, Pages 124-138.

Medical Reviewer's Comments: The use of analgesics (including NSAIDs, acetaminophen, tramadol, and opioid agonists), muscle relaxants, and benzodiazepines in the treatment groups were balanced. Thus, the concomitant medications in the low back pain trials did not bias the efficacy results.

Co-Primary Efficacy Endpoint Results:

Tables 12 displays the results of the first co-primary efficacy endpoint ["Global Impression of Change" (GIC) on Day #3] in the two low back pain studies (i.e., Studies MP502 and MP505).

Table 12: The results of the first co-primary efficacy endpoint ("Global Impression of Change" on Day #3)[1] in Studies MP502 and MP505

Study	Parameter	Placebo	Carisoprodol 250 mg	Carisoprodol 350 mg
MP502	n	269	264	273
	"Global Impression of Change" on Day #3, LS Mean (SE)	1.94 (0.06)	2.16 (0.06)	2.20 (0.06)
	Difference between carisoprodol and placebo (95% CI)	-	0.22 (0.07,0.37)	0.25 (0.10,0.40)
	p-value[2]	-	0.0046[3]	0.0011
MP505	n	278	269	-
	"Global Impression of Change" on Day #3, LS Mean (SE)	1.70 (0.06)	2.24 (0.06)	-
	Difference between carisoprodol and placebo (95% CI)	-	0.53 (0.39,0.68)	-
	p-value[2]	-	<0.0001	-

1 The "Global Impression of Change" scale was a 0-4 Likert scale (4=marked improvement, 3=moderate improvement, 2=mild improvement, 1=no change, and 0=worsening. For this co-primary efficacy endpoint, the mean of two Day #3 assessments were calculated.

2 p-values were calculated using an ANOVA model with treatment and pooled center as terms. The primary statistical population was the ITT population. The primary comparison in Study MP502 was between the 250 mg carisoprodol and placebo groups. Other comparisons in Study MP502 were exploratory.

SE is the standard error of the mean

Reference: Adapted from Volume 1, Table 3.6.2.1-1, Page 49

Medical Reviewer's Comments: The 250 mg carisoprodol group demonstrated statistical significance compared to placebo for the GIC endpoint on Day #3 in both low back pain studies. Although, the treatment effect of the 250 mg carisoprodol group (compared to the placebo group) for this co-primary efficacy endpoint was modest (the effect sizes were 0.2 and 0.5 in Studies MP502 and MP505, respectively, on the 5-point GIC scale).

Although in Study MP502 the comparison between the carisoprodol groups was exploratory, there appeared to be no differences in the treatment effects of the carisoprodol groups for GIC. Since the 350 mg carisoprodol dose regimen is approved for the treatment of pain associated with acute painful musculoskeletal conditions (including low back pain), demonstration of similar efficacy of the 250 mg and 350 mg groups supports the efficacy of the 250 mg dose regimen.

For the GIC endpoint, the effect size of the 250 mg carisoprodol dosing regimen, compared to placebo, was similar compared to the effect size of similar products — approved for the treatment of acute discomfort associated with musculoskeletal conditions — compared to

placebo in analogous back pain trials. This also supports the efficacy of the 250 mg dosage regimen.

Table 13 displays the results of the second co-primary efficacy endpoint ["Relief from Starting Backache" (RSB) on Day #3] in the two low back pain studies (i.e., Studies MP502 and MP505).

Table 13: The results of the second co-primary efficacy endpoint ("Relief from Starting Backache" on Day #3) in Studies MP502 and MP505

Study	Parameter	Placebo	Carisoprodol 250 mg	Carisoprodol 350 mg
MP502	n	269	264	273
	"Relief from Starting Backache" on Day #3, LS Mean (SE)	1.40 (0.07)	1.75 (0.07)	1.82 (0.07)
	Difference between carisoprodol and placebo (95% CI)	-	0.35 (0.17,0.54)	0.42 (0.24,0.60)
	p-value[2]		0.0001[3]	<0.0001
MP505	n	278	269	-
	"Relief from Starting Backache" on Day #3, LS Mean (SE)	1.12 (0.07)	1.83 (0.08)	-
	Difference between carisoprodol and placebo (95% CI)	-	0.71 (0.52,0.89)	-
	p-value[2]	-	<0.0001	-

1 The "Relief from Starting Backache" scale was a 0-4 scale (4=complete relief, 3=a lot of relief, 2=some relief, 1=a little relief, and 0=no relief). For this co-primary efficacy endpoint, the mean of two Day #3 assessments were calculated.

2 p-values were calculated using an ANOVA model with treatment and pooled center as terms. The primary statistical population was the ITT population.

3 The primary comparison in Study MP502 was between the 250 mg dose group and placebo. In Study MP502, other comparisons were exploratory.

SE is the standard error of the mean

Reference: Adapted from Volume 1, Table 3.6.2.1-1, Page 49

Medical Reviewer's Comments: The 250 mg carisoprodol group demonstrated statistical significance (compared to placebo) in the RSB endpoint on Day #3 in both low back pain studies. Although, the treatment effect size of the 250 mg carisoprodol group (compared to the placebo group) for RSB was modest (the effect sizes were 0.4 and 0.7 in Studies MP502 and MP505, respectively, on the 5-point RSB scale).

Although in Study MP502 the comparison between the carisoprodol groups was exploratory, there appeared to be no difference in the treatment effects of the carisoprodol groups for RSB. Since the 350 mg carisoprodol dose regimen is approved for the treatment of pain associated with acute painful musculoskeletal conditions (including low back pain), demonstration of similar efficacy of the 250 mg and 350 mg carisoprodol groups supports the efficacy of the 250 mg regimen.

For the RSB endpoint, the effect size of the 250 mg carisoprodol dosing regimen, compared to placebo, was similar compared to the effect size of similar products — approved for the

treatment of acute discomfort associated with musculoskeletal conditions – compared to placebo, in analogous back pain trials. This also supports the efficacy of the 250 mg dosage regimen.

In summary, the 250 mg carisoprodol dose demonstrated statistical significance compared to placebo in both co-primary efficacy endpoints and these results were replicable in two independent trials. Although, the treatment effects of the 250 mg carisoprodol dosing regimen compared to placebo were modest.

Most Important Secondary Efficacy Endpoints – the change in the RMDQ score on Days #3 and #7: These two secondary efficacy endpoints were the change from baseline in the Roland-Morris Disability Questionnaire (RMDQ) score of function [ranging from 0 (no disability) to 24 (maximum disability)] on Study Day #3 and Study Day #7. Tables 14 and 15 display the change in the RMDQ score on Days #3 and #7 (from baseline) in Studies MP502 and Study MP505, respectively.

Table 14: Change from baseline in the RMDQ score[1] on Study Days #3 and #7 in Study MP502

Day	RMDQ score	Placebo n=269	Carisoprodol 250 mg n=264	Carisoprodol 350 mg n=273
Day 1 (baseline)	Mean (SD)	11.2 (5.6)	11.5 (5.3)	11.8 (5.3)
Day 3	Mean (SD)	9.1 (5.6)	8.1 (5.2)	9.1 (5.6)
	Change from baseline[2], LS Mean (SE)	-2.0 (0.3)	-3.0 (0.3)	-2.9 (0.3)
	LS Mean Difference (PL minus carisoprodol), 95% CI	-	1.0 (0.3,1.7)	1.0 (0.3,1.7)
	p-value[3]	-	0.0057	0.0067
Day 7	Mean (SD)	6.0 (5.4)	5.4 (4.9)	5.3 (5.3)
	Change from baseline[4], LS Mean (SE)	-4.4 (0.3)	-5.4 (0.3)	-5.7 (0.31)
	LS Mean Difference (PL minus carisoprodol), 95% CI	-	1.1 (0.3,1.9)	1.3 (0.5,2.1)
	p-value[3]	-	0.0112	0.0017

1 The RMDQ is a 0-24 scale. The change in the RMDQ score from baseline on Days #3 and #7 represents two of the seven pre-specified secondary efficacy endpoints in Study MP502.
2 Change from baseline (Day 3 minus Day 1)
3 No pre-specified multiplicity adjustments were made for the seven pre-specified secondary efficacy endpoints. The ANCOVA model was used with treatment, pooled center, and baseline value as covariates. The primary statistical population was the ITT population and imputation was performed by LOCF (except for baseline values).
4 Change from baseline (Day 7 minus Day 1)
Reference: Adapted from Volume 18, Table 11-11, Page 68; Volume 18, Table 11-12, Page 69.

Table 15: Change from baseline in the RMDQ score[1] on Study Days #3 and #7 in Study MP505

Day	RMDQ score	Placebo (n=278)	Carisoprodol 250 mg (n=269)
Day 1 (baseline)	Mean (SD)	10.3 (5.0)	10.4 (4.9)
Day 3	Mean (SD)	8.7 (5.4)	6.9 (4.5)
	Change from baseline[2], LS Mean (SE)	-1.4 (0.3)	-3.2 (0.3)
	LS Mean Difference (PL minus carisoprodol), 95% CI	-	1.9 (1.2,2.5)
	p-value[3]	-	<0.0001
Day 7	Mean (SD)	6.2 (5.4)	4.1 (3.9)
	Change from baseline[4], LS Mean (SE)	-3.1 (0.3)	-5.4 (0.3)
	LS Mean Difference (PL minus carisoprodol), 95% CI	-	2.3 (1.6,3.0)
	p-value[3]	-	<0.0001

1 The RMDQ is a 0-24 scale. The change in the RMDQ score from baseline on Days #3 and #7 represents two of the seven pre-specified secondary efficacy endpoints in Study MP505.
2 Change from baseline (Day 3 minus Day 1)
3 No pre-specified multiplicity adjustments were made for the seven pre-specified secondary efficacy endpoints in Study MP505. The ANCOVA model was used with treatment, pooled center, and baseline value as covariates. The primary statistical population was the ITT population and imputation was performed by LOCF (except for baseline values).
4 Change from baseline (Day 7 minus Day 1)
Reference: Adapted from Volume 53, Table 11-10, Page 63, and Volume 53, Table 11-11, Page 64.

<u>Medical Reviewer's Comments</u>: The 250 mg carisoprodol group demonstrated statistical significance, compared to the placebo group, in the change from baseline in the RMDQ scores on Days #3 and #7 in the low back pain studies. In Study MP502, the effect sizes were 1.0 and 1.1 on Days #3 and #7, respectively; and in Study MP505, the effect sizes were 1.9 and 2.3 on Days #3 and #7, respectively. In both studies, the effect size was maintained after seven days of therapy.

Although in Study MP502 the comparison between the carisoprodol groups was exploratory, there appeared to be no difference in the carisoprodol groups for the RMDQ endpoints. This supports the efficacy of the proposed 250 mg dosing regimen.

The statistical significance of the 250 mg carisoprodol dose, compared to placebo; the maintenance of the effect size throughout the study period; the similar results of the 250 and 350 mg carisoprodol groups; and the replicability supports the efficacy of the 250 mg in the treatment of discomfort in acute, low back pain.

Other Secondary Efficacy Endpoints – the change in PRO "Medication Helpfulness": The two secondary efficacy endpoints were PRO "Medication Helpfulness" on Study Days #3 and #7 in Studies MP502 and MP505 (see Tables 16 and 17, respectively).

Table 16: "Medication Helpfulness"[1,2] on Study Days #3 and #7 in Study MP502

Day	"Medication Helpfulness"	Placebo n=269	Carisoprodol 250 mg n=264	Carisoprodol 350 mg n=273
Day 3	LS Mean (SE)	1.2 (0.1)	1.6 (0.1)	1.7 (0.1)
	Difference between carisoprodol and placebo (95% CI)	-	0.4 (0.5,0.2)	0.5 (0.6,0.3)
	p-value[3]	-	<0.0001	<0.0001
Day 7	LS Mean (SE)	1.5 (0.1)	1.9 (0.1)	2.1 (0.1)
	Difference between carisoprodol and placebo (95% CI)	-	0.4 (0.7,0.2)	0.6 (0.8,0.4)
	p-value[3]	-	<0.0001	<0.0001

1 Patient-rated "Medication Helpfulness" score was on a 0-4 scale: Excellent (4), Very good (3), Good (2), Fair (1), or Poor (0). The Medication Helpfulness score on Days #3 and #7 represented two of the seven pre-specified secondary efficacy endpoints in Study MP502.
2 The ITT population was the primary statistical population and missing values were imputed with the LOCF except for baseline measurements. LS Mean and LS Mean differences were calculated using an ANOVA model with treatment and pooled center as covariates.
3 No pre-specified multiplicity adjustments were made for the seven pre-specified secondary efficacy endpoints in Study MP502.
Reference: Adapted from Volume 18, Table 11-15, Page 72

Table 17: "Medication Helpfulness"[1,2] on Study Days #3 and #7 in Study MP505

Day	"Medication Helpfulness"	Placebo n=278	Carisoprodol 250 mg n=269
Day 3	LS Mean (SE)	1.0 (0.1)	1.6 (0.1)
	Difference between carisoprodol and placebo (95% CI)	-	0.6 (0.8,0.4)
	p-value[3]	-	<0.0001
Day 7	LS Mean (SE)	1.4 (0.1)	2.0 (0.1)
	Difference between carisoprodol and placebo (95% CI)	-	0.6 (0.8,0.4)
	p-value[3]	-	<0.0001

1 Patient-rated "Medication Helpfulness" score was on a 0-4 scale: Excellent (4), Very good (3), Good (2), Fair (1), or Poor (0). The Medication Helpfulness score on Days #3 and #7 represented two of the seven pre-specified secondary efficacy endpoints in Study MP502.
2 The ITT population was the primary statistical population and missing values were imputed with the LOCF except for baseline measurements. LS Mean and LS Mean differences were calculated using an ANOVA model with treatment and pooled center as covariates.
3 No pre-specified multiplicity adjustments were made for the seven pre-specified secondary efficacy endpoints in Study MP505.
Reference: Adapted from Volume 53, Table 11-14, Page 67.

Medical Reviewer's Comments: In the low back pain studies, the 250 mg carisoprodol group had statistically significant higher "Medication Helpfulness" scores compared to placebo on Days #3 and #7, although the effect size was modest. The treatment effect size was maintained throughout the study periods in the low back pain studies.

Other Secondary Efficacy Endpoints – the change in forward flexion of the lower back: The two secondary efficacy endpoints were the change (from baseline) in forward flexion of the lower back in centimeters (the mean value for forward bending minus the mean value for standing straight up) on Study Days #3 and #7. Tables 18 and 19 display the results of the change in forward flexion in Studies MP502 and MP505, respectively.

Table 18: Mean change[1] from baseline in the amount of forward flexion[2] of the lower back (in cm) on Study Days #3 and #7 in Study MP502

Day	Forward Flexion (in cm)	Placebo n=269	Carisoprodol 250 mg n=264	Carisoprodol 350 mg n=273
Day 1 (baseline)	Mean (SD)	6.6 (3.2)	6.6 (3.3)	6.5 (3.0)
Day 3	Mean (SD)	7.6 (3.4)	7.7 (3.4)	7.8 (2.9)
	Change from baseline[2], LS Mean (SE)	0.9 (0.1)	0.9 (0.1)	1.1 (0.1)
	LS Mean Difference (PL minus carisoprodol), 95% CI	-	0.01 (-0.3,0.4)	-0.2 (-0.5,0.2)
	p-value[3]	-	0.95	0.34
Day 7	Mean (SD)	8.6 (3.4)	8.4 (3.2)	8.6 (3.3)
	Change from baseline[3], LS Mean (SE)	1.5 (0.2)	1.7 (0.2)	1.8 (0.2)
	LS Mean Difference (PL minus carisoprodol), 95% CI	-	-0.2 (-0.6,0.3)	-0.3 (-0.8,0.1)
	p-value[3]	-	0.46	0.12

1 The mean change was the average of three measurements.
2 The change from baseline in the amount of forward flexion of the lower back on Days #3 and #7 represented two of the seven pre-specified secondary efficacy endpoints in Study MP502.
3 No pre-specified multiplicity adjustments were made for the seven pre-specified secondary efficacy endpoints in Study MP502. The ANCOVA model was used with the ITT population (the primary statistical population).
Reference: Adapted from Volume 18, Table 11-13, Page 70; Volume 18, Table 14.2.5.3.1, Pages 251-252.

Table 19: Mean change[1] from baseline in the amount of forward flexion[2] of the lower back (in cm) on Study Days #3 and #7 in Study MP505

Day	Forward Flexion (in cm)	Placebo n=278	Carisoprodol 250 mg n=269
Day 1 (baseline)	Mean (SD)	5.9 (2.8)	6.3 (3.0)
Day 3	Mean (SD)	6.7 (3.0)	7.3 (2.9)
	Change from baseline[2], LS Mean (SE)	0.7 (0.1)	0.9 (0.1)
	LS Mean Difference (PL minus carisoprodol), 95% CI	-	-0.2 (-0.5,0.1)
	p-value	-	0.12
Day 7	Mean (SD)	7.7 (3.0)	8.2 (3.1)
	Change from baseline[3], LS Mean (SE)	1.3 (0.1)	1.6 (0.1)
	LS Mean Difference (PL minus carisoprodol), 95% CI	-	-0.3 (-0.7,0.03)
	p-value	-	0.07

1 The mean change was the average of three measurements.
2 The change from baseline in the amount of forward flexion of the lower back on Days #3 and #7 represented two of the seven pre-specified secondary efficacy endpoints in Study MP505.
3 No pre-specified multiplicity adjustments were made for the seven pre-specified secondary efficacy endpoints in Study MP502. The ANCOVA model was used and the primary statistical population was the ITT population.
Reference: Adapted from Volume 53, Table 11-12, Page 65, and Volume 53, Table 14.2.5.3.1, Pages 189-190.

Medical Reviewer's Comments: There was no difference in the change in forward flexion at Days #3 and #7 (from baseline) between the 250 mg carisoprodol and placebo groups in Studies MP502 and MP505. In addition, there was no difference in the change in forward flexion at Days #3 and #7 (from baseline) between the two carisoprodol groups in Study MP502.

6.1.5 Clinical Microbiology

Since carisoprodol is not an antimicrobial, the microbiology of carisoprodol was not performed.

6.1.6 Efficacy Conclusions

The efficacy of the 250 mg carisoprodol dose regimen in the treatment of discomfort associated with acute idiopathic mechanical low back pain was established because the 250 mg regimen, compared to the placebo group, demonstrated:

1) Statistical significance for the co-primary efficacy endpoints;
2) Numerical improvement for the two RMDQ secondary endpoints;
3) Replicability for the two primary and the two important secondary endpoints in two studies; and
4) Similar effect size compared to the effect size of recently approved muscle relaxants for the identical efficacy endpoints in analogous acute, low back pain studies.

Although the comparison between the carisoprodol groups in Study MP502 was exploratory, the similar efficacy results between the 250 mg carisoprodol regimen and the approved 350 mg carisoprodol regimen for the co-primary efficacy and the RMDQ endpoints also supports the efficacy of the 250 mg carisoprodol regimen.

In summary, the clinical data from the two studies of patients with acute, idiopathic, mechanical low back pain **support the efficacy** of the new 250 mg carisoprodol regimen in the short-term treatment of discomfort associated with acute, painful musculoskeletal conditions in adults.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

There were no deaths in the four carisoprodol studies.

7.1.2 Other Serious Adverse Events

There were no serious adverse events (SAEs) in Studies MP500, MP501, and MP505. In Study MP502, one patient in the 350 mg carisoprodol group had a non-fatal SAE (see Table 20 for the patient narrative).

Table 20: Non-fatal SAE narrative[1]

Patient ID (Study)	Summary of Non-fatal SAE	Medical History
245/0005 (Study MP502)	Hospitalized for lumbar disc herniation which required surgery	54 year old male [with a past medical history of obesity (body mass index of 33.7), GERD, HTN, smoking, sleep apnea, HTN, depression] with one day of severe back pain received **carisoprodol 350 mg QID**. On Study Day #3 (1/19/06), he had right leg cramping and difficulty walking (without back pain). He took his last dose of carisoprodol in the morning of Study Day #4 (1/20/06). Three days after his last dose of study medication (b) (4) after a MRI of his lumbar spine showed L2-3 disc herniation, he was hospitalized for pain control and surgery. (b) (4) days after his last dose of study medication (b) (4) he had a (b) (4) He was discharged on (b) (4) The investigator thought his SAE was unlikely related to the study drug.

1 Only one patient had a nonfatal SAE (in Study MP502) in the four carisoprodol studies. There were no deaths in the four carisoprodol studies.
Reference: Adapted from narrative summary in Volume 19, Section 14.3.3.2, Page 21 and the case report form in Volume 181, Pages 260-287.

The rates of nonfatal SAEs in the placebo, 250 mg carisoprodol, and 350 mg carisoprodol groups were 0%, 0%, and 0.4% (1/279), respectively.

Medical Reviewer's Comments: The one non-fatal SAE was unlikely related to the study medication (i.e., 350 mg carisoprodol) because the non-fatal SAE can be reasonable explained by other factors (i.e., complications of underlying disease). This patient most likely had acute back pain from a herniated disc and developed progressive neurologic deficit that required hospitalization and decompression surgery. Therefore, there were no treatment-related SAEs in the three treatment groups in the four carisoprodol studies.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Table 21 delineates the most common reasons for study discontinuation in the low back pain studies.

Table 21: The most common reasons for study discontinuation in the low back pain studies

Reason for discontinuation	Placebo n=560[1] n (%)	Carisoprodol 250 mg n=548[1] n (%)	Carisoprodol 350 mg n=279[1] n (%)
Total discontinuations	91 (16.3)	57 (10.4)	42 (15.1)
Unsatisfactory therapeutic effect	39 (7.0)	10 (1.8)	7 (2.5)
Lost to follow-up	16 (2.9)	17 (3.1)	11 (3.9)
Adverse event[2]	15 (2.7)	11 (2.0)	15 (5.4)
Patient withdrew consent	9 (1.6)	11 (2.0)	6 (2.2)
Other	9 (1.6)	5 (0.9)	1 (0.4)
Protocol violation	2 (0.4)	2 (0.4)	1 (0.4)
Abnormal test procedure	1 (0.2)	1 (0.2)	1 (0.4)
Administrative	0 (0)	0 (0)	0 (0)

1 The safety population (patients who received at least one dose of study medication).
2 AE leading to discontinuation (DAE): see Section 7.1.3.2 for an analysis of the DAEs in the low back pain studies.
Reference: Adapted from Volume 1, Table 3.6.3.1-1, Page 51

Medical Reviewer's Comments: A lower proportion of patients in the 250 mg carisoprodol group discontinued treatment compared to the placebo and 350 mg carisoprodol groups. The disparity in overall dropouts between the placebo and 250 mg carisoprodol groups was due to a higher proportion of patients in the placebo group, compared to the 250 mg carisoprodol group, who had an unsatisfactory effect. The disparity in overall dropouts between the 350 and 250 mg carisoprodol groups was due to a higher proportion of patients in the 350 mg carisoprodol group, compared to the 250 mg carisoprodol group, who had AEs leading to discontinuations (DAEs).

All three treatment groups had a small proportion of patients who were lost to follow-up (< 4% in each treatment group).

7.1.3.2 Adverse Events associated with dropouts

Table 22 displays all of the DAEs in the low back pain studies. No patient in the PK studies (i.e., Studies MP500 and MP501) had a DAE.

Table 22: DAEs[1] in the low back pain studies[2]

DAE	Placebo n=560[3] n (%)	Carisoprodol 250 mg n=548[3] n (%)	Carisoprodol 350 mg n=279[3] n (%)
Patients with ≥ 1 DAE	15 (2.7)	11 (2.0)	15 (5.4)
Dizziness	1 (0.2)	3 (0.5)	2 (0.7)
Headache	1 (0.2)	3 (0.5)	1 (0.4)
Diarrhea	1 (0.2)	1 (0.2)	0 (0)
Stomach discomfort or upper abdominal pain	0 (0)	1 (0.2)	2 (0.7)
Somnolence	2 (0.4)	0 (0)	2 (0.7)
Nausea	2 (0.4)	0 (0)	1 (0.4)
Rash	1 (0.2)	0 (0)	1 (0.4)
Nephrolithiasis	1 (0.2)	0 (0)	1 (0.4)
Intervertebral disc protrusion	0 (0)	1 (0.2)	1 (0.4)[4]
Pain in extremity	0 (0)	1 (0.2)	0 (0)
Abdominal distension	0 (0)	1 (0.2)	0 (0)
Fatigue	0 (0)	0 (0)	1 (0.4)
Disorientation	0 (0)	0 (0)	1 (0.4)
Paraesthesia	0 (0)	0 (0)	1 (0.4)
Skin papilloma	0 (0)	0 (0)	1 (0.4)
Food poisoning	1 (0.2)	0 (0)	0 (0)
Back pain	1 (0.2)	0 (0)	0 (0)
Gastrointestinal viral	1 (0.2)	0 (0)	0 (0)
Muscle spasms	1 (0.2)	0 (0)	0 (0)
Spinal fracture	1 (0.2)	0 (0)	0 (0)
Irritability	1 (0.2)	0 (0)	0 (0)

1 DAEs were AEs leading to discontinuation. This table includes all the DAEs in the low back pain studies. DAEs were coded by preferred term using MedDRA Dictionary Version 8.0.
2 The low back pain studies were Studies MP502 and MP505.
3 The safety population (patients who received at least one dose of study medication).
4 The disc protrusion that lead to discontinuation was also a non-fatal SAE in Study MP502 (see Section 7.1.2 for the narrative of Patient 245/0005)
Reference: Adapted from Volume 18, Table 12-7, Page 87 and Volume 53, Section 14.3.3.3, Pages 260-263.

Medical Reviewer's Comments: A lower proportion of patients in the 250 mg carisoprodol group had DAEs compared to the 350 mg carisoprodol group. Patients in the 250 mg carisoprodol group had a similar proportion of DAEs compared to patients in the placebo group. This supports the safety of the 250 mg carisoprodol dose group and suggests a possible improved safety profile compared to the approved 350 mg carisoprodol regimen.

Since there were few DAEs in each category and there was no significant differences between the three treatment groups, it is not possible to state whether a specific DAE was likely treatment-related or if specific DAEs were dose-related.

7.1.3.3 Other significant adverse events

There were no other significant AEs in the PK studies (i.e., Studies MP500 and MP501).

7.1.4 Other Search Strategies

All dizziness, somnolence, and disorientation DAEs in the three treatment groups in the low back pain studies were combined to evaluate for possible carisoprodol-associated central nervous system (CNS) toxicity (see Table 23).

Table 23: CNS DAEs[1] in the low back pain studies[2]

Reason	Placebo n=560[3] n (%)	Carisoprodol 250 mg n=548[3] n (%)	Carisoprodol 350 mg n=279[3] n (%)
Patients with ≥ 1 CNS DAE	3 (0.5)	3 (0.5)	5 (1.8)
Dizziness	1 (0.2)	3 (0.5)	2 (0.7)
Somnolence	2 (0.4)	0 (0)	2 (0.7)
Disorientation	0 (0)	0 (0)	1 (0.4)

1 Neurologic DAEs that were likely central nervous system (CNS) in origin. DAEs were coded by preferred term using MedDRA Dictionary Version 8.0.
2 The low back pain studies were Studies MP502 and MP505.
Reference: Adapted from Volume 18, Table 12-7, Page 87 and Volume 53, Section 14.3.3.3, Pages 260-263.

Medical Reviewer's Comments: A lower proportion of patients in the 250 mg carisoprodol and placebo groups had CNS DAEs (including dizziness, somnolence, and disorientation), compared to the 350 mg carisoprodol group. This supports the safety of the lower 250 mg carisoprodol group.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

The two low back pain studies (i.e., Studies MP502 and MP505) had identical procedures in evaluation of AE data. See the "Study Monitoring" subsection of Section 10.1.1.1.7 in the Appendix for the procedures for evaluation of AEs in Study MP502. Study MP505 had the identical procedures as Study MP502.

Medical Reviewer's Comments: In the two low back pain studies, the last safety visit occurred on Study Day #7 or early termination (± one day). For short-term trials, it is optimal to have a follow-up safety visit (off therapy) to assess product withdrawal symptoms or AEs that make time to develop (e.g., liver enzyme test abnormalities). For these trials, it may have been useful to

evaluate the frequency of withdrawal symptoms in the two carisoprodol dose groups. Therefore, the follow-up safety evaluations were suboptimal.

Despite the above limitations, the safety monitoring in the low back pain studies were acceptable because:

- **The proposed carisoprodol 250 mg dose is about 29% lower than the approved carisoprodol 350 mg dose, which has been approved in the United States since 1959; and**
- **The currently approved carisoprodol label contains WARNINGS regarding carisoprodol-associated withdrawal symptoms.**

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Studies MP502 and MP505 used the Medical Dictionary for Regulatory Activities (MedDRA) Terminology version 8 nomenclature to classify AEs.

7.1.5.3 Incidence of common adverse events

Data from Studies MP502 and MP505 were pooled to evaluate common AEs because these studies:

- Were randomized, double-blinded, placebo-controlled studies;
- Had identical patient populations (acute, idiopathic, mechanical low back pain); and
- Had identical study durations (i.e., one week).

Studies MP500 and MP501 were not included in the pooled data to evaluate common AEs because these studies:

- Were single dose studies;
- Had healthy subjects; and
- Were open label.

7.1.5.4 Common adverse event tables

Table 24 displays the most common AEs in the low back pain studies. Preferred terms somnolence and sedation were combined and the terms stomach discomfort, abdominal discomfort, and upper abdominal pain were combined. Table 25 displays all the possible CNS-related AEs in the low back pain studies.

Table 24: The most common AEs (≥ 0.5% in any treatment group) in the low back pain studies

Preferred Term[1]	Placebo n=560[2] n (%)[3]	Carisoprodol 250 mg n=548[2] n (%)[3]	Carisoprodol 350 mg n=279[2] n (%)[3]
Patients with ≥ 1 AE	111 (20.3)	166 (30.3)	95 (34.1)
Somnolence or sedation	31 (5.5)	73 (13.4)	47 (16.9)
Dizziness	11 (2.0)	43 (7.8)	19 (6.8)
Headache	11 (2.0)	26 (4.7)	9 (3.2)
Nausea	15 (2.7)	6 (1.1)	12 (4.3)
Stomach discomfort, abdominal discomfort, or upper abdominal pain	7 (1.3)	10 (1.8)	5 (1.8)
Fatigue or lethargy	2 (0.4)	8 (1.5)	3 (1.1)
Diarrhea	6 (1.1)	5 (0.9)	1 (0.4)
Dry mouth	4 (0.7)	3 (0.5)	2 (0.7)
Irritability	0 (0)	3 (0.5)	0 (0)
Blood CPK increased	3 (0.5)	2 (0.4)	2 (0.7)

1 The preferred terms were coded using MedDRA Dictionary Version 8.0.
2 The safety population (patients who received at least one dose of study medication).
3 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
Reference: Adapted from Volume 16, Table 8.2.2-2, Pages 86-94.

Table 25: CNS AEs[1] in the low back pain studies

Preferred Term[2]	Placebo n=560[3] n (%)[4]	Carisoprodol 250 mg n=548[3] n (%)[4]	Carisoprodol 350 mg n=279[3] n (%)[4]
Patients with ≥ 1 CNS AE[1]	44 (7.9)	122 (22.3)	70 (25.1)
Somnolence or sedation	31 (5.5)	73 (13.4)	47 (16.9)
Dizziness	11 (2.0)	43 (7.8)	19 (6.8)
Irritability	0 (0)	3 (0.5)	0 (0)
Disorientation	0 (0)	1 (0.2)	2 (0.7)
Clumsiness	0 (0)	1 (0.2)	0 (0)
Memory impairment	0 (0)	1 (0.2)	0 (0)
Cognitive disorder	0 (0)	0 (0)	1 (0.4)
Euphoric mood	0 (0)	0 (0)	1 (0.4)
Feeling drunk	1 (0.2)	0 (0)	0 (0)
Feeling jittery	1 (0.2)	0 (0)	0 (0)

1 These preferred terms are possible CNS-related AEs
2 The preferred terms were coded using MedDRA Dictionary Version 8.0.
3 The safety population (patients who received at least one dose of study medication).
4 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
Reference: Adapted from Volume 16, Table 8.2.2-2, Pages 86-94.

Medical Reviewer's Comments: A higher proportion of patients in the 250 mg and 350 mg carisoprodol groups, compared to the patients in the placebo group, had total AEs; somnolence or sedation AEs; and CNS AEs (i.e., somnolence, sedation, or dizziness).

There appeared to be a slight dose-response in AEs – the 350 mg group experienced a higher proportion of total AEs and CNS AEs. This possible dose relationship to AEs supports the safety of the lower 250 mg carisoprodol dosing regimen.

7.1.5.5 Identifying common and drug-related adverse events

Table 26 presents the most common treatment-related (according to the investigator) AEs in the low back pain studies. The preferred terms somnolence and sedation were combined and the terms stomach discomfort, upper abdominal pain, and dyspepsia were combined. Table 27 exhibits all the probable CNS-related treatment-related (according to the investigator) AEs in the low back pain studies.

Table 26: The most common treatment-related AEs[1] (≥ 2 events in any treatment group) in the low back pain studies as rated by the investigator

Preferred Term[2]	Placebo n=560[3] n (%)[4]	Carisoprodol 250 mg n=548[3] n (%)[4]	Carisoprodol 350 mg n=279[3] n (%)[4]
Patients with ≥ 1 treatment-related AE	66 (11.8)	132 (24.1)	77 (27.6)
Somnolence or sedation	29 (5.2)	70 (12.8)	45 (16.2)
Dizziness	9 (1.6)	41 (7.5)	19 (6.8)
Headache	6 (1.1)	14 (2.6)	7 (2.5)
Nausea	13 (2.3)	6 (1.1)	10 (3.6)
Stomach discomfort, upper abdominal pain, or dyspepsia	7 (1.3)	9 (1.9)	4 (1.5)
Fatigue	2 (0.4)	6 (1.1)	2 (0.7)
Dry mouth	4 (0.7)	3 (0.5)	2 (0.7)
Rash	1 (0.2)	1 (0.2)	2 (0.7)
Disorientation	0 (0)	1 (0.2)	2 (0.7)
Blood CPK increased	0 (0)	1 (0.2)	2 (0.7)
Diarrhea	2 (0.4)	3 (0.5)	0 (0)
Constipation	2 (0.4)	2 (0.4)	0 (0)
Irritability	0 (0)	2 (0.4)	0 (0)

1 Treatment related as judged by the blinded investigator.
2 The preferred terms were coded using MedDRA Dictionary Version 8.0.
3 The safety population (patients who received at least one dose of study medication).
4 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
Reference: Adapted from Volume 16, Table 8.2.2-5, Pages 116-118.

Table 27: Treatment-related CNS AEs[1] in the low back pain studies as rated by the investigator

Preferred Term[2]	Placebo n=560[3] n (%)[4]	Carisoprodol 250 mg n=548[3] n (%)[4]	Carisoprodol 350 mg n=279[3] n (%)[4]
Combined treatment-related CNS AEs[1]	41 (7.3)	117 (21.4)	68 (24.4)
Somnolence or sedation	29 (5.2)	70 (12.8)	45 (16.2)
Dizziness	9 (1.6)	41 (7.5)	19 (6.8)
Feeling drunk	1 (0.2)	0 (0)	0 (0)
Feeling jittery	1 (0.2)	0 (0)	0 (0)
Clumsiness	0 (0)	1 (0.2)	0 (0)
Cognitive disorder	0 (0)	0 (0)	1 (0.4)
Memory impairment	0 (0)	1 (0.2)	0 (0)
Psychomotor hyperactivity	0 (0)	1 (0.2)	0 (0)
Disorientation	0 (0)	1 (0.2)	2 (0.7)
Euphoric mood	0 (0)	0 (0)	1 (0.4)
Irritability	0 (0)	2 (0.4)	0 (0)
Restlessness	1 (0.2)	0 (0)	0 (0)

1 Treatment related as judged by the blinded investigator. These preferred terms are possible CNS-related AEs
2 The preferred terms were coded using MedDRA Dictionary Version 8.0.
3 The safety population (patients who received at least one dose of study medication).
4 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
Reference: Adapted from Volume 16, Table 8.2.2-5, Pages 116-118.

Medical Reviewer's Comments: A higher proportion of patients in the 250 mg and 350 mg carisoprodol groups, compared to the patients in the placebo group, had treatment-related AEs; somnolence or sedation treatment-related AEs; and had treatment-related CNS AEs.

There appeared to be a slight dose-response in treatment-related AEs — the 350 mg group had a numerically greater proportion of total treatment-related AEs and treatment-related CNS AEs than the 250 mg group. This possible dose relationship to treatment-related AEs supports the safety of the lower 250 mg carisoprodol dosing regimen.

See Section 7.3 for conclusions regarding carisoprodol-related AEs.

7.1.5.6 Additional analyses and explorations

Medical Reviewer's Comments: Table 28 presents characteristics of the 11 CNS DAEs. Of the 11 patients who had a CNS DAE; 3 (0.5%), 3 (0.5%), and 5 (1.8%) patients received the placebo, 250 mg carisoprodol, and 350 mg carisoprodol treatment, respectively (see Table 23). The CNS DAEs occurred early after initiation of treatment (for the 8 patients who

received carisoprodol and who had a CNS DAE, the mean number of days of carisoprodol dosing prior to discontinuation was 1.8 days).

The majority of patients who experienced a CNS DAE were female [of the 8 patients on the carisoprodol dose regimens who experienced a CNS DAE; 7 (88%) were female and 1 (12%) were male]. The gender demographics in the low back pain studies does not explain the disparity in the incidence of CNS DAEs in female patients (about 52% and 48% of patients who received one of the carisoprodol regimens were female and male, respectively, in the low back pain trials). The relationship of gender to the CNS DAEs is not clear because all three patients (100%) of the patients in the placebo group who had CNS DAEs were females.

The mean age of the eight patients on the carisoprodol dose regimens who experienced CNS DAEs was similar to the mean age of all the patients who received carisoprodol in the low back pain trials (43 and 41 years old, respectively).

Table 28: Characteristics of CNS[1] DAEs in the low back pain studies[2]

	Patient # (Study #)	Product	Age in years (sex, race)	Event	Day of Onset	Discontinuation Day	Days on treatment
1	241/0008 (Study MP502)	**Placebo**	64 (Female, White)	Somnolence	Day #1	Day #1	1
2	545/0007 (Study MP505)	**Placebo**	48 (Female, White)	Somnolence	Day #1	Day #1	1
3	557/0004 (Study MP505)	**Placebo**	40 (Female, Black)	Dizziness	Day #2	Day #2	2
4	283/0033 (Study MP502)	**250 mg**	55 (Female, Asian)	Dizziness	Day #2	Day #2	2
5	524/0003 (Study MP505)	**250 mg**	41 (Female, White)	Dizziness	Day #2	Day #2	2
6	540/0017 (Study MP505)	**250 mg**	33 (Female, White)	Dizziness	Day #1	Day #1	1
7	253/0004 (Study MP502)	**350 mg**	55 (Female, Black)	Somnolence	Day #2	Day #2	2
8	257/0005 (Study MP502)	**350 mg**	40 (Female, White)	Somnolence	Day #1	Day #1	1
9	259/0027 (Study MP502)	**350 mg**	47 (Female, Other)	Dizziness	Day #2	Day #2	2
10	264/0004 (Study MP502)	**350 mg**	45 (Female, White)	Disorientation	Day #1	Day #1	1
11	283/0032 (Study MP502)	**350 mg**	29 (Male, White)	Dizziness	Day #3	Day #3	3

1 DAEs that were likely CNS-related. DAEs were coded by preferred term using MedDRA Dictionary Version 8.0.
2 The low back pain studies were Studies MP502 and MP505.
Reference: Adapted from narratives in Volume 19, Section 14.3.3.3, Pages 21-27 and Volume 53, Section 14.3.3.3, Pages 260-263.

The carisoprodol-associated CNS AEs (i.e., somnolence, sedation, and dizziness) were likely drug related because there was a higher frequency of CNS AEs; CNS DAEs; and CNS investigator-determined, treatment-related AEs in the carisoprodol groups compared to the

placebo groups. Furthermore, CNS related AEs are known toxicities of carisoprodol. There appears to be a slight dose-dependency of the carisoprodol-associated CNS AEs (i.e., the 350 mg carisoprodol group had a higher incidence of CNS AEs, CNS DAEs, and CNS investigator-determined treatment-related AEs compared to the 250 mg carisoprodol group). However, there does not appear to be relationship between age or concomitant drug use (i.e., drug-drug interactions) and carisoprodol-associated CNS AEs.

7.1.6 Less Common Adverse Events

Since the safety database was small (827 patients were exposed to the 250 or 350 mg carisoprodol regimens in the low back pain studies) and there were no concerning rare AEs, less common AEs are not presented. See Section 7.1.2.4 for the most common AEs (≥ 0.5% in any treatment group) in the low back pain studies.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

In the low back pain studies, blood chemistry and hematology and urinalysis were performed at baseline and on Study Day #7 (or early termination).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Data from Studies MP502 and MP505 were pooled to evaluate the laboratory tests because these studies:

- Were randomized, double-blinded, placebo-controlled studies;
- Had identical patient populations (acute, idiopathic, mechanical low back pain); and
- Had identical study durations (i.e., one week).

Studies MP500 and MP501 were not included in the pooled data to evaluate the laboratory tests because these studies:

- Were single dose studies;
- Had healthy subjects;
- Were open label; and
- Laboratory tests were not performed after each study medication was given; rather, they were performed after subjects received all study medications thus making it difficult to ascribe a relationship between possible laboratory test changes to a specific study medication.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Table 29 displays the mean blood chemistry and hematology laboratory tests (i.e., baseline and change from baseline) in the low back pain studies.

Table 29: Mean (SD) blood laboratory tests (i.e., baseline and change from baseline) in the low back pain studies

Laboratory Test	Time point	Placebo n=560[1]	Carisoprodol 250 mg n=548[1]	Carisoprodol 350 mg n=279[1]
CPK, units per liter	Baseline	182.5 (604.9)	138.5 (154.7)	136.3 (152.6)
	Day 7* minus baseline	-46.0 (540.5)	-11.4 (141.3)	-8.6 (126.3)
Creatinine, mg/dL	Baseline	1.0 (0.2)	1.0 (0.2)	1.0 (0.3)
	Day 7* minus baseline	0 (0.1)	0 (0.1)	0 (0.2)
BUN, mg/dL	Baseline	14.0 (4.7)	14.1 (4.0)	13.8 (4.8)
	Day 7* minus baseline	-0.3 (3.7)	-0.2 (3.7)	-0.1 (3.7)
Sodium, meq per liter	Baseline	140.9 (2.5)	140.8 (2.2)	141.1 (2.4)
	Day 7* minus baseline	-0.2 (2.8)	-0.1 (2.5)	-0.3 (2.4)
Potassium, meq per liter	Baseline	4.3 (0.4)	4.3 (0.5)	4.3 (0.4)
	Day 7* minus baseline	-0.1 (0.4)	-0.1 (0.5)	-0.1 (0.4)
Calcium, mg/dL	Baseline	9.5 (0.4)	9.5 (0.4)	9.5 (0.4)
	Day 7* minus baseline	-0.1 (0.4)	-0.1 (0.4)	0 (0.4)
Cholesterol (non-fasting), mg/dL	Baseline	199.8 (43.8)	199.4 (40.7)	198.9 (43.4)
	Day 7* minus baseline	-3.9 (21.8)	-1.2 (20.7)	2.4 (20.1)
Triglyceride (non-fasting), mg/dL	Baseline	182.2 (121.9)	182.1 (108.5)	196.0 (154.1)
	Day 7* minus baseline	-1.7 (111.0)	1.2 (92.4)	10.9 (107.0)
LDH, units per liter	Baseline	146.7 (35.6)	145.9 (29.2)	148.2 (42.6)
	Day 7* minus baseline	-3.0 (27.3)	-3.3 (20.3)	-2.4 (21.9)
Glucose (non-fasting), mg/dL	Baseline	98.7 (27.2)	99.6 (36.6)	98.1 (30.4)
	Day 7* minus baseline	3.0 (26.4)	4.2 (24.1)	4.9 (23.9)
Phosphorus, mg/dL	Baseline	3.8 (0.6)	3.7 (0.5)	3.7 (0.6)
	Day 7* minus baseline	-0.1 (0.8)	-0.1 (0.6)	0 (0.7)
Uric acid, mg/dL	Baseline	5.0 (1.5)	5.1 (1.4)	5.1 (1.6)
	Day 7* minus baseline	0.1 (0.8)	0.1 (0.8)	0 (0.9)
WBC in thousands per MCL	Baseline	7.1 (2.0)	7.2 (2.0)	7.2 (2.1)
	Day 7* minus baseline	-0.2 (1.5)	-0.1 (1.6)	-0.1 (1.6)
Hematocrit, %	Baseline	42.5 (4.4)	42.7 (4.2)	42.6 (4.3)
	Day 7* minus baseline	-0.4 (2.0)	-0.5 (2.1)	-0.2 (2.0)
Platelet count in thousands	Baseline	282.5 (67.1)	282.0 (66.5)	274.5 (67.6)
	Day 7* minus baseline	-2.1 (30.5)	-1.4 (29.3)	-0.8 (31.9)

1 The safety population (patients who received at least one dose of study medication).
* Day 7 or final visit (if patients dropped out of the study)
Reference: Adapted from Volume 16, Table 8.2.4-1, Pages 210-255 and Volume 16, Table 8.2.4-2, Pages 257-267.

Medical Reviewer's Comments: All three treatment groups had similar baseline chemistry and hematology laboratory tests and had similar changes from baseline on Study Day #7 (except for the CPK and non-fasting triglyceride laboratory tests). Since non-fasting triglyceride levels are very variable (depending upon food intake), the differences in baseline and change from baseline on Study Day #7 (or early termination) in all three treatment groups were not clinically meaningful. See Section 7.2.9 for a discussion of the differences between the baseline CPK values between the placebo and carisoprodol groups.

There was no evidence of a carisoprodol-associated change in urinalysis parameters.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 30 presents the proportion of patients who had outlier blood chemistry or hematology laboratory values (a shift from a normal baseline value to an abnormal value on Study Day #7 or study termination) in the low back pain studies. Table 31 displays the predefined normal ranges of laboratory values.

Table 30: Proportion of patients who shifted from a normal[1] to an abnormal blood laboratory value in the low back pain studies[2]

Laboratory Test	Placebo	Carisoprodol 250 mg	Carisoprodol 350 mg
Elevated CPK, %	3.4 (n=440)	4.4 (n=430)	6.4 (n=220)
High creatinine level, %	0.4 (n=495)	0.8 (n=490)	2.5 (n=240)
High BUN level, %	1.0 (n=495)	1.2 (n=483)	0.8 (n=239)
Hyponatremia, %	0.8 (n=499)	0.4 (n=486)	0.4 (n=239)
Hypernatremia, %	0.8 (n=499)	1.0 (n=486)	0 (n=239)
Hypokalemia, %	0.2 (n=494)	0.4 (n=479)	1.2 (n=241)
Hyperkalemia, %	1.0 (n=494)	0.6 (n=479)	1.2 (n=241)
Hypocalcemia, %	0 (n=492)	0.2 (n=481)	0.4 (n=237)
Hypercalcemia, %	1.2 (n=492)	0 (n=481)	0.4 (n=237)
Hypercholesterolemia (non-fasting), %	12.4 (n=267)[3]	16.3 (n=257)[3]	17.7 (n=124)[3]
Hypertriglyceridemia (non-fasting), %	15.7 (n=343)[4]	17.0 (n=330)[4]	15.6 (n=160)[4]
High LDH, %	0.6 (n=492)	0.6 (n=486)	0.4 (n=241)
Hyperglycemia (non-fasting), %	10.2 (n=443)	10.4 (n=434)	12.3 (n=211)
Hypoglycemia, %	3.6 (n=443)	1.8 (n=434)	1.4 (n=211)
Hyperphosphatemia, %	5.2 (n=465)	5.5 (n=458)	7.0 (n=230)
Hypophosphatemia, %	1.1 (n=465)	1.3 (n=458)	1.7 (n=230)
Hyperuricemia, %	0.9 (n=469)	1.3 (n=458)	0.5 (n=221)
Increased WBC, %	2.5 (n=472)	2.4 (n=449)	3.0 (n=234)
Decreased WBC, %	1.5 (n=472)	2.0 (n=449)	1.1 (n=234)
Increased hematocrit, %	2.6 (n=462)	1.6 (n=434)	3.2 (n=221)
Decreased hematocrit, %	1.7 (n=462)	3.7 (n=434)	3.6 (n=221)
Increased platelet count, %	1.2 (n=484)	1.5 (n=463)	0.4 (n=239)
Decreased platelet count, %	0.4 (n=484)	0.4 (n=463)	1.3 (n=239)

1 See Table 31 for the predefined ranges of normal blood laboratory tests
2 Ranges of normal laboratory values were identical in Studies MP502 and MP505.
3 47%, 48%, and 49% of the placebo, 250 mg carisoprodol, and 350 mg carisoprodol treatment groups, respectively, had hypercholesterolemia at baseline.
4 32%, 33%, and 34% of the placebo, 250 mg carisoprodol, and 350 mg carisoprodol treatment groups, respectively, had hypertriglyceridemia at baseline.
Reference: Adapted from Volume 16, Table 8.2.4-3, Pages 268-313 and Volume 17, Table 8.2.4-4, Pages 4-14.

Table 31: Normal values[1] of blood laboratory tests in the low back pain studies[2]

Laboratory Test	Normal Range[1]
CPK	0 to 235 units/L in males and 0 to 190 units/L in females
Creatinine	0.5 to 1.4 mg/dL
BUN	7 to 25 mg/dL
Sodium	135 to 146 meq per liter
Potassium	3.5 to 5.3 meq per liter
Calcium	8.5 to 10.3 mg/dL
Cholesterol (non-fasting)	< 200 mg/dL
Triglycerides (non-fasting)	< 200 mg/dL
LDH	0 to 250 units per liter
Glucose (non-fasting)	70-115 mg/dL in 18 to 49 year olds and 70-125 in 50 to 65 year olds
Phosphorus	2.5 to 4.5 mg/dL
Uric acid	4 to 8.5 mg/dL in males and 2.5 to 7.5 mg/dL in females
WBC	3.8 to 10.8 times 10^9 per liter
Hematocrit	41 to 50% in males and 35 to 46% in females
Platelet count	130 to 400 times 10^9 per liter

1 Normal values were based on adults 18 to 65 years old.
2 Ranges of normal laboratory values were identical in Studies MP502 and MP505.
Reference: Adapted from Volume 23, Section 16.1.10, Pages 294 to 322; Volume 55, Section 16.1.10, Pages 88-117; Volume 23, Section 16.1.10, Pages 294 to 322; and Volume 55, Section 16.1.10, Pages 88-117

Medical Reviewer's Comments: There were no clinically meaningful shifts in laboratory values in all three treatment groups. The variations in the non-fasting glucose, triglycerides, and cholesterol values are not clinically meaningful because the variations are more likely related to food intake prior to testing and changes in these tests were similar in all three treatment groups. The sponsor should consider assessing fasting glucose, triglycerides, and cholesterol levels in future carisoprodol trials.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

There were no patients who discontinued from the Soma trials due to laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

Since there were no clinically meaningful laboratory abnormalities, additional analyses for dose dependency, time dependency, drug-demographic, drug-disease, and drug-drug interactions were not performed.

7.1.7.5 Special assessments – liver enzyme tests

Table 32 displays the mean liver enzyme test values (i.e., baseline and change from baseline) in the low back pain studies.

Table 32: Mean (SD) liver enzyme test values (i.e., baseline and change from baseline) in the low back pain studies

Liver enzyme test	Time point	Placebo n=560[2] n (%)[3]	Carisoprodol 250 mg n=548[2] n (%)[3]	Carisoprodol 350 mg n=279[2] n (%)[3]
Albumin, grams/dL	Baseline	4.4 (0.3)	4.4 (0.3)	4.4 (0.3)
	Day 7* minus baseline	0 (0.3)	0 (0.2)	0 (0.2)
Total bilirubin, mg/dL	Baseline	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)
	Day 7* minus baseline	0 (0.2)	0 (0.2)	0 (0.2)
SGOT, units per liter	Baseline	22.5 (13.2)	22.3 (13.2)	24.5 (23.7)
	Day 7* minus baseline	-0.9 (9.1)	-0.8 (7.3)	-0.1 (10.6)
SGPT, units per liter	Baseline	24.4 (19.0)	26.1 (22.2)	27.1 (26.2)
	Day 7* minus baseline	-0.5 (8.6)	-1.1 (10.3)	-0.8 (13.2)
Alkaline phosphatase units per liter	Baseline	78.3 (26.2)	76.4 (23.0)	77.3 (27.9)
	Day 7* minus baseline	-0.4 (9.3)	-0.3 (9.0)	0.2 (8.4)

1 The preferred terms were coded using MedDRA Dictionary Version 8.0.
2 The safety population (patients who received at least one dose of study medication).
3 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
* Day 7 or final visit (if patients dropped out of the study)
Reference: Adapted from Volume 16, Table 8.2.4-1, Pages 210-255.

Table 33 presents the proportion of patients who had outlier liver test values (a shift from a normal baseline value to an abnormal value on Study Day #7 or study termination) in the low back pain studies. Table 34 displays the predefined normal ranges of liver test values.

Table 33: Proportion of patients who shifted from a normal[1] to an abnormal liver enzyme test value in the low back pain studies[2]

Laboratory abnormality	Placebo	Carisoprodol 250 mg	Carisoprodol 350 mg
Hyperalbuminemia, %	0.6 (n=505)	0.2 (n=486)	0.4 (n=243)
Hyperbilirubinemia, %	0.4 (n=496)	1.0 (n=486)	0.4 (n=239)
Elevated SGOT, %	2.1 (n=484)	1.3 (n=469)	1.7 (n=230)
Elevated SGPT, %	2.3 (n=476)	2.4 (n=451)	1.4 (n=222)
Elevated alkaline phosphatase, %	1.0 (n=484)	0.2 (n=474)	1.7 (n=235)

1 See Table 34 for the predefined ranges of normal blood laboratory tests
2 Ranges of normal laboratory values were identical in Studies MP502 and MP505.
Reference: Adapted from Volume 16, Table 8.2.4-3, Pages 268-313.

Table 34: Normal[1] values of liver enzyme test values in the low back pain studies[2]

Liver enzyme test	Normal range[1]
Albumin	3.2 to 5.0 grams/dL
Total bilirubin	0 to 1.3 mg/dL
SGOT	0 to 42 units per liter
SGPT	0 to 48 units per liter
Alkaline phosphatase	20 to 125 units per liter

1 Normal values were based on adults 18 to 65 years old.
2 Ranges of normal laboratory values were identical in Studies MP502 and MP505.
Reference: Adapted from Volume 23, Section 16.1.10, Pages 294 to 322 and Volume 55, Section 16.1.10, Pages 88-117.

Medical Reviewer's Comments: There were no significant liver test abnormalities in the carisoprodol and placebo groups in the low back pain studies.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

In the low back pain studies, vital signs were performed at baseline and on Study Days #3 and #7 (or early termination).

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Data from Studies MP502 and MP505 were pooled to evaluate the vital signs because these studies:

- Were randomized, double-blinded, placebo-controlled studies;
- Had identical patient populations (acute, idiopathic, mechanical low back pain); and
- Had identical study durations (i.e., one week).

Studies MP500 and MP501 were not included in the pooled data to evaluate the vital signs because these studies:

- Were single dose studies;
- Had healthy subjects;
- Were open label; and
- Vital signs were not performed after each study medication was given; rather, they were performed after subjects received all study medications thus making it difficult to ascribe a relationship between possible vital sign changes to a specific study medication.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Table 35 displays the mean vital sign values (i.e., baseline and change from baseline on Days #3 and #7) in the low back pain studies.

Table 35: Mean (SD) vital sign values (i.e., baseline and change from baseline) in the low back pain studies

Vital sign	Time point	Placebo n=560[2] n (%)[3]	Carisoprodol 250 mg n=548[2] n (%)[3]	Carisoprodol 350 mg n=279[2] n (%)[3]
Systolic BP, mmHg	Baseline	122.7 (13.3)	124.7 (13.9)	123.7 (14.8)
	Day 3 minus baseline	0 (10.5)	-1.4 (10.1)	-0.6 (10.9)
	Day 7* minus baseline	-0.4 (10.9)	-1.4 (11.6)	-1.8 (11.4)
Diastolic BP, mmHg	Baseline	77.1 (9.5)	78.2 (9.7)	77.9 (9.2)
	Day 3 minus baseline	-0.1 (8.0)	-0.8 (7.4)	-0.3 (8.3)
	Day 7* minus baseline	-0.1 (8.1)	-1.1 (8.3)	-1.2 (8.4)
Heart rate, beats per minute	Baseline	74.5 (9.9)	73.9 (9.2)	74.9 (9.6)
	Day 3 minus baseline	0.3 (8.3)	1.2 (7.7)	1.0 (9.4)
	Day 7* minus baseline	0.5 (9.6)	0.9 (8.4)	0.6 (10.0)
RR, respirations per minute	Baseline	16.7 (2.5)	16.8 (2.4)	16.7 (2.7)
	Day 3 minus baseline	0 (2.5)	-0.1 (2.2)	0 (2.3)
	Day 7* minus baseline	-0.1 (1.8)	-0.2 (2.2)	0.2 (4.2)
Temperature, Fahrenheit	Baseline	98.1 (0.7)	98.0 (0.7)	97.9 (0.7)
	Day 3 minus baseline	0 (0.7)	0 (0.7)	0 (0.7)
	Day 7* minus baseline	0 (0.7)	-0.1 (0.7)	0 (0.7)

1 The preferred terms were coded using MedDRA Dictionary Version 8.0.
2 The safety population (patients who received at least one dose of study medication).
3 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
* Day 7 or final visit (if patients dropped out of the study)
Reference: Adapted from Volume 17, Table 8.2.4-6, Pages 169-179.

Medical Reviewer's Comments: There was no evidence of carisoprodol-associated changes in vital signs (i.e., systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) in the low back pain studies.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 36 displays the number and proportion of patients with changes in vital signs > 30% compared to baseline (vital signs were measured on Days #3 and #7).

Table 36: Number and proportion of patients with changes in vital signs[1] > 30% compared to baseline in the low back pain studies1

	Study MP502			Study MP505	
Vital Sign Parameters	**Placebo n=276[2] n (%)[3]**	**Carisoprodol 250 mg n=271[2] n (%)[3]**	**Carisoprodol 350 mg n=279[2] n (%)[3]**	**Placebo n=277[2] n (%)[3]**	**Carisoprodol 250 mg n=284[2] n (%)[3]**
Respiratory rate	16 (5.8)	17 (6.3)	21 (7.5)	10 (3.5)	14 (5.1)
Heart rate	18 (6.5)	14 (5.2)	18 (6.5)	11 (3.9)	8 (2.9)
Diastolic BP	9 (3.3)	9 (3.3)	3 (1.1)	6 (2.1)	7 (2.5)
Systolic BP	6 (2.2)	2 (0.7)	5 (1.8)	1 (0.4)	3 (1.1)

1 Vital signs were measured on Day #3 and Day #7 during the treatment period.
2 The safety population (patients who received at least one dose of study medication).
3 n (%) is the number (percentage) of patients who had at least one event. Patients were only counted once per criterion per vital sign parameter
Reference: Adapted from Volume 18, Table 12-15, Page 96 and Volume 53, Table 12-13, Page 87.

Medical Reviewer's Comments: There was no evidence of carisoprodol-associated changes in vital signs in the low back pain studies.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

There were no dropouts due to vital sign abnormalities in the carisoprodol studies.

7.1.8.4 Additional analyses and explorations

Since there were no clinically meaningful vital sign abnormalities, additional analyses for dose dependency, time dependency, drug-demographic, drug-disease, and drug-drug interactions were not performed.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

No electrocardiograms (ECGs) were performed (at baseline or during the treatment period) in the low back pain studies. In the PK studies (i.e., Studies MP500 and MP501), ECGs were only performed at baseline and at the end of the study. Since ECGs were not performed after administration of each study medication, it is difficult to ascribe changes in ECGs to a specific study medication.

However, carisoprodol has been approved since 1959 (at a higher dose) and no post-marketing concerning ECG abnormalities have been identified. Therefore, the lack of ECGs in the phase III

studies ─ and suboptimal ECG testing in the phase I studies ─ is not ideal, but it is acceptable for a product that has been marketed for over 40 years in the United States.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See Section 7.1.91.

7.1.9.3 Standard analyses and explorations of ECG data

See Section 7.1.91.

7.1.9.4 Additional analyses and explorations

See Section 7.1.91.

7.1.10 Immunogenicity

No immunogenicity tests were performed in the carisoprodol studies because carisoprodol is a small molecule. There was no clinical evidence of immunogenicity of carisoprodol (i.e., there were no hypersensitivity AEs and no evidence of reduced efficacy of carisoprodol after repeat dosing).

7.1.11 Human Carcinogenicity

There were no malignancies that developed in the carisoprodol studies. No formal studies of carcinogenic effects of carisoprodol were performed because the proposed indication is of short duration; carisoprodol is not a known immune modulator; and there has been no malignancy signal in post-marketing reports of the approved carisoprodol regimen.

7.1.12 Special Safety Studies

No special safety studies of carisoprodol were conducted. No thorough QT/QTc study of carisoprodol was performed because carisoprodol has been approved since 1959 (at a higher dose) and no post-marketing carisoprodol-related ECG abnormalities or arrhythmias have been identified.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

The carisoprodol studies were not designed to evaluate withdrawal phenomena or abuse potential because post-dosing follow-up safety visits were not performed and patients with a history of poly-substance abuse were excluded from the low back pain studies.

Carisoprodol has never been designated as a federal controlled substance; although its metabolite (i.e., meprobamate) is a Schedule IV controlled drug. On February 11, 1997, the Drug Abuse Advisory Committee Meeting did not recommend scheduling carisoprodol.

The currently approved carisoprodol label contains **WARNINGS** regarding the dependence, abuse, and withdrawal risks of carisoprodol use. Multiple post-marketing cases of carisoprodol-associated abuse have been reported in patients using concomitant medications that have abuse potential (e.g., opioids) and/or abuse of alcohol or illegal drugs. Additionally, most of these reports have occurred in patients receiving carisoprodol chronically. The new proposed carisoprodol dose regimen is less likely to contribute to carisoprodol withdrawal or abuse compared to the approved higher dose regimen. The **Drug Dependence, Withdrawal, and Abuse** subsection of the **WARNINGS AND PRECAUTIONS** section of the carisoprodol label should be revised to highlight that carisoprodol abuse, dependence, and withdrawal has occurred in patients who have used carisoprodol in combination with other drugs with abuse potential and/or in patients who have used carisoprodol chronically [see Section 9.4 (Labeling Review)].

7.1.14 Human Reproduction and Pregnancy Data

No pregnant women enrolled in the carisoprodol studies (i.e., all women of child-bearing potential had negative screening urine pregnancy tests) and no women became pregnant during the carisoprodol studies. According to the approved carisoprodol label, the safety of carisoprodol in pregnancy has not been established. After a literature search, no information was found on the effects of carisoprodol use in pregnant women.

7.1.15 Assessment of Effect on Growth

Since there were no pediatric patients in the carisoprodol development program and the carisoprodol trials were of short-term duration (i.e., ≤ 7 days), an assessment on growth was not performed.

7.1.16 Overdose Experience

There were no reports of overdose of carisoprodol in the carisoprodol studies. In the carisoprodol development program, the highest daily carisoprodol dose was 1.4 grams per day (350 mg QID) which is an approved carisoprodol dose regimen. The new lower proposed carisoprodol dose regimen is less likely to be associated with overdose then the approved higher dose regimen.

There have been post-marketing reports of carisoprodol overdoses which have resulted in CNS depression. Death, hypotension, respiratory depression, seizures, delirium, hallucinations, dystonic reactions, horizontal and vertical nystagmus, blurred vision, mydriasis, euphoria, muscular incoordination, rigidity, and/or headache have been reported with SOMA overdosage. The overwhelming majority of carisoprodol overdoses have been associated with overdoses of multiple drugs including drugs of abuse, illegal drugs, and alcohol. The **OVERDOSAGE** section of the carisoprodol label should be revised to improve its clarity [see Section 9.4 (Labeling Review)].

7.1.17 Postmarketing Experience

The Division of Drug Risk Evaluation (DDRE) in the Office of Surveillance and Epidemiology (OSE) was consulted to assist in the evaluation of the post-marketing safety of carisoprodol. DDRE evaluated U.S. post-marketing SAEs associated with the use of carisoprodol in four age groups (i.e., pediatric patients up to 12 years old, pediatric patients 12 to 16 years old, adults 17 to 64 years old, and geriatric patients) over the past 5 years (from 1/1/02 to 12/31/06). Of the carisoprodol-associated SAEs; 0.4%, 1.1%, 97.3%, and 1.2% occurred in pediatric patients up to 12 years old, pediatric patients 12 to 16 years old, adults between 17 to 64 years old, and geriatric patients, respectively. The age distribution of carisoprodol-associated SAEs can be explained by the disparity in drug usage according to age (the overwhelming majority of patients who received carisoprodol prescriptions were adults between 17 and 64 years old). The most common carisoprodol-associated SAEs in adults patients 17 to 64 years old were multiple drug overdose (e.g., prescription drugs, illegal drugs, and/or alcohol) resulting in death, respiratory arrest, CNS depression, intubation, and hospitalization.

The Division of Surveillance, Research, and Communication Support (DSRCS) in the OSE was consulted to evaluate actual use data of carisoprodol. The following is a summary of the significant findings of the DSRCS consult:

- According to the 2006 Verispan Total Patient Tracker (TPT), about 0.1%, 0.3%, 89%, and 11% of carisoprodol use was in pediatric patients between 0-11 years old, pediatric patients between 12-16 years old, adult patients between 17-64 years old, and adult patients ≥ 65 years old, respectively;
- According to the Verispan Physician Drug and Diagnosis Audit (PDDA), the most common diagnoses listed by physicians for the use of carisoprodol in 2006 were for back and neck pain. In 2006, the proportion of carisoprodol use for back disorder NOS, sprain of back NOS, other cervical spine disease, intervertebral disc disease, and other soft tissue disease was 43.4, 17.3, 4.6, 4.4, and 4.3%, respectively;
- According to the Verispan Vector One Audit (VONA), the numbers of carisoprodol prescriptions dispensed by retail pharmacies to consumers was about (b) (4) or 1999, 2000, 2001, 2002, 2003, 2004, and 2005, respectively;
- According to the 2006 Verispan PDDA, about 13%, 15%, 17%, 19%, 16%, and 20% of carisoprodol use was for 0-7 days, 8-14 days, 15-21 days, 22-30 days, ≥ 31 days, and unspecified number of days, respectively; and
- Carisoprodol prescriptions represented about 15% of the total prescriptions in the muscle relaxant category (see Table 37).

Table 37: Total muscle relaxant prescriptions dispensed in 2005[1]

		(b) (4)
Total Market		
lorazepam		
cyclobenzaprine		
diazepam		
carisoprodol		
metaxalone		
methocarbamol		
carisoprodol/aspirin (Soma Compound)		
carisoprodol/aspirin/codeine (Soma Compound with codeine)		

1 According to Verispan Vector One Audit (VONA). VONA includes retail pharmacies; but excludes mail order pharmacies

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Primary Clinical Data Sources Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Table 38 displays the design (including the treatment groups and study durations) of the four carisoprodol studies submitted in this efficacy supplement. Studies MP500 and MP501 were single-dose pharmacokinetic studies of carisoprodol in healthy subjects; in contrast, Studies MP502 and MP505 were one-week safety and efficacy studies of carisoprodol in patients with acute mechanical low back pain.

Table 38: The four carisoprodol studies submitted in the efficacy supplement

STUDY[1]	DESIGN	TREATMENT GROUPS	DURATION
MP500 (N=24) (12/10/04 to 12/20/04)	Randomized, open-label, single-dose, crossover, pharmacokinetic, single-center, U.S. trial on the effect of food on the absorption of carisoprodol from 350 mg carisoprodol tablets in **healthy subjects**	Two sequences: 1) A then B (n=12) 2) B then A (n=12) A is a single-dose of 350 mg of carisoprodol in fed state B is a single-dose of 350 mg of carisoprodol in fast state	Two single doses separated by 7 days of washout
MP501 (N=24) (2/28/05 to 3/21/05)	Randomized, open-label, single-dose, crossover, pharmacokinetic, single-center, U.S. trial on the absorption of carisoprodol from 150 mg and 250 mg carisoprodol tablets relative to that from 350 mg carisoprodol tablets in **healthy subjects**	Six sequences: (N=24) 1) A then B then C 2) A then C then B 3) B then A then C 4) B then C then A 5) C then A then B 6) C then B than A A is 150 mg of carisoprodol B is 250 mg of carisoprodol C is 350 mg of carisoprodol	Three single doses (each dose separated by a 7 day washout period)
MP502 (N=826) (8/15/05 to 7/18/06)	Randomized, double-blind, placebo-controlled, parallel-group, multi-center, U.S., one week trial of 250 mg and 350 mg carisoprodol tablets in adult **patients** aged 18 to 65 years old **with acute, idiopathic mechanical low back pain**	1) Placebo (n=276) 2) Carisoprodol 250 mg (n=271) 3) Carisoprodol 350 mg (n=279) (all treatment groups dosed four times daily)	Up to 7 days
MP505 (N=561) (8/11/05 to 6/8/06)	Randomized, double-blind, placebo-controlled, parallel-group, multi-center, U.S., one-week trial of 250 mg carisoprodol tablets in adult **patients** aged 18 to 65 years old **with acute, idiopathic mechanical low back pain**	1) Placebo (n=284) 2) Carisoprodol 250 mg (n=277) (all treatment groups dosed four times daily)	Up to 7 days

1 Study columns includes the study initiation date to the study completion date
Reference: NDA 11-792 submission

7.2.1.2 Demographics

Tables 39 and 40 display the baseline demographic characteristics (i.e., age, gender, race, ethnicity, height, and weight) of the patients in the two low back pain studies and of the subjects in the two pharmacokinetic studies, respectively.

Table 39: Baseline demographics in the low back pain studies (i.e., MP502 and MP505)

Demographic Characteristic		Placebo n=560[1]	Carisoprodol 250 mg n=548[1]	Carisoprodol 350 mg n=279[1]
Age	Mean (SD) in years	41.0 (12.4)	40.0 (11.8)	40.4 (12.4)
	< 18, %	0	0	0
	≥18 or ≤ 65, %	98.9	98.9	96.4
	> 65, %	1.1	1.1	0.4
Gender	Males, %	42.0	49.8	44.8
	Females, %	58.0	50.2	55.2
Race	Asian, %	9.5	9.1	5.7
	Black, %	15.2	16.1	15.4
	Caucasian, %	73.9	73.2	76.3
	Other, %	1.4	1.6	2.5
Ethnicity	Hispanic, %	29.5	32.8	25.1
	Non-Hispanic, %	70.5	67.2	74.9
Height	Mean (SD) in meters	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight	Mean (SD) in kg	80.3 (17.7)	82.1 (18.2)	82.0 (18.2)

1 The safety population (patients who received at least one dose of study medication).
Reference: Adapted from Volume 16, Table 8.2.1-2, Pages 72-74.

Table 40: Baseline demographics in the PK studies (i.e., Studies MP500 and MP501)

Demographic Characteristic		Total[1] (N=48)
Age	Mean (SD) in years	23.4 (5.8)
Gender	Males, %	50
	Females, %	50
Race	Asian, %	2.1
	Black, %	2.1
	Caucasian, %	93.8
	Other, %	2.1
Ethnicity	Hispanic, %	10.4
	Non-Hispanic, %	89.6
Height	Mean (SD) in inches	68.0 (3.6)
Weight	Mean (SD) in pounds	159.7 (27.5)

1 The safety population (patients who received at least one dose of study medication). All patients were to receive all study medications.
Reference: Adapted from Study Report MP500, Table 14.1.2, Pages 54-55 and Study Report MP501, Table 14.1.2, Pages 76-77.

<u>Medical Reviewer's Comments</u>: The baseline demographic characteristics of the three treatment groups in the low back pain studies were similar. In the low back pain studies, almost all of the patients were adults between 18 and 65 years old with a mean age of about 41 years old. The mean body mass index (BMI) of the low back pain patients was 27.9 (in

the overweight range). The proportions of Blacks and Asians in the low back pain studies are similar to the proportion of these minorities in the United States. There were a greater proportion of Hispanics in the low back pain studies compared to the proportion of Hispanics in the United States.

The healthy subjects in the single-dose PK studies were young (mean age of about 23 years old), almost all Caucasian, and a BMI of 24.4 (in the normal range).

7.2.1.3 Extent of exposure (dose/duration)

Table 41 presents the summary of the extent of carisoprodol exposure in the low back pain studies.

Table 41: Summary of carisoprodol exposure in the low back pain studies

		Placebo n=560[1]	Carisoprodol 250 mg n=548[1]	Carisoprodol 350 mg n=279[1]
Total carisoprodol dose	**Mean (SD) dose in grams**	0 (0)	6.1 (1.3)	8.3 (2.2)
	Range of total doses in % of patients:			
	0 to 2.45 grams	0	3.6	4.3
	> 2.45 and ≤ 4.9 grams	0	5.1	4.3
	> 4.9 and ≤ 7.35 grams	0	82.1	11.1
	> 7.35 and ≤ 9.8 grams	0	5.3	63.8
	> 9.8 grams	0	0	12.9
Daily carisoprodol dose	**Mean (SD) daily dose in grams**	0 (0)	0.87 (1.1)	1.2 (1.9)
	Range of mean daily dose in % of patients:			
	0 to 0.5 grams	0	2.0	1.8
	> 0.5 and ≤ 1 grams	0	94.0	9.0
	> 1 and ≤ 1.5 grams	0	0.2	85.7
	> 1.5 grams	0	0	0
Number of days dosed	**Mean (SD)**	6.4 (2.0)	6.5 (1.9)	6.6 (1.8)
	Range of the number of days dosed in % of patients:			
	0 days	3.8	4.0	3.6
	1 to 3 days	8.4	4.0	6.5
	4 to 7 days	65.0	69.5	66.3
	> 7 days	22.9	22.4	23.7
Missing values, %		3.6	3.8	3.6

1 The safety population (patients who received at least one dose of study medication).
Reference: Adapted from Volume 16, Table 8.2.1-5, Pages 79-81.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

A literature search for randomized, controlled studies of carisoprodol was performed (Table 42 details the design and results of six randomized, controlled studies of 350 mg of carisoprodol reported in the literature). No studies of 250 mg carisoprodol were found in the literature.

The results from these six studies were not integrated with the primary source data (four studies of 250 mg of carisoprodol) because study reports and case report forms were not available and it is not clear if these studies were adequately conducted to assess the efficacy and safety of carisoprodol in the treatment of acute, musculoskeletal conditions.

Table 42: Randomized, controlled studies of 350 mg of carisoprodol in the literature

Study author (year[1])	Design	Treatment Groups	Endpoints	Results
Boyles[2] (1983)	R, DB, MC, 7-day study in adult patients 19 to 65 years old with acute strain or sprain of the back (≤ 7 days duration)	1) carisoprodol 350 mg QID (n=33) 2) diazepam 5 mg QID (n=32)	PROs including 5-point categorical scales and 100 point numerical VAS scales assessing pain severity, stiffness, activity, sleep impairment, and tension IROs using 5-point categorical scales assessing severity of spasm, tenderness, mobility	Efficacy: Because of multiple endpoints and unclear pre-specified primary endpoint, efficacy results are not reported in this table. Safety: 25% and 43% of patients in the carisoprodol and diazepam groups, respectively had at least one CNS AE
Rollings[3] (1983)	R, DB, MC, 7-day study in adult patients aged 19 to 65 years old with acute back pain (≤ 7days duration)	1) carisoprodol 350 mg QID (n=28) 2) cyclobenzaprine 10 mg QID (n=30)	PRO change from baseline in pain, stiffness, activity impairment, sleep impairment, tension and overall relief on Days #3and #7 using two scales (5-point categorical scale and 100 point numerical VAS) IROs change from baseline in tenderness, spasm, mobility restriction, and overall severity on Days #3and #7 with a 5-point categorical scale	Efficacy: No statistical differences in two groups for the multiple PROs and IROs Safety: 51% and 57% of the patients in the carisoprodol and cyclobenzaprine groups had CNS AEs. In both groups, 8% of patients had an AE leading to discontinuation
Cullen[4] (1976)	R, DB, SC, 10-day study in patients with acute back pain	1) carisoprodol 350 mg QID (n=32) 2) placebo QID (n=31)	IROs of change in pain, spasm, limitation of motion severity on Days #5 and #10 were based on 4-point categorical scales and global improvement at end of study was a 6-point categorical scale	Efficacy: for all 7 endpoints, carisoprodol group was numerically greater than placebo group Safety: 31% and 6% of carisoprodol and placebo patients, respectively, had CNS AEs (e.g., dizziness or drowsiness)
Baratta[5] (1976)	R, DB, SC, 14-day study in patients with acute or chronic back pain	1) carisoprodol 350 mg QID (n=33) 2) propoxyphene 65 mg QID (n=32) 3) placebo QID (n=29)	16 IRO endpoints (difference at the end of the 14-day study and baseline values): pain on active movement, pain on passive movement, flexion, extension, rotation, passive sit-up, knee flexion, side bend, squat, discomfort, stiffness, anxiety, difficulty falling asleep, number of awakenings, total sleep time, global improvement	Efficacy: Because of multiple endpoints and multiple comparisons (3 treatment groups), efficacy results are not reported in this table. Safety: no AEs in all treatment groups
Schreiner[6] (1972)	R, DB, SC, 10-day study of patients with acute back pain	1) carisoprodol 350 mg QID (n=28) 2) placebo QID (n=31)	IROs change in pain, spasm, limitation of motion severity on Days #5 and #10 and global improvement at end of study	Efficacy: for all 7 endpoints, carisoprodol group was numerically greater than placebo group Safety: Not reported

Table 42 Continued: Randomized, controlled studies of 350 mg of carisoprodol in the literature

Study author (year[1])	Design	Treatment Groups	Endpoints	Results
Hindle[7] (1972)	R, DB, SC, 4-day study of patients with acute low back pain. Patients were Mexican migrant workers.	1) carisoprodol 350 mg QID (n=14) 2) batabarbital 15 mg QID (n=15) 3) placebo QID (n=14)	IROs change in pain, spasm, interference with daily activities, limitation of motion, anxiety/tension on Days #2 and #4 compared to baseline were based on 4-point categorical scales and a global improvement on Days #2 and #4 based on a 5-point categorical scale IRO change in flexion on Days #2 and #4 compared to baseline PROs change in 100-point numerical pain intensity scale on Days #2 and #4 compared to baseline	Efficacy: Because of multiple endpoints and multiple comparisons (3 treatment groups), efficacy results are not reported in this table. Safety: only one patient in the batabarbital group had an AE (drowsiness)

R is randomized, DB is double-blind, MC is multi-center, SC is single-center, PRO is patient-reported outcomes, IRO is investigator-reported outcomes

1 year article was published

2 Boyles, WF. Management of acute musculoskeletal conditions: thoracolumbar strain or sprain. *Todays Therap Trends* 1983; 1(1):1-16.

3 Rollings, H.E.,et al. Management of acute musculoskeletal conditions: Thoracolumbar strain or sprain. A double-blind evaluation comparing the efficacy and safety of carisoprodol with cyclobenzaprine hydrochloride. *Curr Ther Res* 1983; 34(6):917-928.

4 Cullen, AP. Carisoprodol ('Soma') in acute back conditions: a double-blind, randomized, placebo-controlled study. *Curr Therap Res* 1976; 20:4(2):557-560.

5 Baratta, RR. A double-blind comparative study of carisoprodol, propoxyphene, and placebo in the management of low back syndrome. *Curr Ther Res Clin Exp.* 1976 Sep; 20(3):233-240.

6 Scheiner JJ. Soma (carisoprodol) compared with placebo for relief of muscle spasm, pain, and limitation of motion in conditions affecting the cervical, thoracic, and lumbar regions of the back. This data is on file with the applicant. It is not clear if this study was reported in the literature.

7 Hindle, TH. Comparison of carisoprodol, butabarbital, and placebo in treatment of the low back syndrome. *Calif Med.* 1972 Aug; 117(2):7-11.

<u>Medical Reviewer's Comments</u>: There were no deaths or SAEs in the six studies from the literature, although study reports and case report forms are not available.

The six literature reports of studies of 350 mg of carisoprodol are a lower quality of data compared to the primary data source (i.e., the four submitted studies of 250 mg of carisoprodol) because these studies were small (about 30 patients per arm), most were single-center studies, the pre-specified primary efficacy endpoint was not identified, and the statistical analysis plans did not account for multiple efficacy comparisons and multiple endpoints. However, some of the literature reports had longer treatment durations (i.e., three of the studies were 10-14 day studies) then the primary source data (i.e., 7 days).

Since the literature reports do not involve the 250 mg carisoprodol dose regimen, these studies do not provide evidence of durability of effect for this dose regimen.

7.2.2.2 Postmarketing experience

See Section 7.1.17 (Postmarketing Experience).

7.2.2.3 Literature

See Section 7.2.2.1 (Other Studies) for the literature review.

7.2.3 Adequacy of Overall Clinical Experience

Medical Reviewer's Comments: An adequate number of subjects/patients were exposed to carisoprodol for the proposed short-term indication (i.e., treatment of acute musculoskeletal conditions) because of the following reasons:

- **The number of low back pain patients exposed to the proposed carisoprodol dose regimen was similar to the number of low back pain patients exposed in the recently approved lower dose regimen for another muscle relaxant (i.e., the cyclobenzaprine 5 mg TID regimen);**
- **The proposed carisoprodol dose regimen contains a lower daily carisoprodol dose (i.e., 1 gram per day) compared to the daily dose of the 350 mg dose regimen (i.e., 1.4 grams per day) which has been approved and marketed in the United States since 1959; and**
- **The proposed duration is for short-duration.**

The eligibility criteria in the low back pain studies were acceptable to select a population of patients with acute, mechanical, idiopathic low back pain. However, exclusion of geriatric patients and patients with a history of alcohol abuse, drug abuse, or drug dependence limit the generalizability of the studies to these populations. Geriatric patients may be more susceptible to carisoprodol's sedative effects than younger patients. Since patients with a history of alcohol abuse, drug abuse, or drug dependence patients are more likely to develop drug abuse or drug dependence to carisoprodol, the low back pain studies may have underestimated the frequency of drug abuse or drug dependence in a typical low back pain population. The label should reflect the deficiencies in the carisoprodol database.

The duration of the low back pain studies (i.e., 7 days) is reasonable to assess the safety and efficacy of the carisoprodol 250 mg regimen for seven days of therapy. However, the 7-day duration limits the evaluation of the efficacy of the carisoprodol 250 mg regimen for longer durations (e.g., up to three weeks ─ the sponsor's proposed duration). It is important to assess the durability of treatment effect since patients with acute idiopathic, mechanical low back pain may have symptoms that persist for several weeks. Therefore, the recommended duration in the label should be similar to the duration in the low back pain studies (i.e., up to seven days).

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No new animal pharmacology, animal toxicology, or *in vitro* studies were required for this efficacy supplement because carisoprodol has been approved and marketing in the United States for almost 50 years and the proposed carisoprodol dose is lower then the currently approved dose.

7.2.5 Adequacy of Routine Clinical Testing

Medical Reviewer's Comments: The type and frequency of vital sign and routine laboratory tests in the carisoprodol development program were adequate for the proposed lower carisoprodol dose regimen. In addition, the methods to elicit AEs and the frequency of assessment of AEs in the carisoprodol development program were adequate.

No ECGs were performed (at baseline or during the treatment period) in the low back pain studies. However, carisoprodol has been approved since 1959 (at a higher dose) and no post-marketing concerning ECG abnormalities have been identified. Therefore, the lack of ECGs in the phase III studies is not optimal, but it is acceptable.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

See Section 5.1 and Dr. Zhang's review for information about the metabolism and elimination of carisoprodol. See Section 8.2 for information about possible drug-drug interactions with carisoprodol.

7.2.7 Adequacy of Evaluation for Potential Adverse Events; Recommendations for Further Study

Medical Reviewer's Comments: The most common adverse reactions associated with muscle relaxants include CNS toxicity (e.g., sedation and dizziness). The carisoprodol program adequately evaluated CNS AEs.

The lack of a follow-up safety visit to assess withdrawal symptoms off treatment is a limitation of the safety monitoring program since there have been post-marketing reports of withdrawal symptoms after cessation of carisoprodol dosing. Despite this limitation of safety monitoring, the safety database was adequate to support the safety of the 250 mg carisoprodol regimen for the short-term treatment of discomfort associated with acute, musculoskeletal conditions because:

- **The carisoprodol label conveys the above limitation (there are WARNINGS regarding the withdrawal potential of carisoprodol);**
- **The lower-dose carisoprodol regimen (250 mg QID or 1 gram per day) is less likely to contribute to withdrawal symptoms compared to the approved, higher-dose, carisoprodol regimen (350 mg QID or 1.4 grams per day);**
- **The higher-dose carisoprodol regimen has been approved and marketed in the United States for almost 50 years;**
- **The 250 mg regimen demonstrated a slightly improved safety profile compared to the 350 mg dose regimen in the low back pain studies (i.e., a lower incidence of CNS DAEs and CNS ADRs); and**
- **There were a sufficient number of subjects/patients exposed to carisoprodol for the proposed short-term indication.**

Future studies of carisoprodol should contain post-dosing safety evaluations for withdrawal symptoms.

7.2.8 Assessment of Quality and Completeness of Data

The overall quality and completeness of the data was adequate for conducting the safety review.

7.2.9 Additional Submissions, Including Safety Update

Medpointe's most important clinical submissions included their March 28, 2007 response to DAARP's March 13, 2007 information request (IR) and their Safety Update (submitted on April 3, 2007).

March 13, 2007 IR:
DAARP's March 13, 2007 IR asked MedPointe to "provide safety/efficacy studies literature reports, pharmacokinetic data, or other data to support the use of carisoprodol in pediatric patients aged 12 to 16 years old." In their March 28, 2007 response, MedPointe stated that they know of no data regarding the use of carisoprodol in pediatric patients (see Section 8.4 for more details).

DAARP's March 13, 2007 IR asked MedPointe to "provide 'other clinical experience' of the safety and/or efficacy of the use of carisoprodol in geriatric patients, compared to younger patients [see 21 CFR 201.57(c)(9)(v)(B)(1)]." In their March 28, 2007 response, MedPointe stated that they are not aware of safety and/or efficacy data regarding the use of carisoprodol in geriatric patients compared to younger patients.

DAARP's March 13, 2007 IR asked MedPointe to explain why the placebo group had a significantly greater mean baseline CPK value, compared to the mean baseline CPK values of the carisoprodol groups, given that the low back pain studies were randomized [the mean (SD) baseline CPK value for the pooled placebo group in Studies MP502 and MP505 was 182.5 (604.9) units/liter; whereas, the mean (SD) baseline CPK values for the pooled 250 mg and 350 mg carisoprodol groups were 188.5 (154.7) and 136.3 (152.6) units/liter, respectively]. In their March 28, 2007 response, MedPointe stated "that there were a small number of patients who were extreme outliers at baseline with very high CPK values." Table 43 presents the results of the sponsor's exploratory analysis of the baseline and during treatment CPK values after removal of CPK outliers (i.e., baseline CPK values > 5 times the upper limit of normal). In the low back pain studies, 6 (1.1%) and 4 (0.5%) patients in the placebo and carisoprodol groups had baseline CPK values that were > 5 times the upper limit of normal.

Table 43: Mean (SD) blood CPK values in the low back pain studies (including and excluding outliers)[1]

Laboratory Test	Time point	Placebo n=560[2]	Carisoprodol 250 mg n=548[2]	Carisoprodol 350 mg n=279[2]
CPK, units per liter (including all values)	Baseline	182.5 (604.9)	138.5 (154.7)	136.3 (152.6)
	Day 7* minus baseline	-46.0 (540.5)	-11.4 (141.3)	-8.6 (126.3)
CPK, units per liter (excluding outliers – baseline CPK > 5 times the upper limit of normal)	Baseline	128.4 (122.1)	130.2 (107.9)	132.0 (135.2)
	Day 7* minus baseline	-0.1 (124.6)	-4.5 (97.3)	-8.6 (126.3)

1 Baseline CPK outliers were defined as CPK values > 5 times the upper limit of normal. In the two low back pain studies, 6 (1.1%) and 4 (0.5%) patients in the placebo and carisoprodol groups had baseline CPK values that were > 5 times the upper limit of normal, respectively.
2 The safety population (patients who received at least one dose of study medication).
* Day 7 or final visit (if patients dropped out of the study)
Reference: Adapted from March 18, 2007 submission (response to our March 13, 2007 information request), Pages 69-70; Volume 16, Table 8.2.4-1, Pages 210-255; Volume 16, Table 8.2.4-2, Pages 257-267.

Medical Reviewer's Comments: The baseline CPK values in the placebo and carisoprodol treatment groups appeared similar after exclusion of patients with baseline outlier values (i.e., CPK values > 5 times normal). A small number of patients with outlier baseline CPK values (i.e., 10 patients) accounted for the difference in baseline CPK values between the placebo and carisoprodol treatment groups.

Safety Update: Medpointe's April 3, 2007 Safety Update evaluated trials, post-marketing reports, and literature reports of carisoprodol-associated AEs that occurred after the submission of the efficacy supplement. There were no additional AEs reported from the submitted clinical trials of carisoprodol. Since the efficacy supplement submission, there have not been any new safety findings "that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the ... labeling" [21 CFR 314.50(d)(vi)(b)].

7.3 Summary of Adverse Reactions, Important Limitations of Data, and Conclusions

Medical Reviewer's Comments: The most important carisoprodol dose-related ADRs were CNS ADRs (e.g., sedation, dizziness, and headache). See Sections 7.1.5.4, 7.1.5.5, and 7.1.5.6 for more details.

The lack of a follow-up safety visit to assess withdrawal symptoms off treatment is a limitation of the safety monitoring program since there have been post-marketing reports of withdrawal symptoms after cessation of carisoprodol dosing. Despite this limitation of safety monitoring, the safety database was adequate to support the safety of the 250 mg carisoprodol regimen for the short-term treatment of discomfort associated with acute, musculoskeletal conditions because:

- **The carisoprodol label conveys the above limitation (there are WARNINGS regarding the withdrawal potential of carisoprodol);**
- **The lower-dose carisoprodol regimen (250 mg QID or 1 gram per day) is less likely to contribute to withdrawal symptoms compared to the approved, higher-dose carisoprodol regimen (350 mg QID or 1.4 grams per day);**
- **The higher-dose carisoprodol regimen has been approved and marketed in the United States for almost 50 years;**
- **The 250 mg regimen demonstrated a slightly improved safety profile compared to the 350 mg dose regimen in the low back pain studies (i.e., a lower incidence of CNS DAEs and CNS ADRs); and**
- **There were a sufficient number of subjects/patients exposed to carisoprodol for the proposed short-term indication.**

In summary, the submitted carisoprodol studies support the safety of the 250 mg carisoprodol regimen for the short-term treatment of discomfort associated with acute, painful musculoskeletal conditions.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Data from Studies MP502 and MP505 were pooled to evaluate the safety database because these two studies:

- Were randomized, double-blinded, placebo-controlled studies;
- Had identical patient populations (acute, idiopathic, mechanical low back pain); and
- Had identical study durations (i.e., one week).

Studies MP500 and MP501 were not included in the pooled data to evaluate the safety data because these studies:

- Were single dose studies;
- Had healthy subjects (not low back pain patients); and
- Were open label and uncontrolled.

7.4.1.2 Combining data

In pooling data, the numerator events and denominators for the two low back pain studies were combined.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The carisoprodol 250 mg group (e.g., 1 gram of carisoprodol daily) had a slightly lower incidence of CNS DAEs and CNS AEs compared to the carisoprodol 350 mg group (e.g., 1.4 grams of carisoprodol daily). For more details, see Tables 23 and 25 in Sections 7.1.4 and 7.1.5.4, respectively.

7.4.2.2 Explorations for time dependency for adverse findings

Most of the carisoprodol-associated significant AEs (e.g., CNS DAEs) occurred within 1-3 days of dose initiation.

7.4.2.3 Explorations for drug-demographic interactions

See Section 8.3 for explorations for drug-demographic interactions.

7.4.2.4 Explorations for drug-disease interactions

Since the overwhelming majority of low back pain patients were healthy without significant concomitant medical problems, explorations for drug-disease interactions cannot be evaluated.

7.4.2.5 Explorations for drug-drug interactions

There was no evidence of any drug-drug interactions in the low back pain studies. However, explorations for drug-drug interactions were limited because patients were prohibited from receiving a wide-range of medications throughout the study period including the following medications:

- Analgesics including: acetaminophen, combination products that include acetaminophen, centrally acting agents such as tramadol and clonidine hydrochloride, narcotics, combination

products containing narcotics, opioid agonist/antagonist combination products, over-the-counter (OTC), or prescription NSAIDs (including COX-2 inhibitors and nonselective NSAIDs);
- Muscle relaxants including skeletal muscle relaxants and acetylcholine inhibitors such as Botox;
- Sedatives and hypnotics including: barbiturates, benzodiazepines, prescription and OTC sleep aids, and other sedatives (e.g., promethazine hydrochloride);
- Antiepileptic drugs;
- Antineoplastic agents;
- Immunosuppressive or immune modulators;
- Systemic corticosteroids; and
- Hormones and agents to correct disorders of bone metabolism (e.g., Fosamax).

7.4.3 Causality Determination

The most important carisoprodol dose-related ADRs were CNS ADRs (e.g., sedation, dizziness, and headache). See Sections 7.1.5.4, 7.1.5.5, and 7.1.5.6 for more details.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Medpointe proposed the following language for the dosage and administration of carisoprodol:

[redacted]

Medical Reviewer's Comments: There is no data on the efficacy of the [redacted] The only carisoprodol trial that included both the 250 mg and the 350 mg carisoprodol regimens (i.e., Study MP502) had a parallel-group design. Furthermore, in Study MP502, patients [redacted] Therefore, Medpointe's proposed dosing language is not acceptable.

The approval of the 350 mg carisoprodol regimen for almost 50 years supports the safety of the 250 mg and 350 mg carisoprodol regimens for up to [redacted] duration. However, Medpointe's proposed maximum duration of carisoprodol treatment (i.e., [redacted]) is not acceptable for the following reasons:

- **There is no data on the efficacy of the 250 mg carisoprodol regimen after seven days of therapy and there is no significant data (e.g., in the submitted trials, in the literature) on the efficacy of the 350 mg carisoprodol regimen after seven days of therapy;**
- **In multiple pre-marketing communications with the applicant, DAARP strongly recommended a duration of at least two weeks for the low back pain trials to assess the durability of response; and**
- **There have been post-marketing reports of carisoprodol abuse, withdrawal, and dependence associated with prolonged use of carisoprodol. Limiting the duration of use in the label may reduce these known adverse reactions.**

A dosing regimen of four times a day (QID) is simpler and potentially less confusing to prescribers compared to the applicant's proposed regimen (i.e., three times a day and at bedtime). Furthermore, the dosing instructions in the patient medication diaries (take study medication during the morning, midday, evening, and bedtime) in the low back pain trials were more consistent with QID dosing. Compliance data regarding the timing of patient dosing during each study day was heterogeneous and was not consistent with Medpointe's proposed carisoprodol regimen (i.e., three times a day and at bedtime).

Therefore, the following carisoprodol dosing language is recommended:

> **"The recommended dose of SOMA is one 250 mg or 350 mg tablet four times a day and the recommended maximum duration of SOMA use is up to seven days."**

8.2 Drug-Drug Interactions

The carisoprodol trials did not have any unequivocal drug-drug interactions. Many patients were young (i.e., mean age was about 41 years old), healthy, and were taking no concomitant medications.

The currently approved carisoprodol label contains WARNINGS regarding the potential additive sedative adverse reactions with use of carisoprodol and other CNS depressants.

Medical Reviewer's Comments: The following language is recommended in the WARNINGS AND PRECAUTIONS section to improve the clarity of the drug-drug interaction risk with the use of concomitant CNS depressants: "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."

8.3 Special Populations

8.3.1 Patients with Renal Insufficiency

The low back pain studies did not include a significant number of patients with renal insufficiency to determine if there were efficacy or safety differences between patients with renal insufficiency compared to patients with normal renal function.

8.3.2 Patients with Hepatic Insufficiency

The low back pain studies did not include a significant number of patients with hepatic insufficiency to determine if there were efficacy or safety differences between patients with hepatic insufficiency compared to patients with normal hepatic function.

8.3.3 Geriatric Patients

Since there were a limited number of geriatric patients in the low back pain studies [13 (0.9%) of the patients in the low back pain studies were > 65 years old], efficacy and safety differences could not be determined between adult patients aged 18 to 64 and geriatric patients.

8.3.4 Female and Male Patients

Gender- Efficacy: Dr. Ted Guo, the statistical reviewer, conducted subgroup efficacy analyses of the co-primary efficacy endpoints by gender in the two low back pain studies (see Dr. Guo's review for more details). In both studies, there appeared to be no significant differences in the efficacy of the 250 mg carisoprodol regimen in males and females.

Gender - Safety: Table 44 displays the most common AEs by gender in the low back pain studies. Women had a higher incidence of AEs in all three treatment groups. In female patients, the 250 mg and 350 mg carisoprodol groups had an equal incidence of CNS AEs (e.g., somnolence or sedation and dizziness); however, both carisoprodol groups had a higher incidence of CNS AEs compared to the placebo group. In contrast, in male patients, there appeared to be increased incidence of AEs with higher carisoprodol doses.

Table 44: The most common AEs (≥ 2% in any treatment group) by gender[1] in the low back pain studies

Preferred Term[2]	Gender	Placebo n (%)[3]	Carisoprodol 250 mg n (%)[3]	Carisoprodol 350 mg n (%)[3]
Patients with ≥ 1 AE	Women	72 (22.2)	109 (39.6)	54 (35.1)
	Men	41 (17.4)	57 (20.9)	41 (32.8)
Somnolence or sedation	Women	17 (5.2)	52 (18.9)	25 (16.2)
	Men	14 (6.0)	21 (7.7)	22 (17.6)
Dizziness	Women	7 (2.2)	30 (10.9)	12 (7.8)
	Men	4 (1.7)	13 (4.8)	7 (5.6)
Headache	Women	8 (2.5)	19 (6.9)	6 (3.9)
	Men	3 (1.3)	7 (2.6)	3 (2.4)
Nausea	Women	7 (2.2)	2 (0.7)	6 (3.9)
	Men	8 (3.4)	4 (1.5)	6 (4.8)
Stomach discomfort, abdominal discomfort, or upper abdominal pain	Women	7 (2.2)	8 (2.9)	3 (2.4)
	Men	0 (0)	1 (0.4)	2 (1.6)
Fatigue, lethargy, or asthenia	Women	2 (0.6)	7 (2.5)	3 (1.9)
	Men	1 (0.4)	1 (0.4)	1 (0.8)

1 There were 325, 275, and 154 females in the placebo, 250 mg, and 350 mg groups, respectively, and there were 235, 273, and 125 males in the placebo, 250 mg, and 350 mg groups, respectively in the safety population (patients who received at least one dose of study medication).
2 The preferred terms were coded using MedDRA Dictionary Version 8.0.
3 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
Reference: Adapted from Volume 16, Table 8.2.3-2, Pages 151-159.

Medical Reviewer's Comments: The differences in the incidences of AEs in males and females may be explained by higher carisoprodol exposure in females compared to males after administration of a single carisoprodol dose. Carisoprodol exposure from a 250 mg carisoprodol dose in females is similar to carisoprodol exposure from a 350 mg carisoprodol dose in males (see Dr. Zhang's review). The incidence of AEs in females who received the 250 mg carisoprodol regimen is similar to the incidence of AEs in men who received the 350

mg carisoprodol regimen. This suggests higher carisoprodol exposure results in a greater incidence of AEs.

Administration of the 250 mg carisoprodol regimen (compared to the use of the 350 mg regimen) in females would not likely reduce the incidence of AEs. Administration of the 250 mg carisoprodol regimen (compared to administration of the 350 mg regimen) in males may reduce the incidence of AEs. However, the 250 mg carisoprodol regimen cannot be recommended over the 350 mg regimen in males because:

- **The male subgroup analysis of safety data included a small number of patients;**
- **Different dosing recommendations for males and females may be confusing to prescribers; and**
- **Since the comparative efficacy of the 250 mg and 350 mg carisoprodol regimens in males is equivocal, a full risk-benefit analysis of the 250 mg carisoprodol regimen, compared to the 350 mg regimen, cannot be performed.**

However, it is reasonable to include the PK differences in males and females in the label.

8.3.5 Caucasian, Black, and Asian Patients

Race - Efficacy: Dr. Ted Guo conducted subgroup efficacy analyses of the co-primary efficacy endpoints by race (Caucasians, Blacks, Asians, and Other) in the two low back pain studies (see Dr. Guo's review for more details). There appeared to be no clear differences in the efficacy of the 250 mg carisoprodol regimen in Caucasians, Blacks, Asians, and Other races.

Race - Safety: Table 45 displays the most common AEs by race (i.e., Caucasians, Blacks, and Asians) in the low back pain studies.

Table 45: The most common AEs (≥ 2 patients in any treatment group and ≥2% in any treatment group) by race[1] in the low back pain studies

Preferred Term[2]	Race	Placebo n (%)[3]	Carisoprodol 250 mg n (%)[3]	Carisoprodol 350 mg n (%)[3]
Patients with ≥ 1 AE	Caucasian	82 (19.8)	121 (30.2)	77 (36.2)
	Black	11 (12.9)	17 (19.3)	11 (25.6)
	Asian	16 (30.2)	24 (48.0)	4 (25.0)
Somnolence or sedation	Caucasian	18 (4.3)	52 (13.0)	36 (16.9)
	Black	0 (0)	4 (4.5)	7 (16.0)
	Asian	12 (22.6)	15 (30.0)	3 (18.8)
Dizziness	Caucasian	6 (1.4)	27 (6.7)	16 (7.5)
	Black	2 (2.4)	3 (3.4)	1 (2.3)
	Asian	3 (5.7)	11 (22.0)	1 (6.3)
Headache	Caucasian	9 (2.2)	18 (4.5)	7 (3.3)
	Black	0 (0)	5 (5.7)	1 (2.3)
	Asian	1 (1.9)	2 (4)	1 (6.3)
Stomach discomfort, abdominal discomfort, or upper abdominal pain	Caucasian	5 (1.2)	12 (2.9)	6 (2.9)
	Black	—	—	—
	Asian	2 (3.8)	0 (0)	0 (0)
Nausea	Caucasian	12 (2.9)	4 (1.0)	7 (3.3)
	Black	2 (2.4)	1 (1.1)	3 (7.0)
	Asian	—	—	—
Diarrhea	Caucasian	—	—	—
	Black	0 (0)	2 (2.3)	0 (0)
	Asian	—	—	—

1 There were 414, 401, and 213 Caucasians in the placebo, 250 mg, and 350 mg groups, respectively; 85, 88, and 43 Blacks in the placebo, 250 mg, and 350 mg groups, respectively; and 53, 50, and 16 Asians in the placebo, 250 mg, and 350 mg groups, respectively, in the safety population (patients who received at least one dose of study medication). In the safety database in the two low back pain studies, there were about 74% Caucasian, 16% Black, 9 % Asian, and 2% other.
2 The preferred terms were coded using MedDRA Dictionary Version 8.0.
3 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
Reference: Adapted from Volume 16, Table 8.2.3-3, Pages 160-171.

Medical Reviewer's Comments: For Caucasians and Blacks (the overwhelming majority of patients in the studies), there was a higher incidence of AEs with higher carisoprodol doses. The small Asian subgroup limits the ability to make conclusions regarding the relationship of carisoprodol dosing and AEs in the Asian subgroup.

8.4 Pediatrics

The currently approved carisoprodol label states that the "efficacy and safety of carisoprodol in patients under 12 years of age has not been determined." Medpointe's proposed new label contains similar language in the **Pediatric Use** (b) (4)

(b) (4) However, the currently approved and proposed carisoprodol labels are silent regarding the use of carisoprodol in pediatric patients aged 12 to 16 years old.

To satisfy the Pediatric Research Equity Act (PREA) of 2003, Medpointe requested a partial waiver to conduct studies of carisoprodol in pediatric patients ages birth to 12 years old. Medpointe argued that according to 21 CFR 314.55(c)(3)(i), a partial waiver can be granted with respect to pediatric patients from birth to 12 years old because the "drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients in that age group, and is not likely to be used in a substantial number of patients in that age group." Medpointe argued that since 1959, the carisoprodol label has not prohibited carisoprodol use in pediatric patients 12 to 16 year old; and therefore, additional pediatric studies should not be required in pediatric patients 12 to 16 years old.

Medical Reviewer's Comments: There are no data from efficacy/safety studies, literature reports, pharmacokinetic studies, or other data on the use of carisoprodol in the entire pediatric population (i.e., pediatric patients from birth to 16 years old). According to 21 CFR 201.57(c)(9)(iv)(F):

> **"If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this section (i.e., Pediatric Use section) must contain the following statement: Safety and effectiveness in pediatric patients have not been established."**

Therefore, the Pediatric Use (b) (4) section of the label should contain a statement that the safety and effectiveness of carisoprodol in all pediatric populations (i.e., pediatric patients less than 16 years old) have not been established.

A full waiver is recommended for pediatric studies (for all pediatric age groups) that are required under the 2003 Pediatric Research Equity Act because the "drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients."

Carisoprodol does not represent a meaningful therapeutic benefit over existing treatment for the treatment of acute, painful musculoskeletal conditions in pediatric patients [(e.g., muscle relaxants are generally less effective than non-steroidal anti-inflammatory drugs (NSAIDs) in pediatric patients in these conditions].

Verispan prescription data support the applicant's claim that carisoprodol is not likely to be used in a substantial number of patients in pediatric patients. According to Verispan's Total Patient Tracker (TPT), there were only about (b) (4) carisoprodol prescriptions filled at retail pharmacies in the United States in 2006 for pediatric patients from birth to 16 years of age. In contrast, there were about (b) (4) carisoprodol prescriptions filled at retail pharmacies in the United States in 2006 for adult patients. Pediatric and adult patients represented 0.4% and 99.6% of total prescriptions filled, respectively.

8.5 Advisory Committee Meeting

No Advisory Committee Meetings were held regarding this carisoprodol efficacy supplement.

8.6 Literature Review

A literature search for randomized, controlled studies of carisoprodol was performed (Table 42 in Section 7.2.2.1 details the design and results of six randomized, controlled studies of the 350 mg carisoprodol regimen as reported in the literature). No studies of 250 mg carisoprodol were found in the literature.

8.7 Postmarketing Risk Management Plan

Medpointe did not submit a postmarketing risk management plan.

8.8 Other Relevant Materials

There are no other relevant materials.

9 OVERALL ASSESSMENT

9.1 Conclusions

Two adequate and well-controlled (i.e., randomized, double-blind, multi-center, placebo-controlled) U.S. trials demonstrated substantial evidence of effectiveness and safety of the 250 mg carisoprodol regimen for the short-term treatment of discomfort in acute, idiopathic, mechanical low back pain. Recommendations for the most important labeling are presented in Section 9.4.

9.2 Recommendation on Regulatory Action

From a clinical perspective, an **approval** action is recommended for the 250 mg Soma® (carisoprodol) tablets for the **short-term treatment of discomfort associated with acute, painful musculoskeletal conditions in adults** with labeling revisions.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Additional risk assessment and risk minimization activities are not indicated.

9.3.2 Required Phase 4 Commitments

Phase 4 commitments are not indicated.

9.3.3 Other Phase 4 Requests

Other phase 4 requests are not indicated.

9.4 Labeling Review

At the time of this review, final internal label discussions and final labeling discussions with Medpointe have not been completed. At this time, the following is a summary of the major labeling changes needed in Medpointe's proposed labeling (refer to Section 10.2 for a line-by-line labeling review):

1) The **INDICATIONS AND USAGE** and the **DOSAGE AND ADMINISTRATION** sections should restrict the use of carisoprodol for short-term use (up to seven days) because the durability of response of 250 mg of carisoprodol has not been established in studies greater than seven days duration; musculoskeletal conditions are generally of short-duration; there have been post-marketing reports of carisoprodol abuse, withdrawal, and dependence associated with prolonged use of carisoprodol; and in multiple pre-marketing

communications to Medpointe, DAARP strongly recommended durations of at least two weeks in the carisoprodol studies to assess the durability of response;

2) The **DOSAGE AND ADMINISTRATION** section should be modified from [redacted] to the "recommended dose of SOMA is one 250 mg or 350 mg tablet four times a day." The low back pain studies were not designed to assess the efficacy of the [redacted] (i.e., the low back pain studies were of parallel design);
3) The dosing regimen in the **DOSAGE AND ADMINISTRATION** section should be modified from "three times a day and at bedtime" to "four times a day" because this is simpler and potentially less confusing to prescribers; patient diaries in the low back pain studies were consistent with QID dosing (diaries asked patients to record the dosing times during the morning, midday, evening, and bedtime); and compliance data suggested that patients did not follow the three times a day and at bedtime dosing schedule. In addition, all the other muscle relaxants that are dosed four times a day have QID dosing; not three times a day and qhs;
4) The risk of seizure should be retained in the post-marketing **ADVERSE REACTIONS** and **OVERDOSAGE** sections; however, the seizure **WARNINGS AND PRECAUTIONS** should be removed because according to the 2006 *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* Draft Guidance there is "no reasonable evidence of a causal association between the drug and the adverse reaction (a causal relationship need not have been established)." There have been no cases of seizures in all the carisoprodol controlled trials submitted in this efficacy supplement and no cases of carisoprodol-associated seizures reported in the literature studies of carisoprodol. Additionally the post-marketing seizures cases are contradictory cases (some seizures are associated with carisoprodol exposure, while others are associated with carisoprodol withdrawal). Many seizure cases have multiple confounders including patients taking concomitant medications that lower the seizure threshold (e.g., tricyclic antidepressants, antipsychotics, bupropion). Finally, the five other approved muscle relaxants approved for the same indication (i.e., Flexeril, Robaxin, Parafon Forte, Norflex, and Skelaxin) do not have seizure **WARNINGS** or **PRECAUTIONS** and do not have a causal relationship with seizures.
5) The **CLINICAL STUDIES** section is disorganized and should be reorganized according to the 2006 *Clinical Studies Section of Labeling for Human Prescription Drug and Biologic Products — Content and Format* Guidance;
6) The [redacted] should be removed from the **CLINICAL STUDIES** section; and
7) The **Pediatric Use** subsection in the **USE IN SPECIFIC POPULATIONS** section should state that the safety and efficacy of carisoprodol in pediatric patients less than 16 years old have not been established.

After internal labeling discussions, DAARP decided to consult the Office of Surveillance and Epidemiology (OSE) regarding the possible removal of the seizure **WARNINGS**. DAARP

decided that the seizure **WARNINGS** should remain in the label until OSE completed their complete evaluation of the seizure risk of carisoprodol use.

DAARP consulted the Study Endpoints and Labeling Development (SEALD) Team for assistance in the labeling of SOMA according to the new Physician Labeling Rule (PLR) format. DAARP accepted most of the format recommendations from SEALD. SEALD also recommended that dosing recommendations should be provided in subgroup populations in the **DOSAGE AND ADMINSTRATION** section of the **HIGHLIGHTS**. Since there is no significant data on the efficacy and safety of SOMA in patients with hepatic insufficiency, renal insufficiency, geriatric patients, and other subgroups, dosing recommendations in these subgroups were not included in the **DOSAGE AND ADMINSTRATION** section of the **HIGHLIGHTS**.

A Medication Guide is not needed for the carisoprodol label.

9.5 Comments to Applicant

There are no additional comments to MedPointe.

10 APPENDICES

10.1 Review of Individual Study Reports

Medpointe submitted two important clinical trials (i.e., Studies MP502 and MP505) to support the safety and efficacy of 250 mg of carisoprodol three times daily and once nightly for the relief of discomfort in acute, musculoskeletal conditions. Since the design of the two trials was almost identical, the complete design of Study MP502 is presented in Section 10.1.1 and the basic design of Study MP505 is presented in Section 10.1.2. The similarities and differences between Studies MP502 and MP505 are presented in Section 10.1.2.

10.1.1 Review of Study MP502

10.1.1.1 Protocol MP502

10.1.1.1.1 Title

Study MP502 entitled "Randomized, Double-Blind Trial of Carisoprodol 250 mg Tablets Compared to Placebo and Carisoprodol 350 mg Tablets in Patients with Acute, Painful Musculoskeletal Spasm of the Lower Back"

10.1.1.1.2 Objective

The primary objective of this study, according to Medpointe, was to determine the efficacy and safety of 250 mg of carisoprodol versus placebo (three times daily and at bedtime) in patients with acute musculoskeletal spasm of the lower back.

10.1.1.1.3 Overall Study Design

A randomized, double-blind, placebo-controlled parallel-group, multiple-center (57 sites), U.S. study of carisoprodol in adult patients between 18 and 65 years old with acute idiopathic, mechanical low back pain. Patients were randomized 1:1:1 to one of the following three treatments four times a day for seven days: 250 mg of carisoprodol tablets, 350 mg of carisoprodol tablets, and placebo.

<u>Medical Reviewer's Comments</u>: The study was well-designed and well-controlled. The study only included patients between 18 and 65 years old. Optimally, geriatric patients should have been included in the low back pain studies because geriatric patients develop acute, idiopathic, mechanical low back pain. In addition, since geriatric patients are more likely to have sedative AEs with the use of CNS depressants like carisoprodol, it is important to evaluate if a lower carisoprodol dose reduces the incidence of sedative effects in the geriatric population. Since geriatric patients were not included in these studies, the sponsor's proposal (i.e., to include a statement in the Geriatric Use section of the label that the safety and efficacy of carisoprodol has not been evaluated in geriatric patients) is acceptable.

The carisoprodol low back pain trials were similar to the design of the cyclobenzaprine immediate-release and cyclobenzaprine extended-release trials in patients with acute back pain (see Table 7). All of the trials were short-term, randomized, double-blind, placebo-controlled trials in patients with acute, idiopathic, mechanical back pain. Most of these trials had a dose-ranging control. The cyclobenzaprine immediate-release and cyclobenzaprine extended-release trials included patients with lumbar and cervical back pain; however, the carisoprodol clinical trials included only patients with lumbar back pain. The cyclobenzaprine immediate-release and cyclobenzaprine extended-release trials included geriatric patients; in contrast, the carisoprodol trials did not include geriatric patients. The duration of the cyclobenzaprine extended-release trials were two weeks; whereas, the duration of the cyclobenzaprine immediate-release and the carisoprodol trials were one week.

10.1.1.1.4 Eligibility Criteria

Inclusion Criteria: To be eligible to participate in the study, patients had to have met all of the following criteria:

- Been a male or female 18 to 65 years of age;
- Had moderate to severe muscle spasm, as rated by the investigator and moderate to severe backache, as reported by the patient;
- Had the ability to discontinue all analgesics, NSAIDs, and other muscle relaxants for the duration of the study;
- Had the willingness to participate and provide written informed consent; and
- Been in generally good health, in the opinion of the investigator.

Exclusion Criteria: If patients had any of the following conditions, they were not eligible to participate in the study:

- Duration of current episode > 3 days;
- Presence of sciatic pain (specifically, pain radiating below the knee);
- History of spine pathology such as herniated nucleus pulposis, spondylolisthesis, spinal stenosis;
- Presence of underlying chronic back pain;
- Neurological signs and symptoms such as numbness, tingling, foot drop, paresthesia, unexplained constipation, or urinary retention;
- Underlying rheumatologic disease such as rheumatoid arthritis (RA), ankylosing spondylitis (AS);
- Any abnormalities in the following tests of both lower extremities: ankle or great toe dorsiflexion strength, absent or hypereflexic Achilles or patellar tendon reflexes, abnormal sensory exam (pinprick) in the medial, dorsal, or lateral aspect of the foot, or positive straight leg raise test (positive if there is a pain in the posterior leg that radiates below the knee with the patient lying supine and hip flexed 30 degrees or less);
- Vertebral body or spinous process, percussive tenderness on physical examination;
- History of osteoporosis or at high risk for vertebral fracture such as in patients who have been on prolonged courses of systemic steroids or patients with chronic renal failure;
- Myocardial infarction within one year of study;

- Cancer in remission less than one year;
- HIV or other immunodeficiency syndromes;
- Recent history of major depressive episode, schizophrenia, or other major behavioral disorder;
- Presence of active influenza or other viral syndromes;
- Morbid obesity (BMI > 39);
- Known history of alcohol or drug abuse or drug dependence (including recreational or prescribed use);
- Injury involving high potential for litigation, including worker's compensation or automobile accident cases;
- Participation in any drug study within 30 days of Study Day 1;
- Pregnancy or breast feeding or women of childbearing potential not abstinent or not practicing a medically acceptable method of contraception;
- Hypersensitivity to carisoprodol;
- Any findings on physical examination that might indicate a more serious condition (e.g., newly discovered mass, moderate to severe hypertension, arrhythmia, etc.); or
- Existence of any medical or surgical condition that could interfere with the evaluation of the study medications.

Medical Reviewer's Comments: The eligibility criteria were acceptable to select a population of patients with acute, mechanical, idiopathic low back pain. Patients with red flags (who were at increased risk of having a malignancy, osteoporotic fracture, infection, cauda equina syndrome, severe nerve root compression, or inflammatory back pain), were appropriately excluded from this study. Furthermore, the study excluded patients who had a history of chronic back pain.

In addition, the trial excluded patients with a history of alcohol abuse, drug abuse, or drug dependence. Since these patients are most likely to develop drug abuse or drug dependence to carisoprodol, the trial may underestimate the frequency of drug abuse or drug dependence in a "true" low back pain population.

The two low back pain trials included patients between 18 and 65 years old. Optimally, it is important to include geriatric patients because geriatric patients may respond differently then younger patients (e.g., geriatric patients may be more susceptible to carisoprodol's sedative effects than younger patients).

10.1.1.1.5 Dose and Dose Rationale

Patients were randomized 1:1:1 to one of the following three treatments four times a day for seven days: 250 mg of carisoprodol tablets, 350 mg of carisoprodol tablets, and placebo.

The carisoprodol dosing regimen that is currently approved for the adjunctive relief of discomfort associated with acute, painful musculoskeletal conditions is 350 mg TID and qhs (1.4 grams/day). Since this regimen is associated with drowsiness and other CNS AEs and these CNS AEs frequently require dose reduction, a lower carisoprodol dose regimen [250 mg QID (1 gram/day)] may produce a lower AE profile with retained efficacy. Thus, the risk/benefit profile of carisoprodol administration may improve with a lower dose regimen (i.e., 350 mg QID).

Medical Reviewer's Comments: The sponsor's dose rationale is acceptable because a lower carisoprodol dose (i.e., 1 gram/day) may have similar efficacy and improved safety (e.g., lower incidence of sedative AEs) compared to the approved higher dose (i.e., 1.4 grams/day).

10.1.1.1.6 Concomitant Medication

The following medications are therapies that were prohibited throughout the study period:

- Analgesics including: acetaminophen, combination products that include acetaminophen, centrally acting agents such as tramadol and clonidine hydrochloride, narcotics, combination products containing narcotics, opioid agonist/antagonist combination products, over-the-counter (OTC), or prescription NSAIDs (including COX-2 inhibitors and nonselective NSAIDs);
- Muscle relaxants including skeletal muscle relaxants and acetylcholine inhibitors such as Botox;
- Sedatives and hypnotics including: barbiturates, benzodiazepines, prescription and OTC sleep aids, and other sedatives (e.g., promethazine hydrochloride);
- Antiepileptic drugs;
- Antineoplastic agents;
- Immunosuppressive or immune modulators;
- Systemic corticosteroids; and
- Hormones and agents to correct disorders of bone metabolism (e.g., Fosamax).

Medical Reviewer's Comments: The prohibited medications were acceptable.

10.1.1.1.7 Study Monitoring

Table 46 displays the procedures and evaluations in Study MP502.

Table 46: Procedures and evaluations in Study MP502

Procedure	Day #1[1]	Day #2	Day #3 (±1 day)	Day #4	Day #5	Day #6	Day #7 or early termination (±1 day)
Visit #	1		2				3
Written informed consent	X						
Eligibility criteria	X						
Medical history	X						
Physical examination	X						
Vital signs	X		X				X
Blood chemistry and hematology	X						X
Urinalysis	X						X
Urine pregnancy test[2]	X						
Assessment of concomitant medications	X		X				X
Instruction of patients on the proper use of study medication and the completion of the daily diary	X		X				
Administration of the daily diary	X		X				
Administration of the RMDQ	X		X				X
Lower back pain evaluation including range of motion	X		X				X
Patient records "Global Impression of Change" and "Relief from Starting Backache"[3]	X[3]	X	X	X	X	X	X
Administration of the patient-rated Medication Helpfulness instrument			X				X
Administration of study medication	X		X				
Collection of unused study medication			X				X
Compliance assessment			X				X
Collection of diaries			X				X
AE assessment[4]			X				X

1 Randomization occurred on Study Day #1. All of these study procedures were performed prior to administration of the first study medication (given on Day #1).
2 All female patients of child-bearing potential
3 "Global Impression of Change" and "Relief from Starting Backache" were the two primary efficacy assessments that were recorded by the patient twice daily (except once in the evening on Study Day #1). These assessments were not recorded at baseline.
4 Any AE that occurs subsequent to the initial dose of study medication will be recorded in the patient's medical record and case report form
Reference: Adapted from Volume 19, Page 191

On Study Visit #1 (on Day 1), the following study procedures were performed:

- Recorded baseline values of the RMDQ assessed by the patient, of lower back range of motion (i.e., flexion) assessed by the investigator, and of the onset and severity of the low back pain assessed by the investigator;

- Medical history including demographics and physical examination (PE) including lower back examination and vital signs (including blood pressure, pulse rate, respiration, oral temperature, height, and body weight);
- Blood chemistry, hematology, and urinalysis and urine pregnancy for all females of child-bearing potential; and
- Written informed consent and confirmation that each patient satisfied all the eligibility criteria and was not taking the prohibited concomitant medication.

During Study Visit #1, patients took their first dose in the clinic. However, unaccompanied patients who must have driven home from the clinic visit may have taken their first dose of study medication at home. These patients must have driven directly home and taken their first dose of study medication on arrival to their home. These patients were instructed to call the investigator immediately after dosing (patients who did not contact the investigator were called by the investigator). During Study Visit #1, patient diaries were dispensed. Patients were instructed to record the following efficacy assessments twice a day (between 6:00 to 9:00 AM and between 6:00 to 9:00 PM) during the 7-day treatment period (the initial assessment was to be taken about 12 hours after the first dose of study medication):

- Degree of relief of lower back pain (Relief from Starting Backache) compared to the baseline back pain [complete relief (4), a lot of relief (3), some relief (2), a little relief (1), or no relief (0)]; and
- Global impression of change from baseline. Patients were asked the following question: "Compared to with how you felt prior to starting study medication, and regardless of whether you think the change was due to the medicine, please indicate if you have experienced marketed improvement (4), moderate improvement (3), mild improvement (2), no change (1), or worsening (0)".

On Study Visit #2 [on Day 3 (± 1 day)] and on Study Visit #3 (on Day 7), the following study procedures were performed:

- RMDQ administered;
- Lower back examined (including range of motion);
- Patient-rated Medication Helpfulness was completed;
- Patient Diary collected and reviewed for completeness;
- Amount of returned medication assessed for compliance;
- Vital signs (including blood pressure, pulse rate, respiration, oral temperature, and body weight) measured;
- Blood chemistry, hematology, and urinalysis obtained;
- AEs recorded; and
- Concomitant medications recorded.

During the study, non-pharmacologic therapies such as trigger point injections, regional anesthetic techniques, or chiropractic or osteopathic manipulation were prohibited.

Medical Reviewer's Comments: No electrocardiograms (ECGs) were performed (at baseline or during the treatment period) in the low back pain studies. However, carisoprodol has been

approved since 1959 (at a higher dose) and no post-marketing concerning ECG abnormalities have been identified. Therefore, the lack of ECGs testing in the phase III studies is not optimal, but it is acceptable.

In the two low back pain studies, the last safety visit occurred on Study Day #7 or early termination (± one day). For short-term trials, it is optimal to have a follow-up safety visit (off therapy) to assess product withdrawal symptoms or AEs that make time to develop (e.g., liver enzyme test abnormalities). For these trials, it may have been useful to evaluate the frequency of withdrawal symptoms in the two carisoprodol dose groups.

However, since 350 mg of carisoprodol has been approved in the United States since 1959 and the proposed carisoprodol 250 mg dose is approximately 29% lower than the approved carisoprodol 350 mg dose, the safety evaluations are reasonable for this proposed lower carisoprodol dose.

10.1.1.1.8 Efficacy Endpoints

10.1.1.1.8.1 Primary Efficacy Endpoints

The **patient-reported** (using diary cards), 5-point categorical co-primary efficacy endpoints were the following:

1) "Relief from Starting Backache": Mean value [of the morning assessment (6:00 to 9:00 AM) and the evening assessment (6:00 to 9:00 PM)] of lower back pain relief on Study Day #3. Lower back pain relief was obtained from responses to the following question, "compared with how you felt prior to starting study medication, and regardless of whether you think the change was due to medicine, please indicate if you have experienced" (compared to baseline) one the following: complete relief (4), a lot of relief (3), some relief (2), a little relief (1), or no relief (0); and
2) "Global Impression of Change": Mean value [of the morning assessment (6:00 to 9:00 AM) and the evening assessment (6:00 to 9:00 PM)] of the "global impression of change" on Study Day #3. The "global impression of change" score was obtained from responses to the following question, "compared with how you felt prior to starting study medication, and regardless of whether you think the change was due to the medicine, please indicate if you have experienced" one of the following: marked improvement (4), moderate improvement (3), mild improvement (2), no change (1), or worsening (0).

Medical Reviewer's Comments: The two low back pain studies had two pre-specified co-primary efficacy endpoints that were one-item patient reported outcomes (PROs) with Likert responses. Both of these endpoints have limitations in the ability to assess pain relief in low back pain patients.

Limitations of the "Relief from Starting Backache" (RSB) PRO instrument include (see the 2006 *Patient-Reported Outcome Measures* Draft Guidance):

- **Responses that did not offer a clear distinction between choices. Low back pain patients are not likely to differentiate between "some relief (2)" and "a little relief (1)";**
- **Recall bias: Patients had to compare their back pain in the morning and evening of Day #3 to their back pain at baseline (which had occurred about 48 to 60 hours earlier on the morning of Day #1). Ideally, it "is usually better to construct items that ask patients to describe their current state than to ask them to compare their current state with an earlier period."**
- **Lack of content validation: The protocol did not contain a description of the following: the generation, modification, and finalization of RSB; the reliability of RSB; the reproducibility of RSB; and the ability of RSB to detect change in acute, mechanical low back pain patients; and**
- **No minimally clinical important difference was identified.**

Limitations of the "Global Impression of Change" (GIC) PRO instrument include (see the 2006 *Patient-Reported Outcome Measures* Draft Guidance):

- **Unbalanced response options: There were more positive responses [marked improvement (4), moderate improvement (3), and mild improvement (2)] then negative responses [worsening (0)] and this may bias the direction of the results.**
- **Recall bias: Patients had to compare their back pain in the morning and evening of Day #3 to their back pain at baseline (which had occurred about 48 to 60 hours earlier on the morning of Day #1). Ideally, it "is usually better to construct items that ask patients to describe their current state than to ask them to compare their current state with an earlier period."**
- **Lack of content validation: The protocol did not contain a description of the following: the generation, modification, and finalization of GIC; the reliability of GIC; the reproducibility of GIC; and the ability of GIC to detect change in acute, mechanical low back pain patients; and**
- **No minimally clinical important difference was identified.**

These co-primary efficacy endpoints are not the most optimal instruments for assessment of pain relief. However, these co-primary efficacy endpoints are acceptable for these two low back pain trials because:

- **Suboptimal endpoints in pain trials may adversely affect the investigational product more than the control;**
- **In multiple meetings with Medpointe; DAARP did not question the adequacy of the primary efficacy endpoints; and**
- **These endpoints have been used in the recent approval of other products for the identical proposed indication [i.e., cyclobenzaprine (Flexeril); cyclobenzaprine extended-release capsules (AMRIX)].**

10.1.1.1.8.2 Secondary Efficacy Endpoints

The seven pre-specified secondary efficacy endpoints for Study MP502 were the following:

1) Roland-Morris Disability Questionnaire (RMDQ) score of function [ranging from 0 (no disability) to 24 (maximum disability)] on Study Day #7 minus the baseline score (see Table 47);
2) RMDQ score on Study Day #3 minus the baseline score;
3) Amount of forward flexion of the lower back in centimeters (the mean value of three measurements for forward bending minus the mean value for standing straight up) on Day #7 minus the baseline score;
4) Amount of forward flexion of the lower back on Day #3 minus the baseline score;
5) Patient-rated Medication Helpfulness on Study Day # 7: Patients were asked, "How would you rate this study medication in improving your condition?" and they could have the following responses: Excellent (4), Very good (3), Good (2), Fair (1), or Poor (0);
6) Patient-rated Medication Helpfulness on Study Day # 3; and
7) Time (in days) from the start study treatment to the first patient-reported moderate improvement (3) or marked improvement (4) on the patient-rated GIC scale.

Table 47: Roland-Morris Disability Questionnaire (RMDQ)[1]

1) I stay at home most of the time because of my back;
2) I change position frequently to try and get my back comfortable;
3) I walk more slowly than usual because of my back;
4) Because of my back, I am not doing any of the jobs that I usually do around the house;
5) Because of my back, I use a handrail to get upstairs;
6) Because of my back, I lie down to rest more often;
7) Because of my back, I have to hold on to something to get out of an easy chair;
8) Because of my back, I try to get other people to do things for me;
9) I get dressed more slowly than usual because of my back;
10) I only stand for short periods of time because of my back;
11) Because of my back, I try not to bend or kneel down;
12) I find it difficult to get out of a chair because of my back;
13) My back is painful almost all the time;
14) I find it difficult to turn over in bed because of my back;
15) My appetite is not very good because of my back pain;
16) I have trouble putting on my socks (or stockings) because of the pain in my back;
17) I only walk short distances because of my back;
18) I sleep less well on my back;
19) Because of my back pain, I get dressed with help from someone else;
20) I sit down for most of the day because of my back;
21) I avoid heavy jobs around the house because of my back;
22) Because of my back pain, I am more irritable and bad tempered with people than usual;
23) Because of my back pain, I go upstairs more slowly than usual;
24) I stay in bed most of the time because of my back.

1 Patients were instructed to answer the question based upon their symptoms on the current day
Reference: Adapted from Volume 54, Page 161, Sample Case Report Form

Medical Reviewer's Comments: The two RMDQ endpoints (the change from baseline on Days #3 and #7) are the most important secondary efficacy endpoints because the RMDQ is a functional endpoint and the RMDQ has been validated. Multiple members of the July 1999 Joint Over-the-Counter and Arthritis Advisory Committee Meeting (advising the FDA regarding the approvability of low dose Flexeril for over-the-counter use) stated that they want to see instruments that measure disability in low back pain trials. In addition, multiple studies in the literature state that the RMDQ has been validated as a functional instrument in low back pain. Finally, the RMDQ endpoints do not reduce recall bias (patients are asked to assess their back pain on the current day at baseline and on Days #3 and #7 during the treatment period).

The Medication Helpfulness endpoints on Days #3 and #7 (secondary endpoints #5 and #6) are very similar to the co-primary efficacy endpoints (i.e., RSB and GIC) because all three endpoints:

- **Are based on a five-point Likert response;**
- **Are measured only during the treatment period (the baseline measurements are not computed in the instruments); and**
- **Measure improvement in low back pain.**

The two flexibility secondary endpoints (i.e., the change in forward flexion from baseline on Days #3 and #7) are not standard evaluations in low back pain studies and these flexibility endpoints have not be validated.

The pre-specified time to event endpoint (i.e., the number of days from the start study treatment to the first moderate or marked improvement on the GIC scale) is not an important secondary endpoint because this survival analysis has too few time points (the analysis is based on full day assessments; not on 12 hour assessments). The results of this secondary endpoint will not be presented given its deficiencies.

10.1.1.1.9 Statistical Analysis Plan

10.1.1.1.9.1 Statistical Populations

There were three statistical populations:

- Safety population: Patients who received at least one dose of study medication. This population was used for the safety analysis.
- Intention to Treat (ITT) population: Patients who received at least one dose of study medication and who had at least one post-baseline efficacy assessment. The ITT population was the primary statistical population for the co-primary efficacy and secondary endpoints; and
- Per Protocol (PP) population: ITT patients, who took at least 70% of the required study medication and completed the study with complete diary data. The definition of the PP population was changed in the January 2006 statistical analysis plan (the proportion of patients who took required study medication was changed from 80% to 70%). The PP population was the confirmatory population for the co-primary efficacy endpoints.

10.1.1.1.9.2 Statistical Methods for the co-primary endpoints

The primary statistical comparison was between the 250 mg carisoprodol group and the placebo group for the co-primary efficacy endpoints. According to the statistical analysis plan (SAP), both co-primary efficacy endpoints must be significant (i.e., the alpha level was established at 0.025 using the Bonferroni adjustment). For the primary efficacy analysis of each co-primary efficacy endpoint, the mean daily value on Study Day #3 was analyzed for differences between the 250 mg carisoprodol group and the placebo group using analysis of variance (ANOVA) terms for fixed effects of treatment and pooled center. If the pooled center was not significant ($p > 0.1$ with a type I error of 0.1), then the analysis by center was removed from the primary efficacy endpoint model.

10.1.1.1.9.3 Statistical Methods for the secondary endpoints

The primary statistical comparison was between the 250 mg carisoprodol group and the placebo group for the secondary efficacy endpoints. For the change from baseline in RMDQ and the change in baseline in forward flexion, ANCOVA was used with fixed effects for treatment and pooled centers. For the Medication Helpfulness secondary endpoints, ANCOVA was used. For the time to symptom improvement secondary endpoint, Kaplan-Meier estimates of median time to symptom improvement, and 95% confidence intervals were calculated. In addition, the 25% and 75% quartiles were calculated.

10.1.1.1.9.4 Imputation Methods for the co-primary endpoints

The co-primary efficacy endpoints assessed mean patient-reported outcomes (PROs) on Study Day #3 (based on the average of the morning and evening PROs on Study Day #3). If one of the two assessments was missing on Study Day #3, then the available assessment was imputed for the mean value. If both the morning and evening assessments were missing on Study Day #3, then the mean daily value on Study Day #2 was imputed. If both assessments were missing on Study Days #2 and #3, then the mean daily value on Study Day #4 was imputed. All other missing data for the co-primary efficacy endpoints was imputed using the last observation carried forward (LOCF) except the baseline data (the baseline data was not be imputed because baseline data for the co-primary efficacy instruments were not obtained in the trial).

10.1.1.1.9.5 Imputation Methods for the secondary endpoints

For the assessment of forward flexion, the mean of three values was calculated in the standing and forward bending positions. If only one value was available for either position, this value was imputed. If only two values were available for either position, then the mean of these two values was imputed.

For forward flexion, Medication Helpfulness, and RMDQ; LOCF was used for imputation of missing data. However, baseline values were not used for imputation for post-treatment data.

For the assessment of time from initiation of study medication to first symptom improvement (i.e., moderate or marketed), if patients did achieve symptom improvement then they were censored at early withdrawal or at study completion.

10.1.1.2 Protocol Amendments

The first patient enrolled in Study MP502 on 8/15/05 and the last patient completed Study MP502 on 7/18/06. There was one protocol amendment (i.e., the 11/9/05 amendment) while Study MP502 was ongoing. The 11/9/05 amendment had the following changes to the study design:

- Added instructions for the administration of the first dose of study drug at home for patients who had to drive home from the first clinic visit; and
- Clarified the procedures for reporting SAEs.

In addition, the final statistical analysis plan was approved on 1/26/06 (while the study was ongoing) and had the following changes from the pre-specified analyses:

- A randomized population was defined;
- The definition of the Per Protocol population was changed from inclusion of patients who took at least 80% of the required study medication to inclusion of patients who took at least 70% of the required study medication;
- Centers were pooled to provide sufficient numbers of patients to examine the possibility of treatment by center interactions;
- Statistical testing on laboratory and vital signs results was performed;
- The co-primary efficacy endpoints was analyzed by non-parametric methods; and
- Additional analyses were performed to investigate the treatment by center interaction.

Medical Reviewer's Comments: The amendments to Study MP502 were minor and were not likely to significantly affect the study conduct or study results.

10.1.1.3 Study Conduct Results

Table 48 displays the location of the disposition, baseline characteristics, overall discontinuations, demographics, and exposure in Study MP502. Study conduct results (from Studies MP502 and MP505) were combined because there were no significant differences in the results from the individual studies, the overall designs were very similar, and the populations were very similar.

Table 48: Location of the results of the conduct of Study MP502 in the NDA review

Results of study conduct	Location
Disposition	Section 6.1.4
Baseline characteristics	Section 6.1.4
Overall discontinuations	Section 7.1.3.1
Demographics	Section 7.2.1.2
Exposure	Section 7.2.1.3

Table 49 displays the protocol violations in Study MP502. Patients in all three treatment groups had a similar incidence of protocol violations.

Table 49: Protocol violations in Study MP502

	Placebo n=276[1]	Carisoprodol 250 mg n=271[1]	Carisoprodol 350 mg n=281[1]
	n (%)	n (%)	n (%)
Patients with ≥ 1 per protocol[2] exclusion	55 (19.9)	37 (13.7)	49 (17.4)
Study drug compliance < 70%	28 (10.1)	20 (7.4)	25 (8.9)
Incomplete diary data	23 (8.3)	17 (6.3)	27 (9.6)
Did not meet eligibility criteria	9 (3.3)	10 (3.7)	8 (2.8)
Took prohibited medication	11 (4.0)	8 (3.0)	2 (0.7)
Were morbidly obese[3]	4 (1.4)	4 (1.5)	7 (2.5)
Had a medical condition that could interfere with the results	7 (2.5)	3 (1.1)	4 (1.4)
Age < 18[4] or age > 65[4]	2 (0.7)	2 (0.7)	3 (1.1)
Duration of back pain > 3 days	0 (0)	0 (0)	3 (1.1)

1 Randomized patients
2 Per protocol patients were patient who received at least one dose of study medication; who had at least one post-baseline efficacy assessment; who took at least 70% of the required study medication; and who completed the study with complete diary data. The definition of the PP population was changed in the January 2006 statistical analysis plan (the proportion of patients who took required study medication was changed from 80% to 70%). The PP population was the confirmatory population for the co-primary efficacy endpoints.
3 Morbidly obese patients were excluded from the study
4 Patients < 18 and patients > 65 years old were excluded from the study
Reference: Volume 18, Section 10.2, Table 10-2, Page 45.

10.1.1.4 Efficacy Results

See Section 6.1.4 for the results of the co-primary and important secondary endpoints in Study MP502.

10.1.1.5 Safety Results

See Section 7.1 for the pooled safety results of Studies MP502 and MP505. See Section 7.4.1.1 for the rationale for pooling the safety results of Studies MP502 and MP505.

10.1.2 Review of Study MP505

10.1.2.1 Protocol MP505

10.1.2.1.1 Title

Study MP505 entitled "Randomized, Double-Blind Trial of Carisoprodol 250 mg Tablets Compared to Placebo in Patients with Acute, Painful Musculoskeletal Spasm of the Lower Back"

10.1.2.1.2 Objective

The primary objective of this study, according to Medpointe, was to determine the efficacy and safety of the 250 mg carisoprodol dose regimen (three times a day and at bedtime) versus placebo in patients with acute musculoskeletal spasm of the lower back.

10.1.2.1.3 Overall Study Design

A randomized, double-blind, placebo-controlled parallel-group, multiple-center (47 sites), U.S. study of carisoprodol in patients between 18 and 65 years old with acute idiopathic, mechanical low back pain. Patients were randomized 1:1 to one of the following two treatments four times a day for seven days: 250 mg of carisoprodol tablets and placebo.

10.1.2.1.4 Comparison between Studies MP502 and MP505

Studies MP502 and MP505 had identical eligibility criteria, study durations (i.e., seven days), prohibited concomitant medication, procedures and evaluations, primary efficacy endpoints, secondary efficacy endpoints, safety monitoring, primary statistical population, and statistical methods (including imputation methods and primary multiplicity adjustments).

The major difference between the two studies was that Study MP505 only contained two arms (carisoprodol 250 mg QID and placebo); whereas, Study MP502 contained three arms (carisoprodol 250 mg QID, carisoprodol 350 mg QID, and placebo).

10.1.2.2 Protocol Amendments

The first patient enrolled in Study MP505 on 8/11/05 and the last patient completed Study MP502 on 6/8/06. There was one protocol amendment (i.e., the 11/9/05 amendment) while Study MP505 was ongoing. The 11/9/05 amendment to Study MP505 had the identical changes as the 11/9/05 amendment to Study MP502 (see Section 10.1.1.2).

<u>Medical Reviewer's Comments</u>: The amendments to Study MP505 were minor and were not likely to significantly affect the study conduct or study results.

10.1.2.3 Study Conduct Results

Table 50 displays the location of the disposition, baseline characteristics, overall discontinuations, demographics, and exposure in Study MP505. The results from Studies MP502 and MP505 were combined because there were no significant differences in the results from the individual studies, the overall designs were very similar, and the populations were very similar.

Table 50: Location of the results of the conduct of Study MP505 in the NDA review

Results of study conduct	Location
Disposition	Section 6.1.4
Baseline characteristics	Section 6.1.4
Overall discontinuations	Section 7.1.3.1
Demographics	Section 7.2.1.2
Exposure	Section 7.2.1.3

Table 51 displays the protocol violations in Study MP505. Patients in both treatment groups had a similar incidence of protocol violations.

Table 51: Protocol violations in Study MP505

	Placebo n=285[1]	Carisoprodol 250 mg n=277[1]
	n (%)	n (%)
Patients with ≥ 1 per protocol[2] exclusion	39 (13.7)	33 (11.9)
Incomplete diary data	24 (8.4)	12 (4.3)
Study drug compliance < 70%	14 (4.9)	16 (5.8)
Took prohibited medication	11 (3.9)	11 (4.0)
Did not meet eligibility criteria	14 (4.9)	7 (2.5)
Were morbidly obese[3]	3 (1.1)	3 (1.1)
Age < 18[4] or age > 65[4]	3 (1.1)	2 (0.7)
Duration of back pain > 3 days	3 (1.1)	1 (0.4)
Had a medical condition that could interfere with the results	2 (0.7)	2 (0.7)
Back pain was not moderate to severe at baseline	1 (0.4)	1 (0.4)

1 Randomized patients
2 Per protocol patients were patient who received at least one dose of study medication; who had at least one post-baseline efficacy assessment; who took at least 70% of the required study medication; and who completed the study with complete diary data. The definition of the PP population was changed in the January 2006 statistical analysis plan (the proportion of patients who took required study medication was changed from 80% to 70%). The PP population was the confirmatory population for the co-primary efficacy endpoints.
3 Morbidly obese patients were excluded from the study
4 Patients < 18 and patients > 65 years old were excluded from the study
Reference: Volume 53, Section 10.2, Table 10-2, Page 43.

10.1.2.4 Efficacy Results

See Section 6.1.4 for the results of the co-primary and important secondary endpoints in Study MP505.

10.1.2.5 Safety Results

See Section 7.1 for the pooled safety results of Studies MP502 and MP505. See Section 7.4.1.1 for the rationale for pooling the safety results of Studies MP502 and MP505.

10.2 Line-by-Line Labeling Review

In the following labeling review, words underlined are recommended additions and words with ~~strikethroughs~~ are recommended deletions to Medpointe's proposed label. The final label will be discussed internally in DAARP and with Medpointe.

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
Initial U.S. Approval: 1959

(b) (4)

12 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

10.3 References

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/s/

Eric Brodsky
9/10/2007 12:43:18 PM
MEDICAL OFFICER

Sarah Okada
9/10/2007 01:00:45 PM
MEDICAL OFFICER

Clinical Team Leader Review Memo

Date	
From	Sarah Okada, M.D. Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Subject	Clinical Team Leader Review
NDA	11-972/S-041
Proprietary / Established (USAN) names	Soma® / carisoprodol
Dosage forms / strength	Oral tablets/250 mg
Proposed Indication(s)	1. Relief of discomfort associated with acute painful musculoskeletal conditions (b) (4)
Action:	Approval, with revisions to proposed labeling

1. Introduction to Review

Soma® (carisoprodol) 350 mg tablets were initially approved in 1959, with a subsequent DESI determination of efficacy for the treatment of acute painful musculoskeletal conditions in 1974. The applicant, MedPointe Pharmaceuticals, is submitting this 505(b)(2) efficacy supplement to seek approval of a lower 250 mg dosage form of Soma® for the same indication, on the basis of two 7 day randomized, double-blind, placebo-controlled clinical trials (MP502 and MP505) in 1387 adults with acute mechanical low back pain. Two single-dose pharmacokinetic (PK) studies conducted in 48 healthy volunteers (MP500 and MP501) assessing food effect and relative bioavailability were also submitted with this application. No new nonclinical studies were conducted, but historical and current information literature pertaining to the pharmacology and toxicology of carisoprodol were submitted.

This memorandum will address the regulatory history of carisoprodol (section 2), the adequacy and implications of the data from the submitted studies (sections 5 and 6), pediatric usage and the sponsor's request for waiver of Pediatric Research and Equity Act (PREA) requirements (section 6.1.3), issues related to carisoprodol's potential for abuse (section 7.2), and issues related to the sponsor's request for Waxman-Hatch exclusivity for the 250 mg dosage form (section 7.3).

Unless otherwise noted, the tables in this memorandum were reproduced or adapted from tables in the primary clinical review by Dr. Eric Brodsky.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

Clinical Team Leader Review
Sarah Okada, M.D.
NDA 11-792/S-041
SOMA® (carisoprodol) 250 mg tablets

Soma® 350 mg tablets were first approved on May 8, 1959 for an array of musculoskeletal conditions [NDA 11792]. As per the current edition of the electronic Orange Book (http://www.fda.gov/cder/ob/default.htm), in addition to MedPointe's Soma® brand 350 mg carisoprodol tablets, 8 other companies are marketing approved 350 mg generic carisoprodol tablets but no other 250 mg formulations are currently approved.

A supplement to NDA 11792 was approved on September 17, 1959 for 250 mg capsules intended for use in children. Subsequently, DESI review determined there was insufficient evidence of effectiveness for the 250 mg capsules (1974), but the Agency re-classified 250 mg capsules as effective after data were submitted to support marketing applications for Soma® compound products (1979). MedPointe's position is that the finding of effectiveness of the 250 mg capsules in 1979 was not supported by the data submitted for the Soma® compounds and therefore, the 250 mg tablets should be entitled to Waxman-Hatch exclusivity if the Agency finds the data in this efficacy supplement support approval. See section 7.2, patent/exclusivity issues, for further detail.

The pre-submission activity for this efficacy supplement included a pre-IND Meeting in June 2004, the IND submission (#71218) in November 2004, and an End of Phase 2 (EOP2) meeting in February 2005. Although agreement was reached on several issues including blinding strategy and sample size, two issues—study duration and primary endpoints, remained unresolved. MedPointe therefore submitted a special protocol assessment (SPA) for Protocol MP502 to obtain the Division's formal position regarding these two unresolved issues. Agreement on these issues could not be reached, and a dispute resolution meeting was held in June 2005. The Division recommended three co-primary outcomes: relief from initial backache, patient global impression of change, and a rating of medication helpfulness, but agreed that the first two outcomes could be considered co-primary with medication helpfulness as a secondary endpoint. The remaining area of disagreement was the duration of the two pivotal trials—MedPointe proposed trials of 7 days duration whereas the Division strongly recommended trials of 14 days to capture the effect of treatment on those patients who would require more extended treatment. Ultimately, since extensive clinical experience supported the efficacy and safety profile of the approved 350 mg dose and since the dose to be studied was lower and likely to be as safe, if not safer, the Division decided that adequate information to support the 250 mg dose could be obtained from 7 day trials.

3. CMC/Microbiology/Device

Refer to the CMC Reviews by Donald Klein, Ph.D.

3.1. General product quality considerations

Both the drug substance and drug product are the subject of USP monographs. A CMC modernization meeting was held on February 7, 2005 to discuss MedPointe's proposals for modernizing the chemistry portion of the NDA.

From this meeting, MedPointe agreed to the following:

- For the drug substance, MedPointe agreed to propose an alternate method (HPLC) to the USP titration method or submit the HPLC method to the USP as a replacement for

the current titration procedure; propose a particle size specification for the drug substance; propose specifications for residual solvents (and/or loss on drying) and heavy metals; and propose limits on specified and unspecified impurities that will comply with ICH Q3B.

- For the drug product, MedPointe agreed to revise identification testing to include TLC and HPLC methods to comply with ICH Q6A; propose acceptance criteria for release testing and shelf-life testing; distinguish between in-process tests and release and/or stability tests; propose specifications for degradation products that comply with ICH Q3B; propose a specification for moisture, hardness, and friability; propose a dissolution specification; and generate dissolution profile data (multi-point).

These agreements were fulfilled in this sNDA submission.

The drug master files for the drug substance (Type II DMF (b) (4)) and drug product (including 10 Type III packaging DMFs) were reviewed and deemed adequate, and test methods were validated by the (b) (4).

3.2. Facilities review/inspection

One drug substance site, one drug product site, and one contract laboratory site were inspected. All sites were determined to be acceptable.

3.3. Notable issues

Medpointe submitted data to support their request of 36 month expiration dating. In their review of the initially submitted data, the CMC team determined that a 24 month expiration dating period would be more appropriate. However, subsequently MedPointe provided additional 18 month real time stability data along with shelf-life statistical analysis. As a result, the CMC team has revised their determination to concur with a 36-month expiration dating period. MedPointe will also (b) (4).

4. Nonclinical Pharmacology/Toxicology

Refer to the Pharmacology/Toxicology Review by L. Steven Leshin, DVM, PhD

4.1. General nonclinical pharmacology/toxicology considerations

No new nonclinical studies were performed to support Soma® 250 mg tablets. The sponsor submitted published literature to support the nonclinical requirements of the sNDA. Although carisoprodol has long been classified as a "centrally acting skeletal muscle relaxant," its mechanism of action has not been clearly defined. Evidence in animals suggests carisoprodol produces muscle relaxation in animals by blocking interneuronal activity in the descending reticular formation and spinal cord and that carisoprodol lacks direct action on the muscle or at the neuromuscular junction.

4.2. Carcinogenicity

As Soma® is intended for short-term use, nonclinical carcinogenicity studies are not required and were not submitted. From the published literature, carisoprodol at concentrations of 400 to 1000 mcg/mL was mutagenic in the *in vitro* mouse lymphoma cell assay in the absence of,

but not in the presence of, metabolizing enzymes. Clastogenicity was demonstrated in the chromosomal aberration assay using Chinese hamster ovary cells at the highest concentration tested (1250 mcg/mL). Carisoprodol was not mutagenic in the Ames reverse assay using S. typhimurium, nor was it clastogenic in an *in vivo* mouse micronucleus assay of circulating blood cells obtained from mice at the end of a 13 week oral carisoprodol toxicology study.

The primary metabolite, meprobamate, has been approved and marketed since 1957, but few data exist regarding its genotoxic potential.

4.3. Reproductive toxicology

General toxicology studies conducted in 1988 and 2000 demonstrated that exposure to carisoprodol at 1200 mg/kg for 3 months was associated with reduced testes weight and reduced sperm motility in mice, but not in rats. There were no indicators of reproductive toxicity in female reproductive organs. In a 1991 study, maternal and paternal reproductive NOAEL in mice was determined to be 750 mg/kg/day. Developmental NOAEL was determined to be 300 mg/kg/day based on decreased postnatal survival, weight gain, and litter size at the next higher dose group of 750 mg/kg/day. No teratogenic effects of carisoprodol were noted in 2 published studies at doses of up to 400 mg/kg/day, but the data were determined to be inadequate to support labeling.

There are no data on the use of carisoprodol during human pregnancy. Limited data show that carisoprodol is present in breast milk and may reach concentrations in nursing infants of two to four times maternal plasma concentrations.

4.4. Notable issues/Conclusions

The nonclinical information submitted to the sNDA were adequate to support this 505(b)(2) application for Soma® 250 mg tablets. However, the Pharmacology-Toxicology team recommends revisions to the proposed label to reflect the uncertainty regarding carisoprodol's mechanism of action and to summarize the available nonclinical toxicology findings in greater detail in the nonclinical toxicology and the pregnancy/nursing mothers section of the label. The pediatric and maternal health team (Dr. Karen Feibus) was consulted for their input regarding appropriate wording for these sections of the label.

5. Clinical Pharmacology/Biopharmaceutics

Refer to the Clinical Pharmacology Review by Lei Zhang, Ph.D.

5.1. General clinical pharmacology/biopharmaceutics considerations, including metabolism, half-life, food effects, variability of bioavailability, and pharmacologic properties other than those related to therapeutic effect.

Two PK studies were submitted with this sNDA: Study 501, a relative bioavailability study of 250 and 350 mg Soma® tablets, and Study 500, a food effect study. Both studies enrolled 12 male and 12 female subjects. Dose-normalized AUC and Cmax for carisoprodol and its active metabolite, meprobamate were equivalent between 250 and 350 mg carisoprodol tablets,

indicating that PK is dose-proportional. Study 500 demonstrated no effect of food or high fat meals on the absorption parameters of carisoprodol.

Absorption, distribution, metabolism and elimination parameters are as follows:
Absorption: Absolute bioavailability of carisoprodol has not been determined. The mean time to peak plasma concentrations (Tmax) of carisoprodol for the 250 and 350 mg doses was 1.5 $\pm$ 0.8 hours and 1.7 $\pm$ 0.8 hours, respectively.
Distribution: Protein binding of carisoprodol was in the range of 41-67%; meprobamate was bound to a lesser extent, in the range of 14-24%.
Metabolism: Carisoprodol is metabolized by CYP2C19 to form its major active metabolite, meprobamate. Tmax is approximately 1.5 hours for carisoprodol and 4 hours for meprobamate. The mean Cmax values for meprobamate increased with increasing dose of carisoprodol. The Cmax of meprobamate was 2.5 $\pm$ 0.5 mcg/mL at the 350 mg dose, which is approximately 30% of that seen following a single 400mg dose of meprobamate (Cmax 8.0 mcg/mL), but the exposure of meprobamate rapidly exceeds that of carisoprodol following ingestion. To a much lesser extent, carisoprodol is metabolized to hydroxyl-carisoprodol by a different, as yet unindentified, enzyme. Hydroxyl-carisoprodol and meprobamate are subsequently metabolized to hydroxyl-meprobamate, which is then conjugated and excreted in urine.
Elimination: Carisoprodol is eliminated by both renal and non-renal routes. The mean terminal plasma elimination half-lives of carisoprodol and meprobamate are approximately 2 and 10 hours, respectively. The impact of hepatic or renal impairment on the metabolism and elimination of carisoprodol has not been studied or characterized.

5.2. Drug-drug interactions

No formal drug-drug interaction studies were submitted with the sNDA. Since carisoprodol is metabolized by CYP2C19, it is likely that drugs that inhibit CYP2C19, such as omeprazole or fluvoxamine, could result in higher levels of carisoprodol and lower levels of the metabolite meprobamate. The reverse could be true with co-administration of CYP2C19 inducers such as St. John's Wort, rifampin or low dose aspirin. However, no data were submitted to confirm or rule out this hypothesis.

5.3. Demographic interactions/special populations

CYP2C19 is a polymorphic enzyme; 15-20% of Asians may be poor metabolizers, compared with approximately 3-5% of Caucasian and Black populations. Published literature suggests that CYP2C19 poor metabolizers have four times the carisoprodol exposure of normal metabolizers, but half the exposure of normal metabolizers for the metabolite meprobamate. The half life of carisoprodol was also longer in poor metabolizers (4 hours vs. 2 hours in normal metabolizers). None of the studies submitted included data on the CYP2C19 genotype of study subjects. Less than 10% of study subjects were Asian (and therefore more likely to be CYP2C19 poor metabolizers) and subgroup analysis did not suggest a difference for this population with respect to efficacy or safety parameters; however, the efficacy studies were not powered to demonstrate differences between the subgroups.

Contrary to previous Soma® labeling that cited data suggesting females had higher clearance, Study 500 and 501 demonstrated that carisoprodol and meprobamate exposure is higher for females than for males. The AUC of carisoprodol is 80-90% higher in females, and the Cmax is 70-110% higher. For meprobamate, AUC and Cmax are 25-35% higher in females. The fact that this difference appeared to be disproportionately greater for carisoprodol versus meprobamate suggests that body weight is not the only factor contributing to the differences between the genders, and that overall metabolism of carisoprodol may be slower in female subjects.

Subgroup analyses based on gender were performed in the evaluation of the pivotal studies MP502 and MP505, with particular attention to MP502, which contained a concurrent comparison of 250 mg and 350 mg Soma®. See Table 3 and Table 7, below. Further details may be found in the statistical review by Dr. Ted Guo, Tables 30 to 33. In Study MP502, women appeared to experience slightly more efficacy for the primary efficacy endpoints than did men, but there were no major differences between the efficacy or safety results of women on 250 mg vs. 350 mg. By contrast, men appeared to experience similar efficacy with the 350 mg dose regimen and fewer AEs on the 250 mg dose regimen. Taken together, these data could suggest that the treatment effects on both efficacy and safety could plateau—for females this plateau is likely already reached at the 250 mg dose, whereas for men the plateau may be at 350 mg or higher. These data corroborate the gender differences in metabolism and exposure noted in the PK studies; however definitive conclusions regarding the relationship of gender, dose, and treatment effects cannot be made on the basis of the data in this submission.

5.4. Thorough QT study or other QT assessment

No formal QT studies or QT assessments were conducted or submitted. Carisoprodol 350 mg tablets have not demonstrated an association with cardiac conduction system related adverse events in over 40 years of marketing, thus a deleterious effect of 250 mg tablets on the conduction system is not expected.

5.5. Notable issues/Conclusions

The clinical pharmacology data support the dose proportionality of carisoprodol and its active metabolite meprobamate across the 250 mg and 350 mg doses. Food appears to have no effect on the absorption of Soma®. CYP2C19 poor metabolizers may be expected to have higher exposures per given dose of carisoprodol, however CYP2C19 genotype was not performed in the clinical pharmacology studies.

The clinical pharmacology studies demonstrated that the same dose results in higher exposures of carisoprodol and meprobamate for females compared with males. However, the extensive clinical experience with the carisoprodol 350 mg dose regimen supports the safety of this dose for both genders and no additional safety signals were noted in the clinical trials of Soma® 250 mg. Therefore no compelling safety issues exist to warrant gender specific dosing recommendations in labeling in the absence of substantial evidence.

6. Clinical/Statistical

Refer to primary medical review: Eric Brodsky, M.D.
Refer to statistical review: Ted Guo, Ph.D.

6.1. Efficacy

6.1.1. Phase 3/essential clinical studies, including design and analytic features

The pivotal efficacy studies submitted were two randomized, double-blind, parallel-group, placebo-controlled trials, Study MP502 and Study MP505, conducted at 119 sites in the US in 1387 adults (ages 18-65) with acute mechanical low back pain. In Study MP502, patients were randomized 1:1:1 to one of the following three treatments given four times a day for seven days: Soma® 250 mg tablets, 350 mg Soma® 350 mg tablets (the currently approved Soma® dose), and placebo; and in Study MP505, patients were randomized 1:1 to Soma® 250 mg or placebo four times a day for seven days.

The primary and secondary efficacy variables were the same for both studies and are described in detail in Dr. Brodsky's primary clinical review. The co-primary efficacy endpoints for both studies were mean scores of "Relief from Starting Backache" and "Global Impression of Change" on Day #3, with the primary statistical comparison of the Soma® 250 mg group versus the placebo group in each study. Both endpoints needed to be significant at an alpha level of 0.025 using the Bonferroni adjustment. Comparisons between the Soma® 350 mg group and placebo and the Soma® 250 mg and 350 mg groups were considered supportive.

As summarized in Table 1, below, treatment groups were similar with respect to baseline demographic characteristics. Approximately 75% of study participants were Caucasian, and 50-58% of study subjects were female.

Table 1: Demographic characteristics in the efficacy studies, MP502 and MP505

Demographic Characteristic		Placebo n=560[1]	SOMA 250 mg n=548[1]	SOMA 350 mg n=279[1]
Age	Mean (SD) in years	41.0 (12.4)	40.0 (11.8)	40.4 (12.4)
	< 18, %	0	0	0
	≥18 or ≤ 65, %	98.9	98.9	96.4
	> 65, %	1.1	1.1	0.4
Gender	Males, %	42.0	49.8	44.8
	Females, %	58.0	50.2	55.2
Race	Asian, %	9.5	9.1	5.7
	Black, %	15.2	16.1	15.4
	Caucasian, %	73.9	73.2	76.3
	Other, %	1.4	1.6	2.5
Ethnicity	Hispanic, %	29.5	32.8	25.1
	Non-Hispanic, %	70.5	67.2	74.9
Height	Mean (SD) in meters	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight	Mean (SD) in kg	80.3 (17.7)	82.1 (18.2)	82.0 (18.2)

1 The safety population (patients who received at least one dose of study medication).
Reference: Adapted from Volume 16, Table 8.2.1-2, Pages 72-74.

The baseline disease characteristics and medication use of patients enrolled in the efficacy trials were also similar across treatment groups (see Dr. Brodsky's review) and were consistent with the intended population of patients with acute mechanical low back pain. Most patients in the trials had moderate low back pain of less than 2 days duration. At baseline, approximately one third of the patients were taking NSAIDs or acetaminophen and very few were taking opioids, benzodiazepines, or other muscle relaxants.

Overall, Studies MP502 and MP505 appeared to be adequately conducted to assure data integrity and minimize bias. The numbers of patients discontinuing from the studies was small. The amount of missing data for the co-primary efficacy endpoints (GIC and RSB at Day #3) was both minimal (less than 7%) and similar across treatment groups. For further details, see Tables 6-7 and Tables 12-13 in the statistical review by Dr. Ted Guo.

Table 2, below, summarizes the results of the co-primary efficacy endpoints.
For the primary endpoint of global impression of change (GIC) on Day #3, patients in the Soma® 250 mg group experienced a mean improvement of 2.2 compared to mean improvements of 1.9 in the placebo group of MP502 and 1.7 in the placebo group of MP505. The difference in the improvement changes between the Soma® 250 mg group and the placebo group was numerically small, but statistically significant. The minimally clinically important difference in the GIC measure in low back pain trials has not been established, however, the magnitude of this change is similar to that noted in the pivotal trials that supported the approval of other skeletal muscle relaxants.

For the primary endpoint of relief from starting backache (RSB) on Day #3, patients in the Soma® 250 mg group experienced a mean improvement of 1.8 compared to mean improvements of 1.4 and 1.1 in the placebo groups of study MP502 and MP505, respectively. As with the GIC, the difference between groups was numerically small but statistically significant for RSB; the minimally clinically important difference has not been established but the magnitude of the changes is similar to that noted in the pivotal trials for other approved muscle relaxants.

In Study MP502, the magnitude of improvement in the GIC and RSB on Day #3 for the Soma® 250 mg group was the same as for the Soma® 350 mg group. This suggests the Soma® 250 mg dose regimen may have similar efficacy to the Soma® 350 mg dose regimen; however the trial was not powered for a comparison of equivalence/non-inferiority between the Soma® 250 mg and 350 mg treatment groups.

Table 2: Results of the co-primary efficacy endpoints: Global Impression of Change (GIC) and Relief from Starting Backache (RSB) on Day #3

Study	Parameter	Placebo	SOMA 250 mg	SOMA 350 mg
MP502	n	269	264	273
	GIC on Day #3, LS Mean (SE)[1]	1.9 (0.1)	2.2 (0.1)	2.2 (0.1)
	Difference between Soma and placebo (95% CI)	-	0.2 (0.1,0.4)	0.3 (0.1,0.4)
	p-value[2]	-	0.0046[3]	0.0011
	RSB on Day #3, LS Mean (SE)[1]	1.4 (0.1)	1.8 (0.1)	1.8 (0.1)
	Difference between Soma and placebo (95% CI)	-	0.4 (0.2,0.5)	0.4 (0.2,0.6)
	p-value[2]		0.0001[3]	<0.0001
MP505	n	278	269	-
	GIC on Day #3, LS Mean (SE)[1]	1.7 (0.1)	2.2 (0.1)	-
	Difference between Soma and placebo (95% CI)	-	0.5 (0.4,0.7)	-
	p-value[2]	-	<0.0001	-
	RSB on Day #3, LS Mean (SE)[1]	1.1 (0.1)	1.8 (0.1)	-
	Difference between Soma and placebo (95% CI)	-	0.7 (0.5,0.9)	-
	p-value[2]	-	<0.0001	-

1 LS Mean is the least squared mean and SE is the standard error of the mean
2 p-values were calculated using an ANOVA model with treatment and pooled center as terms. The primary statistical population was the ITT population.
3 In Study MP502, the primary comparison was between the 250 mg Soma and placebo groups and the other comparisons were exploratory.
Reference: Adapted from Volume 1, Table 3.6.2.1-1, Page 49 (See Tables 12 and 13 in Section 6.1.4 of Dr. Brodsky's review for more details)

Subgroup analyses of the primary efficacy endpoints demonstrated benefit of treatment over placebo for all demographic subgroups, although Black patients appeared to benefit less than other racial subgroups (see Tables 30-33 in the statistical review by Ted Guo).

As noted in section 5.3, above, the clinical pharmacology studies demonstrated higher carisoprodol and meprobamate exposures in females than males for a given dose. Subgroup analysis by gender and dose from Study MP502 demonstrated no difference in efficacy for females taking Soma® 250 mg compared to those taking Soma® 350 mg. However, in both MP502 and MP505 (see Tables 32 and 33 in Dr. Guo's statistical review), the effect of treatment with Soma® appeared to be less for males than for females. These data are consistent with the exposure differences by gender seen in the PK studies (see sections 5.5 and 6.2.2).

Table 3: Subgroup analysis by gender and dose in Study MP502

Subgroup	Differences of Least Squares Means						
	Trt1	Trt2	Estimate	Std Err	p-value	Lower Bound of 95% CI	Upper Bound of 95% CI
Gender: GIC at Day #3							
Female	**250mg**	**350mg**	0.01	0.1125	0.9020	-0.21	0.24
	250mg	**Placebo**	0.35	0.1099	0.0014	0.14	0.57
	350mg	**Placebo**	0.34	0.1079	0.0018	0.13	0.55
Male	**250mg**	**350mg**	-0.04	0.12	0.7577	-0.27	0.20
	250mg	**Placebo**	0.15	0.12	0.2088	-0.09	0.40
	350mg	**Placebo**	0.19	0.12	0.1229	-0.05	0.44
Gender: RSB at Day #3							
Female	**250mg**	**350mg**	-0.01	0.13	0.9494	-0.27	0.26
	250mg	**Placebo**	0.50	0.13	0.0002	0.24	0.76
	350mg	**Placebo**	0.51	0.13	<0.0001	0.26	0.76
Male	**250mg**	**350mg**	-0.09	0.14	0.5236	-0.37	0.19
	250mg	**Placebo**	0.30	0.15	0.0388	0.02	0.59
	350mg	**Placebo**	0.39	0.15	0.0079	0.10	0.68

* Adapted from Tables 30 and 31 of the statistical review by Dr. Ted Guo

Table 4: Secondary endpoint: results of Roland Morris Disability Questionnaire

Study	RMDQ[1]	Placebo	SOMA 250 mg	SOMA 350 mg
MP502	n	269	264	273
	Baseline, Mean (SD)	11.2 (5.6)	11.5 (5.3)	11.8 (5.3)
	Day #3, Mean (SD)	9.1 (5.6)	8.1 (5.2)	9.1 (5.6)
	Change from baseline[2]	-2.0 (0.3)	-3.0 (0.3)	-2.9 (0.3)
	Difference between Soma and placebo (95% CI)	-	1.0 (0.3,1.7)	1.0 (0.3,1.7)
	p-value[3]	-	0.0057	0.0067
	Day #7, Mean (SD)	6.0 (5.4)	5.4 (4.9)	5.3 (5.3)
	Change from baseline[4]	-4.4 (0.3)	-5.4 (0.3)	-5.7 (0.31)
	Difference between Soma and placebo (95% CI)	-	1.1 (0.3,1.9)	1.3 (0.5,2.1)
	p-value[3]		0.0112	0.0017
MP505	N	278	269	-
	Baseline, Mean (SD)	10.3 (5.0)	10.4 (4.9)	-
	Day #3, Mean (SD)	8.7 (5.4)	6.9 (4.5)	-
	Change from baseline[2]	-1.4 (0.3)	-3.2 (0.3)	-
	Difference between Soma and placebo (95% CI)	-	1.9 (1.2,2.5)	-
	p-value[3]	-	<0.0001	-
	Day #7, Mean (SD)	6.2 (5.4)	4.1 (3.9)	-
	Change from baseline[4]	-3.1 (0.3)	-5.4 (0.3)	-
	Difference between Soma and placebo (95% CI)	-	2.3 (1.6,3.0)	-
	p-value[3]	-	<0.0001	-

1 The RMDQ is a 0-24 scale. The change in the RMDQ score from baseline on Days #3 and #7 represents two of the seven pre-specified secondary efficacy endpoints in Study MP502 and MP505.

2 Change from baseline (Day 3 minus Day 1), LS Mean (SE)

3 No pre-specified multiplicity adjustments were made for the seven pre-specified secondary efficacy endpoints. The ANCOVA model was used with treatment, pooled center, and baseline value as covariates. The primary statistical population was the ITT population and imputation was performed by LOCF (except for baseline values).

4 Change from baseline (Day 7 minus Day 1), LS Mean (SE)

Reference: Adapted from Volume 18, Table 11-11, Page 68; Volume 18, Table 11-12, Page 69; Volume 53, Table 11-10, Page 63, and Volume 53, Table 11-11, Page 64

Table 4, above, summarizes the results of treatment on the secondary endpoint of Roland Morris Disability Questionnaire (RMDQ) scores. Treatment with Soma® resulted in a greater improvement in the RMDQ scores at Day 3 and Day 7 than placebo, supporting the primary efficacy results. The RMDQ is a validated instrument for assessing impairment in physical functioning due to low back pain. The MCID for this instrument has been reported to be in the range of 3 to 5 points [Lauridsen et al., BMC Musculoskeletal Disorders 2006]. Though statistically significant, the magnitude of the difference between the Soma® treatment groups and placebo treated groups with respect to change in RMDQ scores may not be clinically distinguishable. By Day 7, all treatment groups, including placebo, achieved at least a minimal clinically important improvement in RMDQ scores.

Table 5: Secondary endpoint: Medication Helpfulness[1,2]

Study	Medication Helpfulness	Placebo	SOMA 250 mg	SOMA 350 mg
MP502	ITT Population, n	269	264	273
	Day #3, LS Mean (SE)	1.2 (0.1)	1.6 (0.1)	1.7 (0.1)
	Difference between Soma and placebo (95% CI)	-	0.4 (0.5,0.2)	0.5 (0.6,0.3)
	p-value[3]	-	<0.0001	<0.0001
	Day #7, LS Mean (SE)	1.5 (0.1)	1.9 (0.1)	2.1 (0.1)
	Difference between Soma and placebo (95% CI)	-	0.4 (0.7, 0.2)	0.6 (0.8,0.4)
	p-value[3]		<0.0001	<0.0001
MP505	ITT Population, n	278	269	-
	Day #3, LS Mean (SE)	1.0 (0.1)	1.6 (0.1)	-
	Difference between Soma and placebo (95% CI)	-	0.6 (0.8,0.4)	-
	p-value[3]	-	<0.0001	-
	Day #7, LS Mean (SE)	1.4 (0.1)	2.0 (0.1)	-
	Difference between Soma and placebo (95% CI)	-	0.6 (0.8,0.4)	-
	p-value[3]	-	<0.0001	-

1 Patient-rated "Medication Helpfulness" score was on a 0-4 scale: Excellent (4), Very good (3), Good (2), Fair (1), or Poor (0). The Medication Helpfulness score on Days #3 and #7 represented two of the seven pre-specified secondary efficacy endpoints in Study MP502 and 505.

2 The ITT population was the primary statistical population and missing values were imputed with the LOCF except for baseline measurements. LS Mean and LS Mean differences were calculated using an ANOVA model with treatment and pooled center as covariates.

3 No pre-specified multiplicity adjustments were made for the seven pre-specified secondary efficacy endpoints.

Reference: Adapted from Volume 18, Table 11-15, Page 72; Volume 53, Table 11-14, Page 67

Table 5, above, summarizes the results of treatment on the secondary endpoint of "Medication Helpfulness" at Days #3 and #7. Overall, patients in both studies reported modest medication helpfulness, but Soma® treated patients rated their medication as slightly more helpful than placebo treated patients did. These results are consistent with and supportive of the findings for the primary and other secondary efficacy variables.

MedPointe also submitted results for change in the amount of forward flexion (in cm) and median time to symptom improvement. Measurement of forward flexion is not a validated endpoint for use in low back pain trials. Forward flexion did not change over the course of the trial, nor did it vary with treatment. Mean change from baseline in the amount of forward flexion of the lower back (in cm) on Study Days #3 and #7—maximum -0.3 compared with placebo, and there was no statistical significance compared to placebo in either study on either day.

Treatment with Soma® appeared to shorten median time to symptom improvement. In study MP502, time to moderate to marked symptom improvement was 5 days for placebo and 4 days for both the Soma® 250 mg and 350 mg treatment arms and in study MP505, time to moderate to marked improvement was 6 days for placebo and 3 days for Soma® 250 mg. However,

several issues hamper the reliability and interpretation of these data: 1) only twice daily assessments were taken, limiting precision and the number of available data points; 2) a discrepancy in the difference between placebo and Soma® groups in Study MP502 versus MP505 was observed (a difference of one day in MP502 vs. 3 days for MP505) and this discrepancy is large relative to the short duration of the studies; and 3) the natural history of acute low back pain itself is extremely variable, and (b) (4)

6.1.2. Discussion of primary and secondary reviewers' comments and conclusions

The clinical team is in agreement that Study MP502 and Study MP505 are adequate and well-controlled studies and that results from these trials provide substantial evidence of the modest efficacy of Soma® 250 mg tablets for relief of symptoms of associated with acute, painful musculoskeletal conditions in adults.

6.1.3. Pediatric use/PREA waivers/deferrals

The sponsor requested a waiver for the pediatric population less than 12 years of age, but did not address the pediatric population over 12 years of age. The currently approved label remains silent on the use of Soma® for pediatric patients over 12. The sponsor was asked to provide data on the efficacy, safety, and usage of Soma® in pediatric patients over 12 years of age. They responded that no data were available.

The Office of Surveillance and Epidemiology (OSE) was consulted to provide information on the use of Soma® in this population. Information from the Verispan Vector One database suggests that Soma® is rarely used in pediatric patients (<1% of all Soma® prescriptions).

Although relatively few epidemiological studies have evaluated the incidence and prevalence of low back pain in children, data available suggest acute mechanical low back pain is not uncommon, affecting from 12-20% of children and adolescents. However few children report LBP sufficient enough to prevent them from attending school or playing sports. [Jones, Arch Dis Child 2005; 90:312-316]. Given the relatively modest symptomatic benefits of Soma® compared to the relatively high risk of CNS adverse effects (as demonstrated by the adult trials), the potential for carisoprodol dependence, and the availability of other therapies, such as analgesics, to treat symptoms in pediatric patients, the risk:benefit ratio of carisoprodol would not appear to favor the use of carisoprodol to treat pediatric acute mechanical LBP. Therefore, I recommend pediatric studies be waived for this treatment and indication. Furthermore, the label should be revised to accurately state that the efficacy and safety of Soma® in pediatric patients of all age groups has not been evaluated in clinical trials.

6.1.4. Notable issues/Conclusions

Data from Studies MP502 and MP505 provided substantial evidence of the modest effectiveness of Soma® 250 mg four times daily in the treatment of acute mechanical low back pain, measured by effect on the co-primary efficacy endpoints of GIC and RSB on Day #3. The effect on the primary efficacy endpoints were maintained in subgroup analyses and further

corroborated by modest but similarly beneficial effects on secondary endpoints such as RMDQ and a rating of medication helpfulness. The modest treatment effect of the 250 mg dose regimen is similar in magnitude to that seen in clinical trials of Soma® 350 mg and other approved skeletal muscle relaxants.

6.2. Safety

6.2.1. General safety considerations

Soma® 350 mg tablets have been approved and marketed since 1959. The adverse effects associated with carisoprodol use have been well-characterized. The submitted safety database for Soma® 250 mg tablets, comprised of 1435 subjects/patients [of which 875 (61.0%) and 560 (39.0%) subjects/patients received carisoprodol and placebo, respectively] was adequate to evaluate the short term adverse effect profile of the Soma® 250 mg dose regimen.

6.2.2. Safety findings from submitted clinical trials

No deaths or treatment-related serious adverse events occurred in the studies submitted. A single SAE occurred in the Soma® 350 mg treatment arm of Study MP502, however this patient was hospitalized for lumbar surgery following diagnosis of a herniated disc, and was attributable to the underlying disease rather than an effect of treatment.

Table 6: The most common AEs (≥0.5% in any treatment group)

Preferred Term[1]	Placebo n=560[2] n (%)[3]	SOMA 250 mg n=548[2] n (%)[3]	SOMA 350 mg n=279[2] n (%)[3]
Patients with ≥ 1 AE	111 (20.3)	166 (30.3)	95 (34.1)
Somnolence or sedation	31 (5.5)	73 (13.4)	47 (16.9)
Dizziness	11 (2.0)	43 (7.8)	19 (6.8)
Headache	11 (2.0)	26 (4.7)	9 (3.2)
Nausea	15 (2.7)	6 (1.1)	12 (4.3)
Stomach discomfort, abdominal discomfort, or upper abdominal pain	7 (1.3)	10 (1.8)	5 (1.8)
Fatigue or lethargy	2 (0.4)	8 (1.5)	3 (1.1)
Diarrhea	6 (1.1)	5 (0.9)	1 (0.4)
Dry mouth	4 (0.7)	3 (0.5)	2 (0.7)
Irritability	0 (0)	3 (0.5)	0 (0)
Blood CPK increased	3 (0.5)	2 (0.4)	2 (0.7)

1 The preferred terms were coded using MedDRA Dictionary Version 8.0.
2 The safety population (patients who received at least one dose of study medication).
3 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
Reference: Adapted from Volume 16, Table 8.2.2-2, Pages 86-94.

The most common adverse effects in the Soma® 250 mg trials were related to CNS effects such as sedation, dizziness, and headache. Both the Soma® 250 mg and 350 mg dose regimens were associated with a higher incidence of adverse effects than placebo. Overall, the incidence of the most common AEs was similar in the Soma® 250 mg and 350 mg treatment groups.

Table 7: Most common AEs (>2% in any treatment group) by gender in MP502 and MP505

Preferred Term[2]	Gender	Placebo n (%)[3]	SOMA 250 mg n (%)[3]	SOMA 350 mg n (%)[3]
Total number in safety population[1]	Women	325	275	154
	Men	235	273	125
Patients with ≥ 1 AE	Women	72 (22.2)	109 (39.6)	54 (35.1)
	Men	41 (17.4)	57 (20.9)	41 (32.8)
Somnolence or sedation	Women	17 (5.2)	52 (18.9)	25 (16.2)
	Men	14 (6.0)	21 (7.7)	22 (17.6)
Dizziness	Women	7 (2.2)	30 (10.9)	12 (7.8)
	Men	4 (1.7)	13 (4.8)	7 (5.6)
Headache	Women	8 (2.5)	19 (6.9)	6 (3.9)
	Men	3 (1.3)	7 (2.6)	3 (2.4)
Nausea	Women	7 (2.2)	2 (0.7)	6 (3.9)
	Men	8 (3.4)	4 (1.5)	6 (4.8)
Stomach discomfort, abdominal discomfort, or upper abdominal pain	Women	7 (2.2)	8 (2.9)	3 (2.4)
	Men	0 (0)	1 (0.4)	2 (1.6)
Fatigue, lethargy, or asthenia	Women	2 (0.6)	7 (2.5)	3 (1.9)
	Men	1 (0.4)	1 (0.4)	1 (0.8)

1 Safety population includes patients who received at least one dose of study medication.
2 The preferred terms were coded using MedDRA Dictionary Version 8.0.
3 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
Reference: Adapted from Volume 16, Table 8.2.3-2, Pages 151-159.

Table 7, above summarizes the most common adverse effects by gender. As noted in section 5, women had higher exposures to carisoprodol and meprobamate than men. In general, although women appeared to have a higher incidence of the most common adverse events (AEs) than men at both 250 mg and 350 mg dose levels, the incidence of AEs in females was similar for both the 250 mg and 350 mg doses. Men treated with Soma® 250 mg appeared to experience fewer AEs than men treated with Soma® 350 mg. However, definitive conclusions regarding differences in treatment effects related to gender or dose cannot be drawn from Study MP502 alone. The extensive history of use of the carisoprodol 350 mg dose regimen supports the safety of this dose for both genders and no additional safety signals were noted in the clinical trials of Soma® 250 mg.

6.2.3. Discussion of primary reviewer's comments and conclusions

The clinical team is in agreement that the safety profile of the Soma® 250 mg dose regimen is consistent with the known safety profile of the approved Soma® 350 mg dose regimen. No new safety signals were identified from the submitted data.

7. Other Regulatory Issues

7.1. Application Integrity Policy (AIP)

No issues have been identified that impugn the integrity of this application or its data.

7.2. Potential for abuse and consideration of controlled substance scheduling

Carisoprodol was developed in the 1950s as a congener of meprobamate with the intent of producing a drug with better muscle relaxant properties and less potential for abuse. Carisoprodol is metabolized via CYP2C19 to meprobamate, although exposure to meprobamate as a result of carisoprodol use is 30% of that expected from the approved 400 mg dose of meprobamate itself (see Section 5, Clinical Pharmacology). The abuse potential of carisoprodol was the subject of a Drug Abuse Advisory Committee meeting on February 10, 1997(http://www.fda.gov/ohrms/dockets/ac/cder97t.htm#Drug%20Abuse%20Advisory%20Committee). The DEA presented information from the STRIDE (System to Retrieve Information from Drug Evidence) and DAWN (Drug Abuse Warning Network) databases on diversion and illicit use of carisoprodol, and provided an Eight Factor Analysis (required under the Controlled Substances Act). FDA, academia, and Carter-Wallace (predecessor to MedPointe) also presented at times conflicting information on the clinical pharmacology and metabolism of carisoprodol, reports/studies assessing carisoprodol withdrawal, and adverse event reports of dependency. Most instances of diversion and illicit use of carisoprodol appeared to be in association with other drugs of abuse. No definitive conclusions were drawn as a result of this meeting and, at present, meprobamate is Schedule IV and carisoprodol remains unscheduled under the Controlled Substances Act of 1970. According to the DEA website (accessed 9-5-07, http://www.deadiversion.usdoj.gov/drugs_concern/carisoprodol.htm), carisoprodol remains a commonly diverted drug and is currently scheduled under state law in 17 states: Alabama, Arizona, Arkansas, Connecticut, Florida, Georgia, Hawaii, Kentucky, Massachusetts, Minnesota, Nevada, New Mexico, Oklahoma, Oregon, Tennessee, Virginia, and West Virginia.

The lower dosage form proposed for approval in this submission would likely not increase the risk for diversion or abuse, since generic 350 mg carisoprodol is widely available. PK and clinical data in this submission support lower exposures and less CNS effects with the 250 mg dose. Adequate descriptions of the risk of drug dependence, withdrawal, and abuse are present in the currently approved Soma® label and will be retained and consolidated into the WARNINGS AND PRECAUTIONS section of the revised label.

7.3. Exclusivity/patent issues

Soma® 350 mg tablets were first approved on May 8, 1959 for an array of musculoskeletal conditions [NDA 11792]. A supplement to NDA 11792 was approved on September 17, 1959 for 250 mg capsules intended for use in children. After DESI review (39 FR 29399, August 15, 1974), the 350 mg tablets were found to be effective but the 250 mg dosage form was found to lack substantial evidence of effectiveness since no data from controlled clinical trials were available. Shortly thereafter, the original sponsor, Carter-Wallace, withdrew the 250 mg capsules from the market. Subsequently, Carter-Wallace submitted data to support a marketing application for Soma® Compound (aspirin 325 mg/carisoprodol 200 mg per tablet) and Soma® compound with codeine (aspirin 325 mg/carisoprodol 200 mg/codeine 16 mg per tablet). However, in addition to approving the Soma® compounds, the Agency concluded that the evidence also supported reclassifying the Soma® 250 mg capsules as effective (44 FR

16165, May 4 1979). Despite this finding, Carter-Wallace did not re-introduce the 250 mg capsules. Carter-Wallace was purchased by MedPointe in 2001, and it is MedPointe's position that the finding of effectiveness of the 250 mg capsules in 1979 was not supported by the data submitted for the Soma® compounds and therefore, the 250 mg tablets should be entitled to Waxman-Hatch exclusivity if the Agency finds the data in this efficacy supplement support approval. Based on currently available information on the Soma® compound clinical trials, which suggests most trial participants received two tablets of the Soma® compound (and therefore 400 mg carisoprodol) per dose, the reclassification of 250 mg capsules would not appear to be supported by these data. [See Table 8: Summary of studies to support the Soma® compounds, below] The 250 mg dosage form could therefore be eligible for Waxman-Hatch exclusivity.

During the review cycle for this submission, on May 31, 2007, representatives from DAARP, Office of Generic Drugs, Office of Regulatory Policy, and the Office of the Chief Counsel met to discuss MedPointe's exclusivity request for Soma® 250 mg tablets. The regulatory history of Soma® and the Soma® compound trials was discussed. Meeting participants generally agreed that MedPointe's arguments for exclusivity of the 250 mg tablets appeared to have merit. Ultimately, the decision to grant exclusivity or not will be made by the Office of Generic Drugs.

Table 8: Summary of studies to support the Soma® compounds

NDA 12-365			
study #:	**by:**	**dose:**	**type of study:**
75008	*Charles Andre, M.D. and Alexander T. Carducci, M.D.	most 2 q.i.d.	double-blind, randomized parallel
75014	*Robert C. Field, M.D. and A. Carducci, M.D.	most 2 q.i.d.	double-blind, randomized parallel
75007	*Richard E. Crompton, M.D.	most 2 q i.d.	double-blind, randomized parallel
75010	*Aubrey P. Cullen, M.D. disqualified	most 2 q.i.d.	double-blind, randomized parallel
75011	*Ronald P. Feldner, M.D.	most 2 q.i.d.	double-blind, randomized parallel
75013	*Richard J. Miller, M.D.---dropped out of he trials	most 2 q i.d.	double-blind, randomized parallel
75015	*Robert C. Mumby, M.D. and J. Shea, M.D.	most 2 q.i.d.	double-blind, randomized parallel
75009	*James J. Scheiner, M.D. disqualified	most 2 q.i.d.	double-blind, randomized parallel
	Dr. Benson	most 2 q i.d.	double-blind, placebo, parallel controlled
	Dana Study	2 t i.d., or 2 q.i.d.	?
	Kappler Study	most 2 q i.d.	double-blind, parallel, randomized
	Shapiro Study	avg. 2 t.i.d. - 2 q.i.d.	double-blind, parallel, randomized
	Guerin Study	2 q.i.d.	double-blind, placebo controlled
	Dr. Hewson's Study	2 q.i.d.	double-blind, parallel, placebo controlled
	Zumpft's Study	2 q.i.d.	double-blind, parallel, placebo controlled
	Miller Study	2 q.i.d.	double-blind parallel
	Kaplan Study	2 q.i.d.	double-blind parallel
75003	M. Gilbert, M.D., Ph.D.	2 q.i.d.	double-blind, randomized, parallel comparison
75004	Harold Silberman, M.D.	2 q.i.d.	double-blind, randomized, parallel comparison
75005	N. William Winkleman, Jr. M.D.	2 q.i.d.	double-blind, randomized, parallel comparison
70022	Dr. F.H. Riordan	2 q.i.d.	placebo controlled
70023	Dr. H.K. Dooley	2 q.i.d.	placebo controlled
70024	Dr. J.H. Brown	2 q.i.d.	double-blind, randomized
70025	Dr. C. Andre	2 q.i.d.	placebo controlled
70049	Bernard K. Guerin, M.D.	2 q.i.d.	double-blind
70053	Drs. Jerome Miller and V. Kumar	2 q.i.d.	double-blind, non-crossover
70075	E. Dubow, M.D.		Absorption in presence of codeine
71012	W.D. Paul, M.D.		BA study
77038	A. Cullen, M.D.	most 2 q i.d.	double-blind, parallel, controlled, randomized pilot
77039	A.T. Carducci, M.D.	2 qid	double-blind, parallel, controlled, randomized pilot
77040	J. Walker, M.D.	2 qid	
77041	O. McKay, M.D.	2 qid	
	Frank Cutler, M.D.	1 or 2 q.i.d.	double-blind, non-crossover
	Toshiaki Kuge, M.D.	1 q.i.d.	double-blind, non-crossover
	Donald T. McFaughlin, M.D.	1 q.i.d.	double-blind, non-crossover
	James R. White, Ph.D. and Donald Brumsfield, M.D.	based on 1 or 2 tablets	open pilot
	Andrial	2 qid	
	Betts	2 qid or tid	
71006	W.D. Paul, M.D.	not sepcified	BA study

*Table provided by Sharon Hertz, M.D., Deputy Director, DAARP

8. Financial Disclosure

Medpointe submitted FDA Form 3454 certifying regulatory requirements pertaining to financial disclosure had been met by the clinical investigators participating in Study MP502 and MP505.

9. Labeling

9.1. Physician labeling

The physician labeling proposed by MedPointe requires substantive revisions in the following areas:

- Recommended dosing: MedPointe proposed that the recommended (b) (4) o data were submitted to support tha (b) (4) would be effective. The studies submitted were not designed to demonstrate differences between the 250 mg and 350 mg dose regimens, and definitive conclusions cannot be made regarding differences in safety or efficacy between these doses on the basis of Study MP502 alone. The label should therefore reflect the acceptability of either dose regimen (b) (4) .
- Use in pediatric patients: The currently approved carisoprodol label is silent regarding its use in pediatric patients over 12 years of age, and MedPointe did not propose changes in this regard. Data were not submitted, from either proprietary clinical trials or published literature, to support the safety and efficacy of carisoprodol use in pediatric patients. The label should reflect the fact that the efficacy and safety of carisoprodol in pediatric patients has not been evaluated in clinical trials.
- Effects related to CYP2C19 metabolism: MedPointe's proposed label does not include wording with respect to effects of CYP2C19 polymorphisms or interactions with drugs that inhibit or induce CYP2C19. The label should reflect the data available regarding the effect of polymorphisms resulting in significantly increased carisoprodol exposure. Although no data were submitted evaluating the effect of CYP2C19 inhibitors or inducers, drug interactions would be expected, and should be addressed in labeling.
- Use in pregnancy and lactation: MedPointe's proposed label maintains previously approved, minimally descriptive statements. Nonclinical information is not included; however, data from animal studies suggest some teratogenic and nonteratogenic adverse effects. The label should be updated to include this information and provide the appropriate Pregnancy Category classification (Pregnancy Category C). The maternal health team (Dr. Karen Feibus) was consulted for input regarding the wording in these sections.
- Nonclinical toxicology: MedPointe's proposed label does not adequately describe the nonclinical toxicology findings related to genotoxicity and reproductive toxicity and will be revised to more specifically convey the available nonclinical data.
- Clinical studies: MedPointe's proposed label (b) (4)

  The label should be revised to include only the primary efficacy findings in the clinical studies section.

9.2. DDMAC labeling comments regarding proposed physician labeling

DAARP consulted the Division of Drug Marketing, Advertising, and Communications (DDMAC) for their input on MedPointe's proposed label. DDMAC's concerns were addressed by DAARP's revisions to the label except in the following areas:

- DDMAC recommended the indication and usage section be changed for consistency with the Skelaxin® PI to incorporate the underlined: "SOMA is indicated <u>as an adjunct to rest, physical therapy, or other measures</u> for the relief of discomfort associated with acute, painful musculoskeletal conditions." The underlined wording is in the currently approved label but MedPointe proposed to remove it. DAARP agrees with removing the underlined wording, since the clinical trials did not study Soma® as an adjunct to nonpharmacologic measures.
- DDMAC recommended that the phrase "psychotropic drugs" be re-added to the Warnings and Precautions section of the highlights to make it consistent with the PI. DAARP removed "psychotropic drugs" from both sections since the term "psychotropic" is less specific and includes agents that are not CNS depressants, whereas the CNS effects of Soma are additive to CNS depressants. Therefore, for clarity, "psychotropic" was removed and examples of CNS depressant drugs were included.
- DDMAC recommended that the brand name SOMA be used instead for each mention of the generic name carisoprodol in the PI. For most instances in the revised label, DAARP used the brand name; however, certain data (e.g., nonclinical and some clinical pharmacology) pertain to the active moiety and were not derived from evaluation of the branded product. In these instances, for accuracy, the term "carisoprodol" was utilized.

9.3. Carton and immediate container labels

The Division of Medication Errors and Technical Support (DMETS) evaluated the proposed carton and container labels and suggested changes to better distinguish between the Soma® 250 mg and Soma® 350 mg carton and container labels. MedPointe submitted changes to address these concerns and these were deemed acceptable by DMETS.

10. DSI Audits

Four clinical sites were selected based on greatest number of patients enrolled and largest treatment effect size on the primary endpoints. Of these, DSI chose to inspect site 263 in Atlanta, Georgia, which enrolled 36 patients. The audit revealed no irregularities or violations that may have impacted data integrity.

11. Conclusions and Recommendations

11.1. Regulatory action

I concur with the primary clinical reviewer, Eric Brodsky, and recommend approval of this sNDA with revisions to the proposed labeling. Studies MP502 and MP505 provided

substantial evidence that Soma® 250 mg tablets taken 4 times daily is effective for modest relief of symptoms associated with acute painful musculoskeletal conditions in adults.

11.2. Safety concerns to be followed postmarketing: Not applicable.

11.3. Risk Minimization Action Plan: Not applicable.

11.4. Postmarketing studies:

11.4.1. Required studies *(PREA; Subpart E/H/I approvals)*: None. I recommend waiver of pediatric studies. Pediatric mechanical low back pain is largely self-limited and does not require treatment with muscle relaxants. CNS effects associated with treatment are not outweighed by potential treatment benefit for the pediatric population.

11.4.2. Commitments (PMCs): Not applicable.

11.4.3. Other agreements: Not applicable.

11.5. Summary of reviewers' comments

Data provided to support the non-clinical, chemistry/manufacturing/controls, and clinical pharmacology aspects of this submission were deemed adequate by the discipline review teams. The statistical review team confirmed the primary and secondary analyses. All disciplines were in agreement that the data in this efficacy supplement were adequate to support approval of the Soma 250 mg dose and regimen, with revisions to the proposed label.

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/s/

Sarah Okada
9/7/2007 10:01:02 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

CHEMISTRY REVIEW(S)

NDA 11-792, SE2-041

DIVISION OF POST-MARKETING EVALUATION
Review of Chemistry, Manufacturing, and Controls

NDA#: 11-792 **DATE REVIEWED: 8/23/2007**

REVIEW #: 2 **REVIEWER:** Donald N. Klein, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
EFFICACY *(paper)*	11/10/06	11/13/06	11/30/06
(BZ) Amendment	3/2/07	3/5/07	3/15/07
Biometrics Consult	4/16/07	4/17/07	*n/a*
Biometrics Review # 1	6/1/07	6/1/07	6/1/07
(BC) Amendment *(final Stability Specs.)*	7/17/07	7/18/07	7/25/07
Stability Update *(e-mail)*	8/16/07	*n/a*	8/16/07
(BC) Amendment *(EDR) (stability update)*	8/16/07	8/16/07	8/22/07
Biometrics Review # 2	8/22/07	8/22/07	8/22/07

NAME & ADDRESS OF APPLICANT:

MedPointe Pharmaceuticals
MedPointe Healthcare Inc.
265 Davidson Avenue
Suite 300
Somerset, NJ 08873-4120

DRUG PRODUCT NAME:

Proprietary: Soma® Tablet.
Established (USAN)(1987): Carisoprodol, USP.
Code: *None listed.*

PHARMACOL. CATEGORY/INDICATION: Relief of discomfort associated with acute, painful musculoskeletal conditions.

DOSAGE FORM: Immediate Release Tablet.

STRENGTHS: 250 mg and 350 mg.

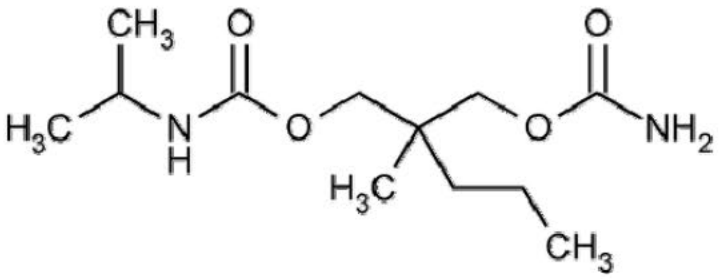
ROUTE OF ADMINISTRATION: Oral.

Rx/OTC: *Rx.*
SPECIAL PRODUCTS: __Yes xx No.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-2-Methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate.

Molecular formula: $C_{12}H_{24}N_2O_4$
MW: 260.33.
CAS: 78-44-4.



SUPPLEMENT PROVIDES FOR:

(1) Drug Substance: **(a)** A new HPLC method as an alternate Identification method to the current USP tlc Identification method; **(b)** The addition of the following residual solvent specifications: [redacted] (b) (4); **(c)** A new HPLC method as the regulatory method for known, unknown, and total impurities and specification limits based on this new method; **(d)** A new stability indicating HPLC assay as an alternate analytical procedure to the current USP titration assay for carisoprodol; **(e)** A Residue on Ignition specification; **(f)** [redacted] (b) (4) of the drug substance by the applicant; and **(g)** A Particle Size specification.

(2) Drug Product (new 250 mg tablet): **(a)** At Release, an Identification specification via tlc and HPLC testing instead of the current Potassium Sorbate and HPLC testing; **(b)** Average Tablet Hardness Test is proposed to be an In-process Test instead of the current Release Test; **(c)** Tightening of the Release Assay specification limit to [redacted] (b) (4). A new alternate HPLC method; **(d)** Using the new HPLC method as the regulatory method for known, unknown, and total impurities and proposed acceptance criteria that comply with ICH Q3B. This applies to Release and Stability; **(e)** The addition of yeast and mold testing at Release; **(f)** DMF [redacted] (b) (4) for the [redacted] (b) (4); **(g)** For Stability testing a new HPLC test method for the Assay of the drug product; and **(h)** A 36 month Expiration dating period is proposed.

SUPPORTING DOCUMENTS: IND 71,218 (active on 12/12/04); DMF [redacted] (b) (4)

CONCLUSION: **Approval from CMC standpoint.**

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Donald Klein
8/23/2007 01:49:42 PM
CHEMIST
Dr. Klein recommends a 36 month Expiration Dating Period be granted for the 250 mg tablet.
Needs to be completed by 8/30/07 (Last Internal Labeling Mtg); PDUFA Due date is 9/13/07.

Jim Vidra
8/23/2007 04:11:11 PM
CHEMIST

NDA 11-792, SE2-041

DIVISION OF POST-MARKETING EVALUATION
Review of Chemistry, Manufacturing, and Controls

NDA#: 11-792 **DATE REVIEWED: 8/6/2007**

REVIEW #: 1 **REVIEWER:** Donald N. Klein, Ph.D.

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Type B Meeting Minutes (CMC)	2/7/05	2/10/05	*n/a*
Internal e-mail regarding EA EIC Calculations	8/4/06	*n/a*	*n/a*
PA *(paper)*	11/10/06	11/13/06	11/30/06
Request for samples *(e-mail)*	12/1/06	12/1/06	12/1/06
Communication with Clinical Pharm. Reviewer *(Lot #s)*	12/6/06	*n/a*	*n/a*
Samples received	12/8/06	12/8/06	*n/a*
Microbiology Consult	12/15/06	12/15/06	12/15/06
Internal Team Meeting	12/19/06	*n/a*	*n/a*
Communication with Clinical Pharm. Reviewer *(Composition: 250 vs 350mg)*	12/19/06	*n/a*	*n/a*
74 Day Letter	1/26/07	1/26/07	1/26/07
Response *(e-mail)*	2/1/07	*n/a*	2/8/07
Desk Copy	2/8/07	*n/a*	2/20/07
(BZ) Amendment	2/8/07	2/9/07	*didn't receive*
Internal Team Meeting	2/20/07	*n/a*	*n/a*
(BZ) Amendment	3/2/07	3/5/07	3/15/07
Internal discussion (OVI Testing) with ONDQA Policy Acting Director	3/14 - 15/07	*n/a*	*n/a*
Information Request *(e-mail)*	3/27/07	*n/a*	*n/a*
Information Request *(e-mail)*	3/30/07	*n/a*	*n/a*
Internal Team Meeting	4/9/07	*n/a*	*n/a*
Information Request *(e-mail)*	4/12/07	*n/a*	4/12/07
(C) Correspondence	4/13/07	4/16/07	5/1/07
Internal e-mail from Dr. Klein to Pharm/Tox Reviewer	4/16/07	*n/a*	*n/a*
Information Request *(e-mail)*	4/16/07	*n/a*	*n/a*
Biometrics Consult	4/16/07	4/17/07	4/17/07
(BC) Amendment	4/24/07	4/25/07	5/1/07
Microbiology Review	5/1/07	5/1/07	5/1/07
Information Request to DMF (b) (4) Holder			

(information provided in SE2-041)(e-mail)	5/2/07	*n/a*	*n/a*
Response from DMF (b) (4) Holder*(e-mail)*	5/2/07	*n/a*	5/2/07
Information Request *(e-mail)*	5/3/07	*n/a*	*n/a*
Submission of the Test Method Validation Package	5/4/07	*n/a*	*n/a*
Information Request	5/7/07	5/7/07	*n/a*
Response *(e-mail)*	5/8/07	*n/a*	5/8/07
Method Validation Package Fed-Exed	5/8/07	*n/a*	5/8/07
EDR Amendent (BC) (Statistical Information)	5/10/07	5/11/07	5/16/07
Internal discussion with Biometrics Reviewer	5/11/07	*n/a*	*n/a*
Information Request from (b) (4) to Applicant	5/14/07	5/14/07	5/14/07
Packaging summary to Review Team from Dr. Klein	5/18/07	*n/a*	*n/a*
Methods Validation Materials Received Letter	5/22/07	5/22/07	5/22/07
Information Request *(e-mail)*	5/23/07	*n/a*	*n/a*
Biometrics Review	6/1/07	6/1/07	6/1/07
Amendment (BC)	6/6/07	6/7/07	6/12/07
Response *(e-mail)*	6/11/07	*n/a*	6/11/07
Response *(e-mail)*	6/12/07	*n/a*	6/12/07
Internal Team Meeting	6/12/07	*n/a*	*n/a*
Method Validation Report Summary from (b) (4)	6/8/07	6/12/07	6/12/07
DMETS Review	6/12/07	6/12/07	6/12/07
Method Validation Worksheets received from (b) (4)	6/22/07	*n/a*	6/25/07
Surveillance and Epidemiology Review	6/27/07	6/28/07	6/28/07
Information Request *(e-mail)*	7/9/07	*n/a*	*n/a*
Response *(e-mail)*	7/9/07	*n/a*	7/9/07
Information Request *(e-mail)*	7/11/07	*n/a*	*n/a*
Internal Team Meeting	7/12/07	*n/a*	*n/a*
Response *(e-mail)*	7/13/07	*n/a*	7/13/07
Information Request from Pharm/Tox Reviewer *(e-mail)*	7/13/07	*n/a*	7/13/07
Response from Dr. Klein to Pharm/Tox Reviewer	7/13/07	*n/a*	*n/a*

Internal Request from Clin. Pharm. Reviewer	7/16/07	*n/a*	7/16/07
Amendment (BC)	7/17/07	7/18/07	7/25/07
CMC Response to Clin. Pharm. Reviewer	7/20/07	*n/a*	*n/a*
Discussion with Branch Chief *(Biometrics Review)*	7/20/07	*n/a*	*n/a*
Updated cartons received	7/10/07	7/11/07	7/23/07
Discussion with Acting ONDQA Policy Director *(Biometrics Review)*	7/23/07	*n/a*	*n/a*
Updated information from Pharm/Tox Reviewer	7/23/07	*n/a*	7/23/07
Internal Team Meeting	7/24/07	*n/a*	*n/a*
Internal Meeting btwn ONDQA Directors and Biometric Directors *(policy discussion)*	7/26/07	*n/a*	*n/a*

NAME & ADDRESS OF APPLICANT:

MedPointe Pharmaceuticals
MedPointe Healthcare Inc.
265 Davidson Avenue
Suite 300
Somerset, NJ 08873-4120

DRUG PRODUCT NAME:

Proprietary: Soma® Tablet.
Established (USAN)(1987): Carisoprodol, USP.
Code: *None listed.*

PHARMACOL. CATEGORY/INDICATION: Relief of discomfort associated with acute, painful musculoskeletal conditions.

DOSAGE FORM: Immediate Release Tablet.

STRENGTHS: 250 mg and 350 mg.

ROUTE OF ADMINISTRATION: Oral.

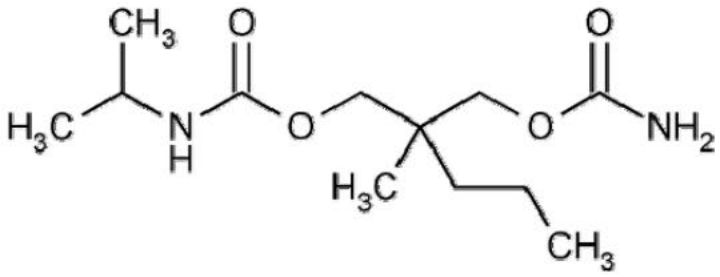
Rx/OTC: *Rx.*

SPECIAL PRODUCTS: __ Yes xx No.

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-2-Methyl-2-propyl-1,3-propanediol carbamate isopropylcarbamate.

Molecular formula: $C_{12}H_{24}N_2O_4$
MW: 260.33.
CAS: 78-44-4.



SUPPLEMENT PROVIDES FOR:

(1) Drug Substance: **(a)** A new HPLC method as an alternate Identification method to the current USP tlc Identification method; **(b)** The addition of the following residual solvent specifications: (b) (4) **(c)** A new HPLC method as the regulatory method for known, unknown, and total impurities and specification limits based on this new method; **(d)** A new stability indicating HPLC assay as an alternate analytical procedure to the current USP titration assay for carisoprodol; **(e)** A Residue on Ignition specification; **(f)** (b) (4) of the drug substance by the applicant; and **(g)** A Particle Size specification.

(2) Drug Product (new 250 mg tablet): **(a)** At Release, an Identification specification via tlc and HPLC testing instead of the curren (b) (4)

SUPPORTING DOCUMENTS: IND 71,218 (active on 12/12/04); DMF (b) (4)

CONCLUSION: **Approval from CMC standpoint.**

39 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Donald Klein
8/6/2007 05:44:10 PM
CHEMIST
Recommend Approval for CMC.

Jim Vidra
8/7/2007 01:50:27 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**11-792**
SERIAL NUMBER:	**SE2 S-041**
DATE RECEIVED BY CENTER:	**Nov 10, 2006**
PRODUCT:	**Soma®, carisoprodol**
INTENDED CLINICAL POPULATION:	**An adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions**
SPONSOR:	**MedPointe Pharmaceuticals, Somerset, NJ**
DOCUMENTS REVIEWED:	**Vols 1, 5-7**
REVIEW DIVISION:	**Division of Anesthesia, Analgesia and Rheumatology Drug Products (HFD-170)**
PHARM/TOX REVIEWER:	**L. Steven Leshin**
PHARM/TOX SUPERVISOR:	**Adam Wasserman**
DIVISION DIRECTOR:	**Bob Rappaport**
PROJECT MANAGER:	**Sharon Turner-Rinehardt**

Date of review submission to Division File System (DFS): August 24, 2007

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. RECOMMENDATIONS

A. Recommendation on approvability

Approve

B. Recommendation for nonclinical studies

None

C. Recommendations on labeling

The following labeling changes are recommended (wording to be removed is indicated by strikeout and new wording is underlined). A consult was submitted to the Maternal Health and Pregnancy labeling team, but they have not finished their review as of this submission date into DFS.

Sponsor's Proposed Label	Reviewer's Revision
INDICATIONS AND USAGE SOMA is (b) (4) indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions.	**INDICATIONS AND USAGE** SOMA is (b) (4) indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions.
8 USE IN SPECIFIC POPULATIONS **8.1 Pregnancy** (b) (4)	**8 USE IN SPECIFIC POPULATIONS** **8.1 Pregnancy** **Pregnancy Category C** (b) (4) Teratogenic Effects: The teratogenic potential of carisoprodol has not been adequately studied. Non teratogenic Effects: Published literature indicates that carisoprodol passes through the placental barrier. Oral administration of carisoprodol to pregnant

	mice resulted in reproductive toxicities that included reduced fetal weights, reduced postnatal weight gain and reduced survival. These toxicities occurred at doses of 1200 mg/kg/day. The no effect level was 300 mg/kg/day, which corresponds approximately to the human equivalent dosage of 350 mg QID, based on a mg/m^2 body surface area comparison.
12 CLINICAL PHARMACOLOGY **12.1 Mechanism of Action** (b) (4) [redacted]	**12 CLINICAL PHARMACOLOGY** **12.1 Mechanism of Action** (b) (4) [redacted]
13 NONCLINICAL TOXICOLOGY **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** (b) (4) [redacted]	**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 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

(b) (4)	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 QID, based on mg/m^2 body surface area comparison. The significance of these findings for human fertility is not known.

II. SUMMARY OF NONCLINICAL FINDINGS

A. Brief overview of nonclinical findings

This supplement is for approval of a lower dose, 250 mg tablet, of SOMA. The 350 mg tablet was originally approved in 1959 and subsequent DESI reviews. The purpose of this review was to update the label to comply with the Physician Labeling Rule. The Sponsor performed no new pharmacological or toxicological studies with SOMA, and no new studies were requested. They provided articles from the published literature and some historical documents from their predecessor company, Wallace Pharmaceuticals, the originator of this NDA. Overall, they provided an adequate summary of the nonclinical aspects of SOMA's development. They did not include a number of studies, especially newer publication of the pharmacology and metabolism of carisoprodol and its metabolite, meprobamate. Many of the toxicological studies were conducted prior to the implementation of GLP. Due to the known genotoxicity and embryotoxicity of other carbamate containing compounds and the potential abuse potential of these drugs, the National Toxicology Program started a series of studies with carisoprodol in 1988,

followed by a more complete reproductive study in 1991, and additional toxicology and genetic toxicology studies in 2000.

Despite the publication of these studies, the Soma label has not yet been updated to reflect this information. The Sponsor proposed language to address these topics in this label with support from submitted studies. This reviewer has obtained additional nonclinical data from publications which inform these nonclinical sections of the label.

Genetic toxicology

Carisoprodol was mutagenic in the *in vitro* mouse lymphoma cell assay at concentrations of 400 to 1,000 μg/mL in the absence of metabolizing enzymes, but not mutagenic in the presence of metabolizing enzymes. Carisoprodol was clastogenic in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells at the highest concentration tested (1,250 μg/mL) with or without the presence of metabolizing enzymes.

Carisoprodol was not mutagenic in the Ames reverse mutation assay using *S. typhimurium* strains (E. coli strains were not tested) with or without incubations with metabolizing enzymes. Carisoprodol was not clastogenic in an *in vivo* mouse micronucleus assay of circulating blood cells obtained from mice at the end of a 13-week oral carisoprodol administration toxicology study. The genotoxic potential of the primary metabolite, meprobamate, has not been adequately studied although meprobamate itself is an approved drug, marketed since 1957.

Reproductive toxicology

Both of the 1988 and 2000 NTP general toxicology studies found that carisoprodol treatment at 1200 mg/kg for 3 months resulted in reduced testes weight and reduced sperm motility in B6C3F_1 mice compared to controls, but not in rats. There were no indicators of reproductive toxicity in female reproductive organs.

In the NTP 1991 study, and using the Reproductive Assessment by Continuous Breeding protocol, carisoprodol was administered by oral gavage to Swiss CD-1 mice doses of 0, 300, 750, or 1,200 mg/kg/day. The maternal reproductive NOAEL was 750 mg/kg/day, based on small decrease in viable offspring and an increase in time spent in estrus at the 1200 mg/kg/day dose. Males at this dose had decreased testicular spermatid concentrations. The developmental NOAEL was 300 mg/kg/day based on 750 mg/kg/day dose findings of decreased postnatal survival and decreased F_1 weight gain at equal to or greater than 750 mg/kg/day as well as decreased live litter size (22% fewer live pups per litter) and weight (8% less) than that of the controls noted for litters of the high dose F_1 generation.

Teratogenicity was not examined in the NTP studies. No teratogenic effects of carisoprodol were observed in the 2 published articles at doses up to 400 mg/kg/day, but the data was inadequate to support labeling.

B. Pharmacologic activity

Carisoprodol produces muscle relaxation in animals by blocking interneuronal activity in the descending reticular formation and spinal cord; however the mechanism of action has not been clearly identified. The 'muscle relaxant' terminology is not based on actual measurement of a muscle relaxation endpoint, but is a conclusion based on animal response and behavior to the drug. The muscle relaxant properties of carsoprodol have been investigated using the Straub tail test in mice, footshock-induced aggression in mice, duration of paralysis in rats, head-drop method in rabbits, decerebration in cats, and other physiological and electrophysiological tests. The evidence for 'centrally-acting' is adequate, although there were no studies to verify the lack of peripheral or direct muscle action. The major studies were performed on decerebrate animals that result in spasicity, and the morphine-induced tail muscle rigidity in the mouse. These studies indirectly indicate the lack of direct action on the muscle or at the neuromuscular junction.

A receptor study indicated carisoprodol did not bind to benzediazepine receptors, but this reviewer was unable to determine if any other receptor studies have been conducted with carisoprodol. It has pharmacologic properties somewhat different from mephenesin and the carisoprodol metabolite, meprobamate, which were other carisoprodol-like compounds used as muscle relaxants of that era (1960-70). More recent studies with meprobamate, also a dicarbamate, found that it potentiates γ-aminobutyric $acid_A$ ($GABA_A$) evoked chloride currents (Rho et al., 1997). Their study indicated that the actions of dicarbamates on $GABA_A$ receptors and chloride channels reveal some similarities to pentobarbital and may be responsible for the sedative effects of, at least, meprobamate. It is not known whether carisoprodol has similar actions.

The current hypothesis is that GABA receptors mediate some of the effects of carisoprodol and meprobamate. In a clinical case report, Roberge et al (2000) found that the benzodiazepine antagonist, flumazenil, reversed the clinical signs of carisoprodol intoxication (serum levels of carisoprodol 7.4 mcg/mL, of meprobamate 30.7 mcg/mL) after naloxone failed.

C. Nonclinical safety issues relevant to clinical use

There is a lack of information concerning the toxicology of the impurites, genotoxic potential of the major metabolite, meprobamate, the teratogenic potential of carisoprodol, and the neurochemical interactions related to carisoprodol's mechanism of action. Carisoprodol has a long history of use since its approval and marketing in 1959 (meprobamate in 1957), followed by approval under the DESI program. There has been no widespread safety concerns during this time, except for its abuse liability. Therefore, these are only useful areas of study for which safety information is inadequate. The clinical impact from this lack of information is not documented and is unknown.

There are high levels of impurities with a structural alert for genotoxicity in the final drug product. The reviewer defers to the CMC reviewer's decisions on these CMC issues (refer to the CMC review for additional information). The impurities have always been

present in the drug product, but have been reduced slightly as new synthesis and analytical methodology evolved. From a toxicological perspective, the genotoxicity and general toxicology of these compounds has not been adequately characterized. However, there is no regulatory requirement for the Sponsor to do this, since the new dosage is lower than the currently approved dose (b) (4) (b) (4) ither singly or in combination with aspirin or conjugated estrogens. According to listings on the 'Drugs at FDA' website, all 61 NDAs and ANDAs have been discontinued, (b) (4) (b) (4) Included in the listing are (b) (4) that have since been discontinued. This reviewer has not been able to find information indicating genetic toxicology testing of (b) (4) There are only 2 published reports, both lacking in description and data. There is no data to correlate the ingestion carisoprodol or these impurities with clinical genotoxic effects or cancer.

There are two published studies concerning the teratogenic effects of carisoprodol in rats, one of skeletal effects and the other of soft tissue effects. It is not clear, but it appears these were from the same group of animals. No teratogenic effects were noted, but the studies lacked data and descriptions, and the highest dose administered was insufficient, since maternal toxicity was not demonstrated. The reproductuive studies performed by the NTP did not examine the fetuses for teratological effects. There is no data to correlate use of carisoprodol with pregnancy-related adverse events, such as miscarriages or spontaneous abortions.

Evidence suggests that carisoprodol acts centrally rather than peripherally to result in muscle relaxation. Its mechanism of action and neuropharmacology is not known. The few receptor studies agree that it does not interact with benzodiazepine receptors. Since carisoprodol has pronounced sedative effects, knowledge of its mechanism of action and neuropharmacological profile would benefit its safe prescribing in presence of other CNS drugs patients may be currently taking or prescribed in the future. In addition, its primary metabolite, meprobamate, has a known history of abuse when it was widely marketed as a drug in the latter half of the twentieth century.

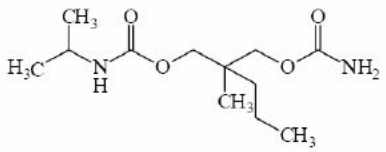
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number	**11-792**
Review number	1
Sequence /date/type of submission	**SE2 S-041**/Nov 10, 2006/commercial
Information to sponsor	
Sponsor and/or agent	**Medpointe Pharmaceuticals,** Somerset, NJ
Manufacturer for drug substance	(b) (4)
Reviewer name	L.S. Leshin
Division name	Division of Anesthesia, Analgesia and Rheumatology Drug Products
HFD	170
Review completion date	August 6, 2007

Drug

Trade name:	**Soma**
Generic name:	**carisoprodol**
Chemical name:	N-isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate
CAS registry number:	78-44-4
Molecular formula:	$C_{12}H_{24}N_2O_4$
Molecular weight:	260.33
Structure:	



Relevant INDs/NDAs/DMFs

IND 71,218 (Carisoprodol, Medpointe Pharmaceuticals)
NDA 12-155 (Nov 1959; Rela Tablets (carisoprodol) , Schering Corp.)
NDA (b) (4)
NDA 12-365 (carisoprodol + aspirin)
NDA 12-366 (carisoprodol + codeine)
DESI 11-792
DESI 294 (NAS-NRC)
DESI 295 (NAS-NRC)
DMF (b) (4)
DMF (b) (4)

Drug class Centrally acting skeletal muscle relaxant

Intended clinical population For the relief of discomfort associated with acute, painful musculoskeletal conditions;
(Current Label states: Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions)

Route of administration Oral

Clinical formulation The formulation for the new 250 and the approved 350 mg tablets are identical.

Table 4.4.2-1 Comparison of Carisoprodol 250 mg Tablet and Soma 350 mg Tablet Formulae

Ingredients	% w/w		mg/Tablet		Batch Formula (kg/Batch)	
	Proposed 250 mg Tablet	Currently Approved 350 mg Tablet	Proposed 250 mg Tablet	Currently Approved 350 mg Tablet	Proposed 250 mg Tablet	Currently Approved 350 mg Tablet
Carisoprodol, USP						(b) (4)
(b) (4) Starch, NF, (b) (4)						
(b) (4) Calcium Phosphate, NF						
Alginic Acid, NF						
Potassium Sorbate, NF (b) (4)						
Magnesium Stearate, NF						
(b) (4)						
Total	100%	100%				(b) (4)

Impurities

The major impurities in the drug product are listed in the following table:

Abbreviation/Name	Chemical Name
	(b) (4)

Structural Alert for Genotoxicity

The drug substance and two of the impurities, [redacted], contain a [redacted], which is a potentially mutatgenic. For a new drug, compounds containing this moiety that have not been qualified by genotoxic assays, the total daily intake should be no more than 1.5 µg/day. With maximumal daily human doses of 1400 mg/day and 1000 mg/day for 350 and 250 mg tablets, respectively, the current specifications allow for amounts of these impurities far in excess of [redacted] µg/day (see table below). For carisoprodol, which has been approved and marketed since 1959, there is no regulatory requirement for maintaining specifications within the newest recommendations that arise as new techniques and technology are incorporated into manufacturing.

Impurities Excess: [redacted] (reviewer created table)

Impurity	[redacted]	Limit on maximun daily dose	Potential Maximum Impurity Daily Dose			Recommendation
			Tablet dose	mg/day	Fold Excess	
[redacted]						

Release and Stability of primary drug product lots 27-02-03S, 27-02-04S and 27-02-05S

For [redacted], stability testing indicated [redacted]% content for 12 month 25°C/60% RH tests, but varied as high as [redacted]% in 6 month higher temperature 40°C/75% RH tests. This corresponds to [redacted] content as high as [redacted] mg for the 1400 mg maximal daily dose and [redacted] mg for the 1000 maximal daily dose. These values exceed the stability specification of [redacted]%, [redacted] mg and [redacted] mg for the 1400 and 1000 mg daily doses, respectively. Furthermore, the specification limit should be reduced to no greater than [redacted]% to meet current recommendations as presented in the Guidance for Industry [redacted] Impurities in New Drug Products, July 2006.

For [redacted], stability testing indicated [redacted] detected in all tests which corresponds to [redacted] content of [redacted] mg for the 1400 maximal daily dose and [redacted] mg for the 1000 maximal dose, both below the identification threshold, and qualification of [redacted] is not required. However, the specification limit should be reduced to no greater than [redacted] to meet [redacted] Guidance for Industry.

Impurity Excess: Release and Stability (reviewer created table)

Impurity	Release /Stability Specification	Limit on Release /Stability Specification	Potential Maximum Impurity Daily Dose			Recommendation
			Tablet dose	mg/day	Fold Excess	
[redacted]						

Reviewer's Comment: The reviewer defers to the CMC reviewer's decisions on these CMC issues (refer to the CMC review for additional information). As manufacturing and analytical methodology has improved over the years, there has been a small reduction in impurity concentration. There is no regulatory requirement for the Sponsor to reduce impurities to the levels recommended in the current ICH S6A and S6B guidances since the drug was approved in 1959. However, from a toxicological perspective, al[(b) (4)] compounds exceed values these recommendations and the toxicological information about these impurities is minimal. Their potential genotoxicity is unknown. This is especially important fo[(b) (4)] which has a [(b) (4)] fold higher AUC exposure than carisoprodol. In the United States, [(b) (4)]. According to listings on the 'Drugs at FDA' website, all 61 NDAs and ANDAs have been discontinued, except for one [(b) (4)]

These include [(b) (4)] that have since been discontinued. This reviewer has not been able to find data that indicated genetic toxicology testing of [(b) (4)] by any Sponsor, and only 2 published reports.

Drug History

Wallace Pharmaceuticals, a Division of Carter-Wallace Inc. was the predecessor of MedPointe Pharmaceuticals that originally developed and marketed SOMA. SOMA was approved in May 8, 1959 and reviewed in 1970 and 1974 under the DESI review program for effectiveness (DESI 11-792). This efficacy supplement is for a 250 mg carisoprodol tablet, a lower dose than the currently marketed 350 mg tablet. Since 1959, Soma has been used at a recommended dose level of 350 mg ("three times daily and at bedtime") for a maximum recommended dose of 1,400 mg for patients 12 years of age and older. The 1970 DESI review (35 FR 13854, DESI 11792, September 1, 1970) concluded that SOMA was ***possibly effective*** for **"symptomatic relief in conditions characterized by skeletal muscle spasm and mild to moderate pain"** and ineffective for all other claims approved in 1959. In response to this DESI notice, Wallace Pharmaceuticals submitted a clinical efficacy supplement to the NDA on March 1, 1971. The 1974 DESI review (40 FR 29399, DESI 11792, August 15, 1974) reevaluated SOMA 350 mg tablets with this new clinical information and concluded it was ***effective*** **"as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions,"** which is still the current NDA indication.

However, the 1974 review (40 FR 29399, DESI 11792, August 15, 1974) also reclassified SOMA 250 mg capsules as ***"lacking substantial evidence of effectiveness"*** for all indications because no carisoprodol 250 mg studies were conducted. Although a notice of an opportunity for a hearing on the proposal to withdraw the 250 mg approval was included in the FR notice, Wallace Pharmaceuticals did not request a hearing and did not provide supportive data for the 250 mg strength. Wallace Pharmaceuticals notified the Division of Neuropharmacological Drug Products in June 1979 that SOMA 250 mg capsules were discontinued in August 1974 and were no longer marketed.

Carisoprodol was also approved in combination with aspirin as SOMA Compound (NDA 12-365, approved September 12, 1960) and in combination with aspirin and codeine phosphate as SOMA Compound with Codeine (NDA 12-366, approved October 5, 1960), both developed by Wallace Pharmaceuticals. The DESI review of May 4, 1979 (44 FR 26165-66) reclassified carisoprodol in combination with phenacetin and caffeine (now aspirin) with or without codeine, and carisoprodol 250 mg capsules as ***effective for use in acute musculoskeletal conditions***. This reclassification was based upon two studies of SOMA combination products conducted by Wallace Pharmaceuticals to support the various SOMA combination products. These studies were designed to show that each component of the combination products makes a contribution to the overall therapeutic effect. The dose utilized in the studies was two 200 mg tablets containing a total of 400 mg of carisoprodol alone or in combination. Neither Wallace Pharmaceuticals nor its successor, MedPointe Pharmaceuticals, submitted additional information requested in the May 1979 FR Notice (i.e. revised labeling, components, composition, methods, facilities, and controls).

Exclusivity: As a basis for requesting exclusivity for a new dosage, the Sponsor claimed that this reclassification of the 250 mg dosage as effective was incorrect because the dose administered in the supporting clinical trials was two 200-mg tablets or 400 mg QID (see previous paragraph). The Sponsor also noted that no data from adequate and well-controlled studies have been submitted, prior to this supplement, that demonstrate the effectiveness of carisoprodol when dosed at less than 350 mg QID.

Sponsor's name change, pre-IND, and IND: On March 27, 2003 (CDER stamp date) Wallace Lab of Cranbury, N.J. notified the FDA of its changed name and address to MedPointe Pharmaceutical of Somerset, N.J. MedPointe Pharmaceuticals was interested in evaluating the efficacy of a lower strength carisoprodol tablet and held a pre-IND meeting with the Division on June 25, 2004. The nonclinica1 pharmacology/ toxicology requirements for the 250 mg carisoprodol development program were discussed and the Division agreed no new nonclinical safety studies were needed and that MedPointe could provide a summary of the available information for the IND and sNDA. IND 71,218 was submitted on November 11, 2004.

Clinical Experience

Carisprodol is a centrally-acting muscle relaxant which was initially approved under NDA 11-792 in May 1959 (SOMA®). It has been marketed alone or in combination with aspirin or codeine as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions since 1960. Because of drowsiness and other CNS side-effects associated with the marketed 350 mg dose of carisoprodol, the Sponsor is developing a 250 mg dose tablet, described in this NDA.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

There were no new nonclinical studies performed by the Sponsor. Volumes 5, 6, and 7 (non-electronic sNDA submission) contain nonclinical published literature. These were not formally reviewed but the information used in this review was obtained from many of the articles.

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2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Carisoprodol produces muscle relaxation in animals by blocking interneuronal activity in the descending reticular formation and spinal cord; however the mechanism of action has not been clearly identified. The mechanistic studies relied on older, mostly *in vivo* methodology that is somewhat dated by today's methodology. Newer studies and insights have not been forthcoming. Most of these agents are nervous system depressants which exhibit a blocking action on the interneurons and appear to modify perception of pain without abolishing peripheral pain reflexes. They do not affect the pain threshold. Sedation is prominent with most skeletal muscle relaxants, including carisoprodol, and it is difficult to thoroughly assess whether carisoprodol is a muscle relaxant or a nonspecific sedative agent, since barbiturates can also depress polysynaptic reflexes (Elenbaas, 1980). Nevertheless, carisoprodol is correctly considered a *'centrally acting muscle relaxant'* based on the available studies.

The 'muscle relaxant' terminology is not based on actual measurement of a muscle relaxation endpoint, but is a conclusion based on animal response and behavior to the drug. The muscle relaxant properties of carsoprodol have been investigated using the Straub tail test in mice, footshock-induced aggression in mice, duration of paralysis in rats, head-drop method in rabbits, decerebration in cats, and other physiological and electrophysiological tests. The evidence for this is presented here, and summarized in the Pharmacology Summary Table along with other pharmacological actions that have been studied.

The evidence for 'centrally-acting' is adequate, although there were no studies to verify the lack of peripheral or direct muscle action. The major studies were performed on decerebrate animals that result in spasicity, and the morphine-induced tail muscle rigidity in the mouse. These studies indirectly indicate the lack of direct action on the muscle or at the neuromuscular junction. Carisoprodol has pharmacologic properties somewhat different from mephenesin and the carisoprodol metabolite, meprobamate, which were other compounds used as muscle relaxants of that era (1960-70).

The neurochemical and receptor interactions of carisoprodol have never been elucidated. Two receptor studies both concluded carisoprodol had negligible affinity to benzodiazepine receptors in rat (Braestrup and Squires, 1978) or human brain homogenates (Speth et al., 1978). This reviewer was unable to locate other receptor studies with carisoprodol. Meprobamate, the major metabolite of carisoprodol and also a dicarbamate, potentiates γ-aminobutyric acid$_A$ ($GABA_A$) evoked chloride currents (Rho et al., 1997). The actions of dicarbamates on $GABA_A$ receptors and chloride channels reveal some similarities to pentobarbital and may be responsible for the sedative effects of at least meprobamate. It is not known whether carisoprodol has similar actions.

2.6.2.2 Primary pharmacodynamics

Early development of centrally acting skeletal muscle relaxants were evaluated according to four pharmacological actions (Berger et al., 1960):

1) Paralysis of intact animals,
2) Effects on spinal reflexes
3) Anticonvulsant properties
4) Effect on decerebrate rigidity

1) Paralytic action

It was difficult to measure muscle relaxation quantitatively, so the activity of centrally acting skeletal muscle relaxants were determined by measuring their paralyzing action. They produced reversible paralysis of voluntary muscles. Paralysis with relaxation of skeletal muscles resulted from the action of such drugs on the central nervous system.

In paralyzed animal, stimulation of the sciatic nerve produced contraction of hind leg muscles, which implies that conduction in the peripheral nerve, transmission at the neuromuscular junction, and contractability of the skeletal muscle were not significantly affected even in completely paralyzed animals. The effect produced by carisoprodol was similar to other centrally acting skeletal muscle relaxants, but differed from curare and related substances that blocked transmission at the neuromuscular junction. An ED_{50} was determined for the absence of the righting reflex in these paralyzed animal models. As indicated in the Table 3, carisoprodol was more effective as a muscle relxanat than either of the older compounds, mephenesin and meprobamate, and had a greater safety margin between the mean effective and mean lethal dose than the other drugs.

2) Effect on spinal reflexes

Carisoprodol has a depressant effect on polysynaptic reflexes. It more readily depresses the crossed extensor reflex in animals than simple reflexes such as the flexor reflex. Two neuron reflexes such as the knee jerk are not usually affected. However, early studies of recordings and stimulation of the reticular formation activity, indicated carisoprodol had marked blocking effect on the reticular formation, in contrast to other interneuronal blocking agents, mephenesin and meprobamate.

Carisoprodol has an effect on actions of the reticulospinal tract, in contrast to substances like mephenesine, which in the cat reduces the activity of both excitatory and inbitory centers in the brainstem. The effects of relaxants and hypnotics/narcotics on the spontaeous EEG and polysynaptic reflexes (lick reaction, jaw-opening, linguo-mandibular, and flexor reflexes) were studied in the awake rabbit with the results of various compounds grouped as follows (Berger et al. 1960):

- Suppress the reflexes tested and produce slowing in the spontaneous EEG activity
  Mephenesine, Phenyramidol, and 3-Aminobenzotrazino-N-carboxylic acid hydroxyethyl ester
- No affect on the reflexes and induced hypersynchronous epileptiform EEG activity
  Carsoprodol and 2-methyl-3,6-bis-(carbethoxyamino)-chinazolon-4.

In the rabbit, all the substances studied at high doses produced narcosis in the brain electrical activity and in the behavior of the animals.

Carisoprodol produced hypersynchronization of EEGs with no effect on polysynaptic reflexes following an intravenous dose of 45 mg/kg in the rabbit (Hoffmeister, 1964). High intravenous doses of carisoprodol resulted in a slowing of the frequency and an increase in amplitude of EEGs at doses up to 40 to 60 mg/g in rabbits and cats (Berger et al., 1960). At higher doses (>60 mg/kg), reduced activity and longer stretches of electric silence were observed in the EEGs. Animals receiving doses of 5 to 10 mg/kg did not appear drowsy, although marked changes in EEGs were observed at these doses. At similar dose levels (5 to 10 mg/kg) in cats, carisoprodol has also been shown to depress the arousal or activation response to peripheral or central stimulation (Berger et al., 1960). These electrophysiological responses occur at doses at which the animals still respond to sensory stimulation and remain alert (i.e., 5 to 10 mg/kg).

3) Anticonvulsant effect

Muscle relaxants, like mephenesin, usually antagonized the convulsant and lethal effect of strychnine. However, carisoprodol is only a weak strychnine antagonist. It was unable to protect animals from convulsions or death, but did prolong the time until death and modified the character of the convulsions. Carisoprodol is also less potent than meprobamate in abolishing the tonic extensor phase of electroshock seizures in mice.

4) Effect of decerebrate rigidity

Decerebrate rigidity is characterized by continuous spasms. These spasms predominate in extensor skeletal muscles, those that normally resist the effect of gravity. Cats were often used in these studies and decerebration was performed by sectioning the midbrain between the colliculi and extensor muscle activity of the fore or hind limbs was recorded. Carisoprodol completely abolished the spasticity due to decebrate rigidity in mice at doses of 3 mg/kg IV, doses 8-fold less than required for mephenesin and meprobamate. Other centrally acting skeletal muscle relaxants were known to be ineffective in counteracting decerebrate rigidity.

In summary, carisoprodol resembles other relaxants in producing reversible paralysis of skeletal muscles and in depressing multineuronal reflexes to a greater extent than it depresses simple ones. Carisoprodol differs from other centrally acting skeletal muscle relaxants in being much more effective in alleviating decerebrate rigidity and in being a poor strychine antagonist. Thus carisoprodol may have a different mode of action or act at different sites than other centrally-acting skeletal muscle relaxants.

Receptor Studies

The only two published receptor studies concluded that carisoprodol had no significant interaction with benzodiazepine receptors. Braestrup and Squires (1978) found that carisoprodol, up to 3 μM, did not displace ^{3}H-diazepan from rat brain homogenates by more than 20% (data was not presented). Speth et al (1978) found that carisoprodol and meprobamate at concentrations up to 100 μM did not influence ^{3}H-flunitrazepam binding to human cerebral cortical homogenates.

More recent studies with meprobamate, the major metabolite of carisoprodol and also a dicarbamate, found that it potentiates γ-aminobutyric acid$_A$ ($GABA_A$) evoked chloride currents (Rho et al., 1997). Their study indicated that the actions of dicarbamates on $GABA_A$ receptors and chloride channels reveal some similarities to pentobarbital and may be responsible for the sedative effects of, at least, meprobamate. It is not known whether carisoprodol has similar actions.

The current hypothesis is that GABA receptors mediate some of the effects of carisoprodol and meprobamate. In a clinical case report, Roberge et al (2000) found that the benzodiazepine antagonist, flumazenil, reversed the clinical signs of carisoprodol intoxication (serum levels of carisoprodol 7.4 mcg/mL, of meprobamate 30.7 mcg/mL) after naloxone failed. However, it is not known if this is a direct or indirect effect.

Reviewer's Comment: Although many of the drugs mentioned in the above pharmacology section are not currently in use or even approved to be marketed, they were common research compounds studied at the time of carisoprodol development in the late 1950's and early 1960's. Unfortunely, by the time other classes of skeletal muscle relaxants were developed, the experimental models had changed and carisoprodol was not commonly used. This apparent knowledge gap, hindered the direct comparison of the pharmacology of carisoprodol with the newer types of skeletal muscle relaxants, such as benzodiazepines cyclobenzaprines. If this information exists, the Sponsor did not provide such literature.

Drug activity related to proposed indication

Inhibition of Straub tail in mice (the morphine induced sustained contraction of the sarcococcygeus dorsalis muscle)
The skeletal muscle relaxant properties of carisoprodol have been evaluated in several Straub tail tests in mice (Ells and Carpenter, 1974; Kameyama and Ukai, 1979; Pong et al.., 1987). The basis for this test is the highly reproducible elevation of the tails of mice due to sustained contraction of the sarcococcygeus dorsalis muscle in response to morphine. An effective dose is considered to be one that inhibits the morphine-induced tail elevation without a loss of righting reflex. In general, intraperitoneal administration of carsoprodol was not considered to be effective in the Straub tail test, although at doses that produced a loss of righting reflex the Straub tail effect subsided (Ellis and Carpenter, 1974; Pong et al., 1987). Inhibition was noted in one study, with 40% and 60% inhibition at doses of 50 and 100 mg/kg, respectively; however, it was not specified whether a loss of righting reflex occurred at these doses in this study (Kameyama and Ukai, 1979).

Inhibition of paralysis
Carisoprodol induced paralysis following a single intraperitoneal dose in rats was dose-dependent (Kato et al., 1961, 1962, 1968; Kato, 1967; Kato and Tanaka, 1967, 1968). Carisoprodol concentrations in plasma and brain tissue were measured upon recovery of the loss of righting reflex in rats.

Morphine-induced increase in electromyographic activity in the gastrocnemius muscle
Carisoprodol suppressed the morphine-induced (morphine hydrochloride, 2.5 mg/kg, s.c.) increase in electromyographic activity in the gastrocnemius muscle of lightly restrained, unanaesthetized rats. Inhibition of 57 and 81% was produced by single intraperitoneal doses of 100 and 200 mg/kg carisoprodol, respectively Watanabe et al. (1983).

Head-drop method in rabbits and in cats made spastic by intercollicular decerebration
The median intravenous head-drop dose (HD_{50}) was 15.7 mg/kg for carsoprodol, which was about 8 times more potent than meprobamate, a known metabolite of carsoprodol. In cats with decerebrate toxicity, the intravenous dose of carsoprodol that blocked spastic electromyographic activity was 3 to 5 mg/kg (Diamantis and Kletzki, 1966). Doses of carisoprodol as low as 1-2 mg/kg increased the efficacy of inhbitory stimulation in the decerebrate cat (Del Castilo and Nelson, 1963). Carsoprodol at intravenous doses of 10 mg/kg depressed the activation response to sciatic stimulation more than the activation response to non painful stimuli in rabbits (Berger et al., 1960).

2.6.2.3 Secondary pharmacodynamics

The Sponsor provided the published articles summarized in the table below.

Summary Table of Secondary Pharmacodynamics

Topic /Reference	Species/test system or model/ Dose	Key Findings
Antipyresis		

Berger et al. 1960	rabbit	**No significant antipyretic activity in rabbits**
Analgesia		
Berger et al. 1960	rat silver nitrate was injected into the joints	**No analgesic activity in the writhing test or hot plate test** **Analgesic occurred at doses that did not induce ataxia**, **muscle relaxation, or paralysis.** analgesia ED_{50}: 130 mg/kg ataxia ED_{50}: 520 mg/kg
Anti-inflammatory Effects		
Berger et al. 1960	rabbit	**No significant anti-inflammatory action** lack of effect on the dermal spreading action of hyaluronidase or on granuloma tissue formation. No significant decrease in the level of circulating eosinophils or the adrenal ascorbic acid levels were observed for carsoprodol in rats Carsoprodol also had no effect on the migration of human leukocytes or on the Schwartzman phenomenon (Note: The Schwarzman phenomenon is a vasculitis, local or systemic, caused by a 2- stage reaction in which a first encounter with endotoxin produces intravascular fibrin thrombi. The subsequent clearance of the thrombi results in a reticuloendothelial blockade that prevents the clearance of thrombi caused by a second encounter with endotoxin (or a variety of polyanions, glycogen or antigen/antibody complexes) resulting in tissue necrosis and/or hemorrhage.
Peripheral Anticholinergic Effects		
Berger et al. 1960	**Overall, the peripheral anticholinergic activity of carisoprodol is considered to be weak**	
	Mice, ? intracerebral injection of acetylcholine	Pupillary response not affected
	Mice,; intracerebral injection of acetylcholine	salivary secretion not reduce
	in vitro isolated guinea pig gut test	Prevented GI spasms induced by acetylcholine or histamine
	ocular administration	
	dogs blood pressure 20 mg/kg; IV	inhibited cardiac bradycardia, decreased blood pressure caused by stimulation of the peripheral stump of the cut vagus nerve or by the administration of acetylcholine
	Dog carotid sinus pressor reflex	no effect
	cats nictitating membrane dose not specified	not significantly reduce contractions of the nictitating membrane (third eyelid) produced by the stimulation of the superior cervical preganglionic nerve
Sedation		
Berger et al. 1960	cats	**Lack of tranquilzing action** suggested by lack of effect on the limbic system as determined by the duration of rhinencephalic seizures induced in cats,

Basal Metabolic Rates			
Lanza and Goude, 1967	Mice, Swiss male 700 mg/kg; oral		**Increase in the basal metabolic rate** (24%) compared to controls. Thus, hyper metabolism is observed at a dose known to induce hypo metabolism in mice. This finding is in contrast to the hypo metabolism observed with the carisoprodol metabolite, meprobamate. The authors concluded that the effect on the metabolic rate was independent of chemical structure or mechanism of action and constituted a secondary characteristic of certain drugs.
Antidiuretic Effect			
Baïsset et al., 1975	Rat, Wistar		no effect
	Dog, normal	700 mg, oral 350 mg in morning and in the evening; oral	no effect
	Dog, hydric overload (5% of body weight)		no effect
	Dog,with diabetes insipidus (due to section of the hypothalamic-hypophseal tract)		no effect
	Dog, after high alcohol intake (300 ml).		moderate effect
Baïsset et al. 1976	Dog, mongrel, (13-18 kg)	700 mg, oral	
	Normal		an antidiuretic effect
	Hydric overload (water at 5% of body weight into esophagus		an antidiuretic effect
	Saline overload (intragastric 1 g NaCl/kg in solution at 30 mM)		No affect (Saline increased Na concentrations in blood from ~148 to a maximum at 2 hours of ~160 mM)

2.6.2.4 Safety pharmacology

The Sponsor provided the published articles summarized the table below. They are not studies considered adequate safety pharmacology studies by current standards, but are helpful in understanding carisoprodol's safety.

Safety Pharmacology

Topic /Reference	Species /test system or model Dose	Key Findings
Neurological		No battery of neurobehavioral tests (Irwin tests) were conducted, however a number of studies have examined various behaviors, reflexes, and EEG patterns; see the Pharmacology section
Cardiovascular		Not studied
Pulmonary		Not studied
Renal		Not studied

Gastrointestinal		
Bossoni et al., 1979	Sprague-Dawley rats, males Swiss mice, Males	Propyphenazone reduced the effect of oral carisoprodol in rats, but not in mice, and not in either species if administered intraperitoneal Evaluations of the duration of action were made using the rotarod method and obtaining ED_{50} for ataxia of 380 (281-513 mg/kg PO) in the mouse and 300 (197-456 mg/kg PO) in the rat Plasma and brain concentrations of carsoprodol were measured, as well as gastric emptying rates. It was **hypothesized** that a difference in early gastric emptying rate (propyphenazone inhibition of gastric emptying rate) could be the cause of both the lower plasma levels found in rats versus mice (in the mouse some carisoprodol passes into the duodenum due to the fast gastric emptying rate in the pouse, before propyphenazone can take effect) and the lack of activity of carisoprodol in rats when administered in combination with propyphenazone
Abuse Liability		
Kato, R. 1967	Rat, Repeated daily doses of 210 or 280 mg/kg for 3 weeks	develop tolerance to carisoprodol-mediated paralysis, as determined by decreased duration of action suggested **tolerance** not due to decreased sensitivity to the drug but rather **do to an increased rate of metabolism**
	Dog, Up to 1 gm/kg/day	**no withdrawal symptoms** occurred after abrupt cessation of carisoprodol
Deneau and Weiss 1968	Dog	Carisoprodol, prevented barbital withdrawal in dogs
Frazer et al., 1961; Frazer and Jasinski 1977	Dog	**Carisoprodol did not produce significant dependence**
Yanagita and Takahashi 1973	Rhesus monkey, males and females; mebrobamate: 50, 100, 200 mg/kg PO	**Meprobamate suppressed pentobarbital withdrawal and produced physiological dependence** single oral dose of 200 mg/kg of meprobamate produced severe motor impairment and inattentiveness 400 mg/kg produced light anesthesia in normal monkeys In the cross-physical dependence test, the withdrawal signs were suppressed partially by a single dose of 50 or 100 mg/kg and almost completely by 200 mg/kg In the physical dependence-producing test for meprobamate in five naive monkeys, oral doses of 200 mg/kg, given twice daily for four weeks, produced intermediate grade withdrawal signs in the five-day withdrawal test. In the second four-week administration period, the dose was doubled from that of time third week. In the second withdrawal test, convulsions and delirium occurred in 3 of 5 monkeys. A self-administratioim experiment was not conducted.

2.6.2.5 Pharmacodynamic drug interactions

The Sponsor provided the published articles summarized the table below. They are not studies considered adequate pharmacodynamic drug interaction studies by current standards, but are helpful in understanding carisoprodol's safety.

Pharmacodynamic drug interactions

Tsuruimi et al., 1977	mice and rats	**phenylbutazone in combination with carisoprodol** phenylbutazone (an NSAID) analgesic activity measured by the acetic acid writhing and modified Haffer's methods in male mice. anti-inflammatory activity measured by caageenan-induced paw edema and cotton pellet methods in female rats. carisoprodol muscle relaxant activity measured by sloped screen and rotarod methods in mice. **combination** analgesic activity: was slightly increased with respect to phenylbutazone alone. anti-inflammatory activity not enhanced **muscle relaxant activity not enhanced** acute toxicity for the individual compounds was increased by the combination: phenylbutazone oral LD_{50} decreased from 960 to 900 mg/kg carisoprodol oral LD_{50} decreased from 4,000 to 1,800 mg/kg
Kato, 1967	Rats	**Phenobarbital in combination with carisoprodol** decrease the duration of paralysis induced by carisoprodol decrease plasma and brain concentrations compared to controls
Kato and Tanaka, 1967		**Phenobarbital in combination with carisoprodol** phenobarbital (dose not specified) effect on the metabolism and duration of paralysis of carisoprodol (250 mg/kg) has been shown to be more pronounced in fasted rats versus fed rats.
Kato et al., 1968		**Phenobarbital in combination with carisoprodol** Phenobarbital increased the metabolism of carisoprodol to a greater extent in tumor-bearing rats than in control rats
Bossoni et al., 1979	Rats and mice	**Propyphenazone in combination with carisoprodol** reduced the effect of oral carisoprodol in rats, but not in mice, and not in either species if administered intraperitoneal Evaluations of the duration of action were made using the rotarod method and obtaining ED_{50} values Plasma and brain concentrations of carsoprodol were measured, as well as gastric emptying rates. It was hypothesized that a difference in early gastric emptying rate could be the cause of both the lower plasma levels found in rats versus mice and the lack of activity of carisoprodol in rats when administered in combination with propyphenazone.
Szabo et al., 1974	Rats, Female	**Steroids in combination with carisoprodol** the toxicity of carisoprodol was not diminished by pretreatment with corticosterone, desoxycorticosterone (DOC) acetate, fluorocortisol acetate, or triamcinolone Toxicity was diminished by pregnenolone-16a-carbonitrile (PCN)

2.6.3 PHARMACOLOGY TABULATED SUMMARY

See individual sections

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

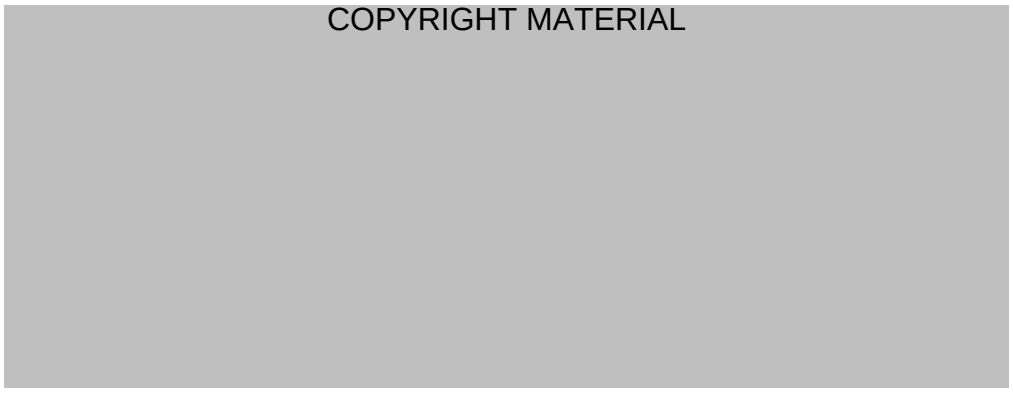
2.6.4.1 Brief summary

Absorption and Distribution

In mice and rats, carisoprodol was rapidly absorbed when administered orally with peak concentrations occurring at 15 to 60 minutes. The bioavailability was 15-38% in male mice and rats. Protein binding was 41-45% in dogs.

Initial studies indicated maximum tissue levels within 30 minutes in liver, spleen, heart, lung, skeletal muscle, and brain (in descending order of concentration), and by 1 hour for the kidney after intraperitoneal administration to rats. The highest concentrations were found in the liver, myocardium, pituitary gland, adrenal cortex, blood, lungs, and skeletal muscle. Autoradiography studies revealed carisoprodol uptake by the brain within 40 sec of intravenous injection, and maximal concentration and greatest distribution within 5 minutes to the gray matter of the cerebral and cerebellular cortex, hippocampus, thalamus, inferior colliculi and spinal cord. A more even brain distribution occurred within another 5 minutes. Meprobamate maximal concentrations in the brain occurred at 15 minutes postinjection. Carisoprodol and meprobamate were also taken up into the fetuses of pregnant mice and uniformly distributed throughout the fetuses within 15 minutes. Protein binding was 41-45% in dogs.

Concentrations of carisoprodol in plasma and brain tissue were measured in numerous studies following single oral dose administration to rats. The single time point selected for measuring concentrations in these studies was typically upon recovery of the loss of righting reflex. Regardless of the dose or the duration of paralysis, plasma concentrations of carisoprodol were similar upon recovery of the loss of righting reflex (Kato et al., 1961)



Regardless of the dose or the duration of paralysis, plasma concentrations of carisoprodol were similar upon recovery of the loss of righting reflex (Kato et al., 1961)

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Path,-Biol., 1967, Vol. 15, No. 3-4, 158-163.

The carisoprodol concentrations in the brain and plasma at the end of the paralysis in the male rats and the female rats, after the administration of the same dose, were higher in the female rats. However, the concentrations of the drug were nearly equal between the males and the females after a similar length of paralysis, although the doses for males and females differed (Table II).

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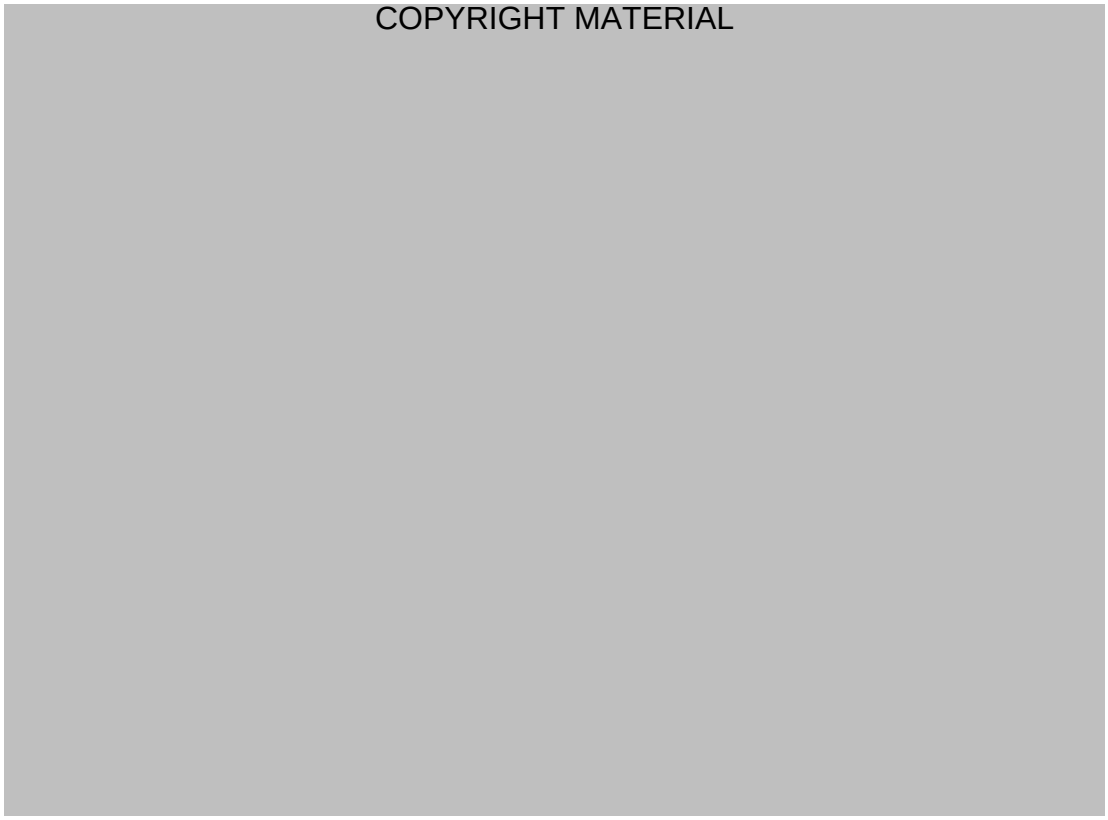
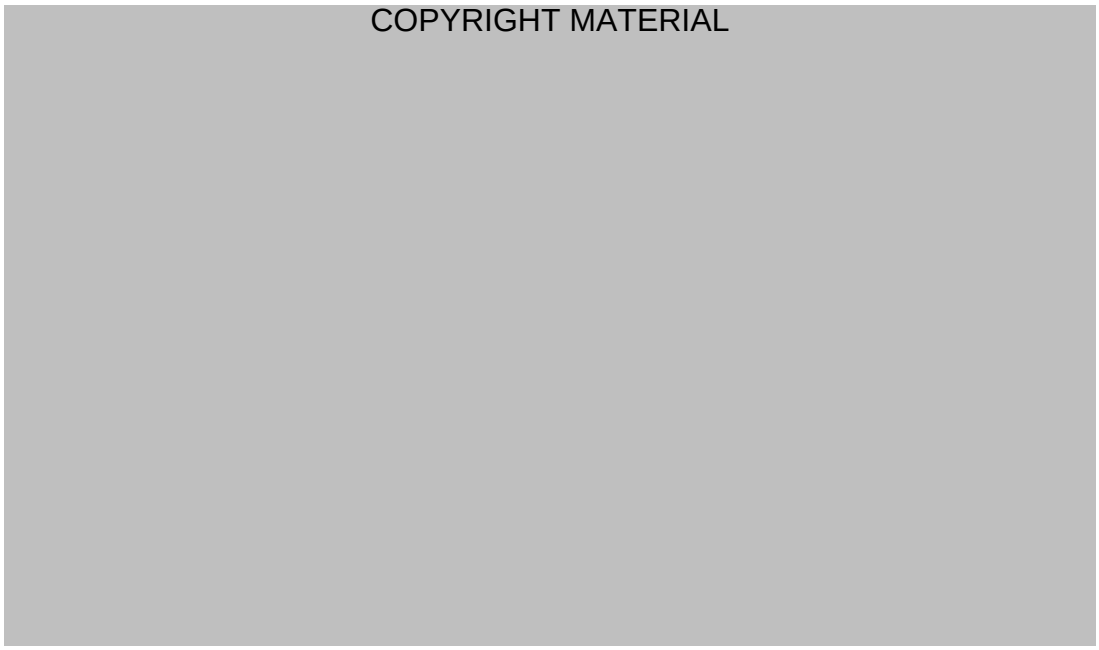
This was later demonstrated to be due to enhanced metabolism in males. Repeated administration of carisoprodol caused the length of the paralysis to decrease. The reduction of paralysis duration induced by prior treatment with carisoprodol was later demonstrated to be due to the induction of an increased liver metabolic enzymes.



Pharmacokinetic data following single dose oral administration of carisoprodol in com oil or in 0.5% methyl cellulose in male mice and rats are summarized in Table 5.2.2-1 (NTP, 2000).



In the 13-week repeated dose studies in mice and rats blood samples were only taken at 1 hour after the final dose.

Plasma concentrations (µg/mL) at 1 hour after the final carisoprodol oral dose at 13 week

	Mice			Rat	
	M	F		M	F
Dose			**Dose**		
0	<1.2	<1.2	**0**	<0.6	0.6
75	<1.2	<1.2	**100**	<0.6	1.10 (n=1) <0.6 (n=4)
300	1.5 (n=1) <1.2 (n=4)	<1.2	**400**	2.24 ± 1.14	19.40 ± 7.38
1200	15.70 (n=1) <1.2 (n=4)	8.10 ± 5.06	**1600**	5.23 ± 1.90	29.44 ± 6.02

Detection limit = 1.2 µg/mL for mice, 0.6 µg/mL for rats

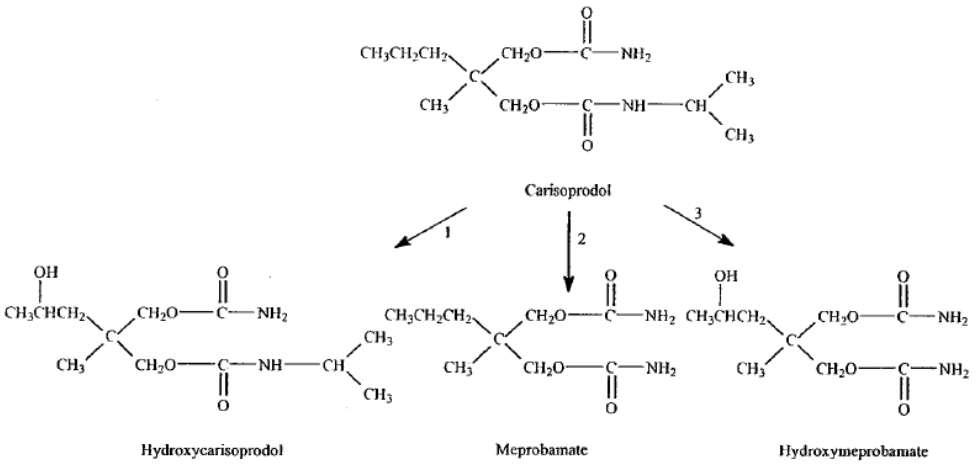
No gender effects were noted in monkeys for either the duration of the loss of ability to maintain an upright posture or the concentration of carisoprodol in serum when they recovered (Mitoma and Scholler, 1967).

Metabolism

Carisoprodol is metabolized via cytochrome P450-mediated dealkylation or oxidation reactions in the liver illustrated in the diagram below. Metabolites identified in animals include hydroxycarisoprodol, meprobamate, hydroxymeprobamate, minor amounts of unchanged carisoprodol and glucuronide conjugates. Metabolism was slower in older rats. In mice, meprobamate, an active metabolite, was the major metabolite. In dogs, hydroxycarisoprodol, hydroxymeprobamate were the main metabolites.

Gender differences in the metabolism of carisoprodol were noted in very early studies in rats (Kato et al., 1961). There were no differences observed in immature rats, but castration of male rats prolonged carisoprodol activity (measured by duration of paralysis, ie. the return of righting reflex), ovariectomy did not alter paralysis duration, and testosterone treatment to females

decreased the duration of action of carisoprodol. The presence of testosterone enhanced carisoprodol metabolism.



Excretion
Excretion was mainly in the urine mostly as metabolites with a small (7.5%) amount as the parent drug.

2.6.4.2 Methods of Analysis

This information was provided in the individual published articles.

2.6.4.3 Absorption

See Summary table.

2.6.4.4 Distribution

See Summary table.

2.6.4.5 Metabolism

See Summary table.

2.6.4.6 Excretion

See Summary table.

2.6.4.7 Pharmacokinetic drug interactions

See Summary table.

2.6.4.8 Other Pharmacokinetic Studies

See Summary table.

2.6.4.9 Discussion and Conclusions

It was demonstrated early in carisoprodol's drug development that it induces enzymes to eliminate its presence in the body. This accounted for some of the tolerance that develops indicated by attenuation of pharmacological effects observed during the first week of repeated dosing studies. In addition in some species, including humans, differences in metabolism exist between genders. In rats and humans, this manifests in females as a more prolonged pharmacodynamic and adverse effects due to a slower metabolism of carisoprodol. In nonhuman primates, the one study of carisoprodol administration to rhesus and squirrel monkeys, no gender differences were noted, but their were few animals studied. Whether this also occurs for meprobamate, an active metabolite of carisorprodol, is not known. Recent human studies demonstrated that polymorphism of the metabolic enzyme CYP2C19 account for some of the individual differences in the rate of carisoprodol metabolism.

2.6.4.10 Tables and figures to include comparative TK summary

Incorparated into the brief summary section 2.6.4.1.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Pharmacokinetics Summary Table

Topic /Reference	Species	Dose	Key Findings
Absorption			
NTP, 2000	Mice; $B6C3F_1$; male	300-1200 mg/kg; single oral gavage dose in 0.5% methylcellulose or corn oil	peak blood concentration in 15 to 60 minutes in mice; bioavailablity 18-38%, similar in methylcellulose and corn oil vehicles, based on AUC
NTP, 2000	Rat, F344/N; male	200-800 mg/kg; single oral gavage dose in 0.5% methylcellulose or corn oil	peak blood concentration in 20 to 60 minutes in rats; bioavailablity 15-32% in methylcellulose, about 5-fold less in corn oil vehicle, based on AUC
Distribution			
Kato et al., 1962	female Sprague-Dawley rats	200 mg/kg IP single dose In 1 % carboxymethyl-cellulose	tissue concentrations were determined at 0.2, 0.5, 1, 2, 3, 5, and 12 hours post-dose (n=4 per time point Maximum tissue and serum concentrations were observed at 30 minutes for most tissues, except kidneys, which reached a maximum concentration by 1 hour. Carisoprodol was detected in the following tissues in decreasing order of concentration: liver, kidney, spleen, heart, lung, skeletal muscle, and brain. Low concentrations were detected in serum and tissues at 12 hours (≤18 μg/g).
Van der Kleijn, 1969a	Swiss Mice, males (20-22 g) and pregnant females 2 days before delivery (~40 g)	120 mg/kg , IV ^{14}C-Carisoprodol (sp act 1.96 mC/mM); 120 mg/kg, IV or oral ^{14}C-Meprobamate (sp. Act. 5.5 mC/mM)	tissue/organ homogenates and frozen section whole body autoradiography 40 sec to 8 hours after drug administration: carisoprodol: taken up by the central nervous system within 40 seconds and was distributed throughout the body within 10 minutes; highest concentrations were found in the liver, myocardium, pituitary, and adrenal cortex, followed by blood, lungs, and skeletal muscle carisoprodol taken up by brain more readily than meprobamate carisoprodol distributed within about 5 min to gray matter of cerebral and cerebellular cortex, hippocampus, thalamus, inferior colliculi and spinal cord; by 10 min more distribution in brain meprobamate max concentration in brain at 15 min. Carisoprodol and meprobamate was taken up slowly into the fetuses of pregnant mice and was uniformly distributed throughout the fetuses within 15 minutes.
Van der Kleijn, 1969b	Dog, Fasted, *in vivo* studies;	radiolabeled intravenous administration of 25 to 40 mg/kg	plasma protein binding 45 to 47% bound to plasma proteins in vitro 41 to 44% bound within 5 minutes in vivo

	in vitro with dog plasma		Protein binding appeared to be independent of the drug concentration over the therapeutic plasma concentration range
Kato 1967	Rats, males Effects of different doses of carisoprodol on the carisoprodol concentration in the brain and plasma at the end of paralysis		The increase of the paralysis time after the administration of various doses of carisoprodol is parallel to the increase of these doses. The concentrations of carisoprodol in the brain and plasma at the end of the paralysis had a significantly higher value among the rats that received greater doses of carisoprodol the duration of paralysis differed in male and female rats due to a difference in the intensity of their metabolism **time of paralysis due to carisoprodol was longer with the female rats than the male rats, and the concentrations of carisoprodol in the brain and plasma was greater in the female rats** if the dose of carisoprodol is increased in the male rats in order to produce a paralysis smilar as for female rats, the concentrations in the brain and plasma at the end of the paralysis was similar for both sexes.
Metabolism			
Kato et al., 1961	Rat	200 mg/kg IP, single dose	**Differences in metabolism of carisoprodol between male and female rats** Not observed in immature rats Castration of male rats prolongs carisoprodol activity (measured by duration of paralysis, ie. the return of righting reflex) Testosterone treatment to females decreased the duration of action of carisoprodol Ovariectomy did not alter paralysis duration
Segelman et al., 1985.	Sprague-dawley CD rats, males	200, 400, 800 mg/kg, oral single daily dose for 5 days	Using a reproducible screening procedure for rat liver cytochrome P450 isoenzyme induction/inhibition, five dicarbamate drugs (meprobamate, mebutamate, carisoprodol, tybamate, and W-554) were compared with sodium Phenobarbital and found to be from 25 to 100 times less potent hepatic cytochrome P450 inducers than Phenobarbital.
NTP, 2000			Carisoprodol undergoes cytochrome-P450-mediated dealkylation and oxidation in the liver
Adams et al., 1975	Human		Meprobamate was the principal metabolite detected in the serum, urine, and gastric contents of a child who ingested approximately 3,500 mg carisoprodol
Van der Kleijn, 1969	Mouse		Meprobamate was the major metabolite
Mitoma and Scholler, 1967	Monkey, rhesus and squirrel	50 mg/kg, IV; (in equal volumes of dimethylacetamide, prpylene glycol, and 50% glycerol)l	No gender effects were noted in monkeys for either the duration of the loss of ability to maintain an upright posture or the concentration of carisoprodol in serum when they recovered
Dalen et al., 1996	Human		**Metabolism of carisoprodol by CYP2C19** An open three-panel single-dose administration study was conducted with 15 healthy volunteers: five poor

			metabo1izers of mephenytoin, five poor metabolizers of debrisoquine and five extensive metabolizers of both substrates. The subjects were given single oral doses of 700 mg carisoprodol and 400 mg meprobamate on separate occasions. The disposition of carisoprodol was clearly correlated to the mephenytoin hydroxylation phenotype. The mean serum clearance of carsoprodol was four times lower in poor metabolizers of mephenytoin than in extensive metabolizers confirms the hypothesis from a previous study that: **N-dealklation of carisoprodol cosegregates with the mephenytoin hydroxylation polymorphism**. Mean serum clearance of meprobamate did not differ between the two groups. Polymorphic debrisoquine hydroxylation did not influence the elimination of carisoprodol or meprobamate. Poor metabolizers of mephenytoin have a lower capacity to metabolize carisoprodol and may therefore have an increased risk of developing concentration dependent side-effects such as drowsiness and hypotension, if treated with ordinary doses of carisoprodol.	
Excretion				
Kato et al., 1962	Rats, Sprague-Dawley, female	200 mg/kg) in 1% carboxymethylcell ulose; IP; Single dose	**Kidney is the major route of excretion of carisoprodol and its metabolites** After 48 hours, only 7.5% of the dose was eliminated as unchanged carisoprodol in the urine, with most of the urinary excretion occurrng within the first l2 hours (5.5%). Only negligible quantities were observed in the feces (<0.3% of the administered dose within 48 hours).	
Douglas et al., 1962	Dog, mongrel		Urinary metabolites were hydroxycarisoprodol (40%), meprobamate (15%), hydroxymeprobamate (40%), unchanged carisoprodol (< 1 %), and glucuronide condensate (1 % to 2%).. Meprobamate was also the major metabolite identified in mice administered carisoprodol (van der Kleijn, 1969). Carisoprodol and its metabolites are excreted by the kidney.	

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General Toxicology

Many of the toxicological studies were conducted prior to the implementation of GLP. Due to the known genotoxic and embryotoxicity of other carbamate containing compounds and the potential abuse potential of these drugs, the National Toxicology Program started a series of studies with carisoprodol in 1988, followed by a more complete reproductive study in 1991, and additional toxicology and genetic toxicology studies in 2000. Early in carisoprodol development, it was noted that high doses of carisoprodol (>1,000 mg/kg) produced a reversible, flaccid paralysis of voluntary muscles that may cause death due to respiratory paralysis. Three month repeated oral dose studies in mice and rats identified the liver and kidney as target organs. High doses caused increased liver weights with minimal to mild centrilobular hypertrophy, probably due to induction of metabolizing enzymes. Increased kidney weights and nephropathy in male and female rats also occurred. Decreased testis weights and sperm motility were observed in male mice, but not rats, administered 1,200 mg/kg/day. Clinical signs included dose-related lethargy, ataxia, tremors convulsions, and prostration. The no-observed-adverse-effect levels (NOAELs) were 75 and 100 mg/kg/day in mice and rats, respectively. Similar clinical signs were observed in repeated dose studies in dogs, and as in rodents, these signs attenuated after a few weeks, as tolerance and/or metabolism of carisoprodol became more efficient.

Genetic Toxicology

Carisoprodol was mutagenic in the *in vitro* mouse lymphoma cell assay at concentrations of 400 to 1,000 µg/mL in the absence of metabolizing enzymes. Carisoprodol was clastogenic in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells at the highest concentration tested (1,250 µg/mL)with or without the presence of metabolizing enzymes.

Carisoprodol was not mutagenic in the *in vitro* mouse lymphoma cell assay in the presence of metabolizing enzymes or in the Ames reverse mutation assay using *S. typhimurium* strains (E. coli strains were not tested) with or without incubations with metabolizing enzymes. Carisoprodol was not clastogenic in an *in vivo* mouse micronucleus assay of circulating blood cells (not bone marrow cells). This was conducted with blood samples obtained from mice at the end of a 13-week oral carisoprodol administration toxicology study. The genotoxic potential of the primary metabolite, meprobamate, has not been adequately studied.

Carcinogenicity toxicology

No carcinogenicity studies were conducted by the Sponsor or found in the literature. A 2-year carcinogenicity study (# C56235C) was listed for study on the NTP website under carisoprodol studies, year unknown, but it was apparently cancelled. Carisoprodol will be labeled (b) (4)

Reproductive toxicology

Carisoprodol was evaluated for reproductive toxicological effects in mice and rats. The Sponsor presented articles from the National Toxicology Program (NTP) which conducted studies using the Reproductive Assessment by Continuous Breeding protocol in mice in 1991. The Sponsor did not reference the 1988 studies also performed by the NTP. Another 13-week toxicology study was conducted by the NTP in 2000. Both the 1988 and 2000 general toxicology studies found some evidence of reproductive toxicity, reduced testes weight and reduced sperm motility in male mice, but not rats. There was no signs of reproductive toxicity in female reproductive organs.

In the 90-day study (NTP, 1988), carisoprodol at 0, 75, 150, 300, 600, and 1200 mg/kg, p.o., was administered to B6C3F_1 mice. Body weight gain was significantly greater than controls in the male mice receiving 15-300 mg/kg/day and in female mice receiving 150. 300. and 600 mg/kg/day. At necropsy, 1200 mg/kg males had reduced testis weights. Also, 150, 300, and 1200 mg/kg animals, but not 600 mg/kg, had decreased testis/body weight ratios when compared to controls. Sperm motility was decreased only in the 150 mg/kg/day group but there were no changes in sperm concentrations. There was no gonadal toxicity noted for female mice. In F344/N rats, daily carisoprodol administration for 13 weeks at doses of 100 to 1600 mg/kg failed to produce any significant changes in the reproductive system of males or females.

In the 3-month studies (NTP, 2000) carisoprodol dosed at 1200 mg/kg resulted in decreased testis weight and decreased epididymal spermatozoa motility in B6C3F_1 mice. These effects were absent in F344/N rats and there were no effect on vaginal cytology or female organ weights in rats or mice.

In the NTP 1991 study, the Reproductive Assessment by Continuous Breeding protocol was used to study carisoprodol in Swiss CD-1 mice. In this protocol, the F_0, and F_1 generations are continuously administered carisoprodol. After a few cycles of F_2 litters, the study is terminated. Carisoprodol was administered by oral gavage to Swiss CD-1 mice doses of 0, 300, 750, or 1,200 mg/kg/day. The maternal reproductive NOAEL was 750 mg/kg/day, based on small decrease in viable offspring, a decrease in testicular spermatid concentration, and an increase in time spent in estrus, at the 1200 mg/kg/day dose. The developmental NOAEL was 300 mg/kg/day based on 750 mg/kg/day dose findings of decreased postnatal survival and decreased F_1 weight gain at equal to or greater than 750 mg/kg/day as well as decreased live litter size (22% fewer live pups per litter) and weight (8% less) than that of the controls noted for litters of the high dose F_1 generation.

Teratogenic effects were not examined in the NTP studies. No teratogenic effects of carisoprodol were observed in the 2 published articles at doses up to 400 mg/kg/day, but the data presented was inadequate to support labeling.

2.6.6.2 Single-dose toxicity

Single-Dose Toxicity

Study	Animal or Model	Dose	Findings
Berger et al., 1959 Sax 1984	Mouse	180 mg/kg, IP, in 5% gum acacia	**reversible flaccid paralysis of voluntary muscles** no tremors or twitching not alter heart rate corneal reflex absent righting reflex absent (higher doses blocked pinna reflex) Response to painful stimule intact (peripheral nerve, neuromuscular junction, and muscles not affected)
		>1000 mg/kg; IP	death from respiratory paralysis
			IV LD_{50} = 165 mg/kg;
			IP LD_{50} = 800 mg/kg IP LD_{50} = 980 mg/kg
			Oral LD_{50} = 1800 mg/kg Oral LD_{50} = 2340 mg/kg
Berger et al., 1959 Sax 1984 Service Center Bulletin Vol. 2 pg 17, (1963)	Rat		IV LD_{50} = 450 mg/kg
			IP LD_{50} = 450 mg/kg
			Oral LD_{50} = 1320 mg/kg
	Dog	100 mg/kg; oral	loss of muscle tone in the limbs and unsteady gait no sign of excitement
	Dog	200 mg/kg; oral	muscular weakess and ataxia with excitement: tail wagging whinning and howling withdrawal reflex intact corneal reflex intact pina reflex intact and
	Dog	400 mg/kg; oral	ataxia righting reflex absent paralysis with tremors and clonic movements of the the extremities (recovery by the following day)
Diamantis and Kletzkin, 1966	Rabbit	LD_{50} = 124 mg/kg; IV	sense organs and special senses other:eye Behavioral altered sleeo time (including change in righting reflex) Behavioral rigidity

2.6.6.3 Repeat-dose toxicity

StudyTitle: NTP Technical Report on the Toxicity Studies of Carisoprodol (CAS No. 78-44-4) Administered by Gavage to F344/N Rats and B6C3Fl Mice

Chan PC., NTP (National Toxicology Program). 2000.
Department of Health and Human Services (DHHS). National Toxicology Program (NTP); Research Triangle Park, North Carolina. Toxicity Report Series, No. 56.
NDA 11-792, SE2 S-041, Vol. 7, p. 3
GLP: yes

Drug:

Carisoprodol, Lot 58764 Purity; 99.5% (CAS No. 78-44-4, Carter Wallace, Inc., New York. NY)
Vehicle: corn oil or 0.5% methylcellulose

Analyses of stock solution after the study indicated that there was no detectable change in carisoprodol during the study period.

Experimental Design				
Species	**$B6C3F_1$ Mice**		**F344/N Rats**	
Vehicle	**Corn oil**	**0.5% methylcellulose**	**Corn oil**	**0.5% methylcellulose**
n/sex/dose	**10**	**10**	**10**	**10**
Carisoprodol dose (mg/kg) 13 week study	**0 75 150 300 600 1200**	**0 600 1200 1600**	**0 100 200 400 800 1600**	**0 100 200 400 800**
Results				
Survival	**Deaths** **Accidental Deaths:** 0: 2 F 75: 2 F 150: 1 F 600: 1 F	**Deaths** 1600: 1 F, 1 M **Accidental Deaths:** 7 mice	No difference from vehicle control **Deaths:** 1600: 1 F, 1 M	No difference from vehicle control after adjustment for **Deaths** 400: 2 F 800: 1 F, 2 M **Accidental Deaths:** 150: 1 F 600: 1 F
Body Weights	**Similar to vehicle controls**	**All groups less than control**	1600 F: >control 800 F: > control	200 M: >control 800 F: > control 100 F: > control
Body Weight Gain	**Similar to vehicle controls**	**All groups less than control**	1600 M: < control 1600 F: >control 800 F: > control	200 M: >control 800 F: > control 100 F: > control

Experimental Design				
Species	**B6C3F$_1$ Mice**		**F344/N Rats**	
Vehicle	**Corn oil**	**0.5% methylcellulose**	**Corn oil**	**0.5% methylcellulose**
n/sex/dose	**10**	**10**	**10**	**10**
Carisoprodol dose (mg/kg) 13 week study	**0** **75** NOAEL **150** **300** **600** **1200**	**0** **600** **1200** **1600**	**0** **100** NOAEL **200** **400** **800** **1600**	**0** **100** NOAEL **200** **400** **800**
Results				
Clinical Findings	In males and females Signs: lethargy ataxia tremors prostration	In males and females All doses Signs: lethargy ataxia convulsions prostration	Incidences dose-related F more sentive than M Signs: lethargy ataxia diarrhea prostration	
Hematolgy	Not studied	Not studied	No consistent pattern in differences	Not studied
Clinical Chemistry	Not studied	Not studied	No consistent pattern in differences	Not studied
Organ Weights	**Liver** ↑ ≥ 300 in M, ≥ 150 in F, **Testes** ↓ 1200, **sperm motility** ↓		**Liver** ↑ ≥ 200 in M, F **Kidney** ↑ ≥ 200 in M, F	**Liver** ↑ 400 in M 800 in M, F **Kidney** no consistent effect
Pathology	**No treatment findings**	**Liver:** Centrilobular hypertrophy of hepatocytes; Minimal to mild; All doses in M 1200, 1600 in F	**Liver:** Centrilobular hypertrophy of hepatocytes 1600 in 4M **Kidney:** Nephropathy ≥ 400 in M No lesions in females	**Kidney:** Nephropathy M: ≥ 200 in F: greater inicidence in for 800
Toxicokinetics	**Above detection limit** in only 1 M for 300, 1200 4 F for 1200 Single dose: Increase with increasing dose Peak: M at 20-120 min F at 60-120 min	 Single dose: Increase with increasing dose only in F Peak: M, F: at 30 min	Increase with increasing dose Single dose: Increase with increasing dose	

Experimental Design				
Species	**B6C3F$_1$ Mice**		**F344/N Rats**	
Vehicle	**Corn oil**	**0.5% methylcellulose**	**Corn oil**	**0.5% methylcellulose**
n/sex/dose	**10**	**10**	**10**	**10**
Carisoprodol dose (mg/kg) 13 week study	**0** **75 NOAEL** **150** **300** **600** **1200**	**0** **600** **1200** **1600**	**0** **100 NOAEL** **200** **400** **800** **1600**	**0** **100 NOAEL** **200** **400** **800**
Results				
proportionality and bioavailability	single gavage doses of 300 to 1,200 mg/kg carisoprodol in 0.5 % methylcellulose in mice were dose proportional; absolute bioavailability values increased with increasing dose, ranging from 18% to 38% for mice. no significant difference was observed in the bioavailability of carisoprodol in 0.5 % methylcellulose or in corn oil However, Cmax values of the dose in 0.5% ethylcellulose were 1.5 to 1.75 times those of the dose in corn oil		For single gavage doses of 200 to 800 mg/kg carisoprodol in 0.5 % methylcellulose the absolute bioavailability values increased with increasing dose, ranging from 15% to 32 % for rats the bioavailability of carisoprodol in 0.5 % methylellulose was approximately fivefold that of carisoprodol in com oil Cmax values of the dose in 0.5% methylcellulose were approxitely threefold those of the dose in corn oil	

Additional Repeated-Dose Studies

Study	Animal	Dose	Findings
Muni et al., 1984 (abstract only) Not GLP	**Mouse,** B6C3F$_1$, **Rats**, Fischer.	0, 25, 50, 100, 200, 400 mg/kg; oral; once daily for 3 months	**dose-range finding study** to find MTD for carcinogenicity studies **dose-related effect on sperm motility and density** no effect on study days 30, 60 and 90 on: mortality, clinical signs, food consumption, body weights, forelimb and hind limb girp strength sperm morphology and vaginal cytology organ weights gross pathology.
Margolin, 1958a Prior to GLP regulations	**Rat,** males, N=10/dose	0, 0.5, 1.0, or 2.0% in diet for 52 weeks (approximately 250, 500, and 1,000 mg/kg/day)	1 animal died (2% dose group) during month 11 **clinical signs only in 2% dose group during the first 3 to 5 weeks,** **ataxia and partial paralysis** no neurological effects at the end of the study **also in first 3 to 5 weeks:** **decreased food intake and body weight gains in 2% dose group** **body weights recovered by month 5** **decreased leukocyte counts in 1% and 2% diet**

			groups **enlargement and increased weight of the liver and kidneys in the 2% dose group** no histopathologic findings
Margolin, 1958b Prior to GLP regulations	**Dog** n=3	100 mg/kg/day; Oral; (50 mg/kg twice daily); 5 days per week for 26 weeks (***Comment:*** due to short plasma half-life in dog, dividing the dose is unlikely to result in effects observed by a single 100 mg/kg dose)	**Neurological alterations during the first 2 weeks slight ataxia associated with loss in muscle tone and changes in gait.** No effect on body weight or body weight gain No effect on hematology No effect on gross pathology (with the exception of lung infection-related findings in 1 dog such as inflammation of the bronchi, pneumonia; and brain lesion indicative of distemper)
Hazelton, 1959 Prior to GLP regulations	**Dog,** adult mongrel n=2/sex/dose	0, 150, 200, 250 mg/kg/day; Oral; for 5 days/week for 12 weeks months	**9 of 12 carisoprodol treated dogs exhibit mild effects:** **mild or moderate ataxia** **occasional tremors** **hyperexcitability** **loss of placement reflex** No major changes in hematology, biochemistry, or urinalysis No gross abnormalities No histopathological changes
NTP, 1988	Mouse, $B6C3F_1$ Rats, 344/N Males and females 5/sex/dose	0, 75, 150, 300, 600, 1200 mg/kg; oral gavage; for 90 days rats: 0, 600, 1200, 1600 mg/kg	Body weight gain was significantly greater than controls in the male mice receiving 150 and 300 mg/kg/day and in female mice receiving 150, 300. and 600 mg/kg/day. Relatíve 1iver weight was increased in both male at doses >300 and female mice >150 mg/kg/day No effect on female reproductive parameters Relative right testis weight was decreased at 75. 180. 300. and 1200 mg/kg/day

2.6.6.4 Genetic toxicology

There were no genetic toxicology studies performed by the Sponsor. The few published studies are summarized here. Only the studies performed by the National Toxicological Program (NTP 2000) were indicated as GLP studies.

Carisoprodol was mutagenic in the *in vitro* mouse lymphoma cell assay at concentrations of 400 to 1,000 µg/mL in the absence of metabolizing enzymes. Carisoprodol was clastogenic in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells at the highest concentration tested (1,250 µg/mL) with or without the presence of metabolizing enzymes.

Carisoprodol was not mutagenic in the *in vitro* mouse lymphoma cell assay in the presence of metabolizing enzymes or in the Ames reverse mutation assay using *S. typhimurium* strains (E. coli strains were not tested) with or without incubations with metabolizing enzymes. Carisoprodol was not clastogenic in an *in vivo* mouse micronucleus assay of circulating blood cells (not bone marrow cells). This was conducted with peripheral blood samples obtained from mice at the end of a 13-week oral carisoprodol administration toxicology study. The genotoxic potential of the primary metabolite, meprobamate, has not been adequately studied.

Genetic Toxicology

Study (Reference)	Cells/Species	Dose	Metabolic Activation	Findings
Carisoprodol				
Mutation				
***In vitro* Bacteria Mutagenicity (Ames assay)** NTP, 2000 Zeiger et al., 1987 **GLP**: **yes**	*Salmonella typhimurium* TA98 TA100 TA1535 TA1537 **No assays with *E. coli***	up to 10,000 µg/plate (10, 33, 100, 333, 1000, 3333, 10,000 µg/plate)	no	Negative
			yes	Negative
***In vitro* mouse lymphoma** (NTP, 2000) **GLP: yes**	Mouse lymphoma L5178YTK$^{+/-}$ cells	up to 1000 µg/mL	no	**Positive** in 3 of 4 trials at ≥400 µg/mL
			yes	negative
Clastogenicity				
***In vitro* mammalian sister chromatid exchange (SCE) assay** (NTP, 2000) **GLP: yes**	Chinese hamster ovary cells	up to 1250 µg/mL	no	**Equivocal** Positive only at the lowest doses (5 and 16 µg/mL); Toxicity at higher doses?
			yes	**Equivocal** Positive in trial 2 at the 500 and 1250 µg/mL, but not at intermediate doses

***In vitro* mammalian Chromosome aberration assay** (NTP, 2000) **GLP: yes**	Chinese hamster ovary cells	up to 1250 µg/mL	no	**Positive** (≥500 µg/mL)
			yes	**Positive** (≥1000 µg/mL)
***In vivo* mouse peripheral blood micronucleus test** (NTP, 2000) **GLP: yes**	$B6C3F_1$ mice (Performed with same mice after the 3 month chronic toxicity study)	Daily oral doses 0, 75, 150, 300, 600, or 1200 mg/kg/day in corn oil for 13-weeks		Negative
***In vitro* mammalian cell transformation assay** (Matthews et al., 1993) **GLP**: not indicated	1-13 clone of A31 BALB/c-3T3 cells	0.5 to 4.00 mM = 130 - 1040 µg/mL; LD_{50} = 3.33 mM = 866 µg/mL		Negative
Meprobamate				
Mutation				
Bacteria Mutation Assay Takeda and Kanaya, 1981 GLP: not indicated	*Salmonella typhimurium* TA98 TA100	0.8 – 8 µmol/plate (174-1740 µg/plate)	no	Negative
			yes	Negative
Clastogenicity				
Dominant lethal assay Epstein et al., 1972 GLP : before GLP regulations	Mice, ICR/Ha Swiss, males	80 or 400 mg/kg, IP		Negative

CARISOPRODOL STUDIES

Study title: Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals
Zeiger, E.; Anderson, B.; Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W. 1987.
Environ Mutagen 9(Suppl. 9):1-20, 39.
NDA 11-792, SE2 S-041, Vol. 7, p. 224
GLP: not indicated

Key findings: Carisoprodol, at doses up to 10,000 µg/plate, was not mutagenic in *Salmonella typhimurium* strains TA98 and TA 100, TA1535, and TA1537 in the Ames bacterial mutation assay.

Reviewer's Comment: The data in the copy of the article was difficult to read as submitted. However, it appears this same data is presented 13 years later in a more extensive format in the NTP, 2000, Toxicity Report Series No. 56,

Methods
A wide variety of 255 chemicals were tested for their ability to induce mutations in *Salmonella typhimurium* strains TA98, TA 100, TA1535, and TA1537, and/or TA97 with and without metabolic activation with S9 liver fraction of Aroclor 1254-induced, male Sprague-Dawley rat and male Syrian hamster. The preincubation assay was performed as described previously (Haworth et al., 1983). The test chemical, Salmonella culture, and S9 mix or buffer were incubated at 37°C, without shaking, for 20 min. The top agar was added, and the contents of the tubes were mixed and poured onto the surface of petri dishes that contained Vogel- Bonner medium (Vogel and Bonner, 1956). The histidine-revertant (his+) colonies arising on these plates were counted following 2 days incubation at 37ºC. The plates were hand-counted when a precipitate was present; otherwise automatic colony counters were used.

All chemicals were tested initially in a toxicity assay to determine the appropriate dose range. The toxicity assay was performed by using TA100 or the system developed by Wa1eh et al (1982). Toxic concentrations were those at which a decrease in the number of his + colonies was seen or at which there was a clearing in the density of the background lawn.

At least five doses of the chemical were tested in triplicate. Experiments were repeated at least 1 week following the initial trial. Each chemical was tested initially at half-log doses up to a dose that elicited toxicity; subsequent trials occasionally used narrower dose increments. Chemicals that were not toxic were tested to a maximum dose of 10 mg/plate. Chemicals that were poorly soluble were tested up to a dose defined by their solubility. A maximum of 0.05 mL solvent was added to each plate. Concurrent solvent and positive controls were run with each trial. The positive controls in the absence of metabolic activation were sodium azide (TA1535 and TA100), 9-aminoacridine (TA97 and TA1537), and 4-nitro-o-phenylenediamine (TA98). The positive control for metabolic activation was 2-aminoanthracene for all strains. Although there were no specific response ranges established for the solvent and positive controls, each laboratory rejected experiments in which the positive control chemical did not produce a mutagenic response or in which the solvent control values were higher (or lower in the case of TA100 and TA97) than their expected values. During the initial stages of the testing program,

chemicals were tested with 10% S9. Other levels of S9 were used when an equivocal result was obtained with 10%. The protocol evolved to one that used 30% S9 when a negative response was obtained with 10% S9.

An individual trial was judged mutagenic (+) if a dose-related increase in revertants over the corresponding solvent control was seen, and it was judged weakly mutagenic (+W) if a low-level dose response was seen. A trial was considered questionable (?) if a dose-related increase was judged insufficiently high to justify a call of "+ W," if only a single dose was elevated over the control, or if a non-dose-related increase was seen. The distinctions between a weak mutagenic response and a mutagenic response or between a weak mutagenic response and a questionable mutagenic response were highly subjective. A chemical was judged to be mutagenic (+), or weakly mutagenic (+W), if it produced a reproducible, dose-related increase in his+ revertants over the corresponding solvent controls in replicate trials. A chemical was considered to be questionable (?) if a reproducible increase of his + revertants did not meet the criteria for either a " +" or "+ W," or if only single doses produced an increase in his + revertants in repeat trials. The chemicals were decoded by the chemical repository only after a determination had been made regarding their mutagenicity or nonmutagenicity.

Results

Carisoprodol treatment did not increase the number of revertants with or without metabolic activation (see Tables below).

NA, without metabolic activation
HLI, hamster liver homogenate induced with Aroclor 1254
RLI, rat liver homogenate induced with Aroclor 1254

NA, without metabolic activation
HLI, hamster liver homogenate induced with Aroclor 1254
RLI, rat liver homogenate induced with Aroclor 1254

Study title: NTP Technical Report on the Toxicity Studies of Carisoprodol (CAS No. 78-44-4) Administered by Gavage to F344/N Rats and B6C3Fl Mice.
NTP (National Toxicology Program). 2000.
Department of Health and Human Services (DHHS). National Toxicology Program (0NTP); Research Triangle Park, North Carolina. Toxicity Report Series, No. 56.
NDA 11-792, SE2 S-041, Vol. 7, p. 3
GLP: yes

Key findings: In genetic toxicity studies, carisoprodol was not mutagenic in *Salmonella typhimurium* with or without metabolic activation and did not induce increases in the frequency of micronuclei in mouse peripheral blood erythrocytes. However, carisoprodol did induce mutations in L5178Y mouse lymphoma cells without metabolic activation, but not with metabolic activation. Results of a sister chromatid exchange test with carisoprodol in cultured Chinese hamster ovary cells were considered equivocal with and without metabolic activation. Chromosomal aberrations in cultured Chinese hamster ovary cells were c1early increased by carisoprodol treatment, particularly in the presence of metabolic activation.

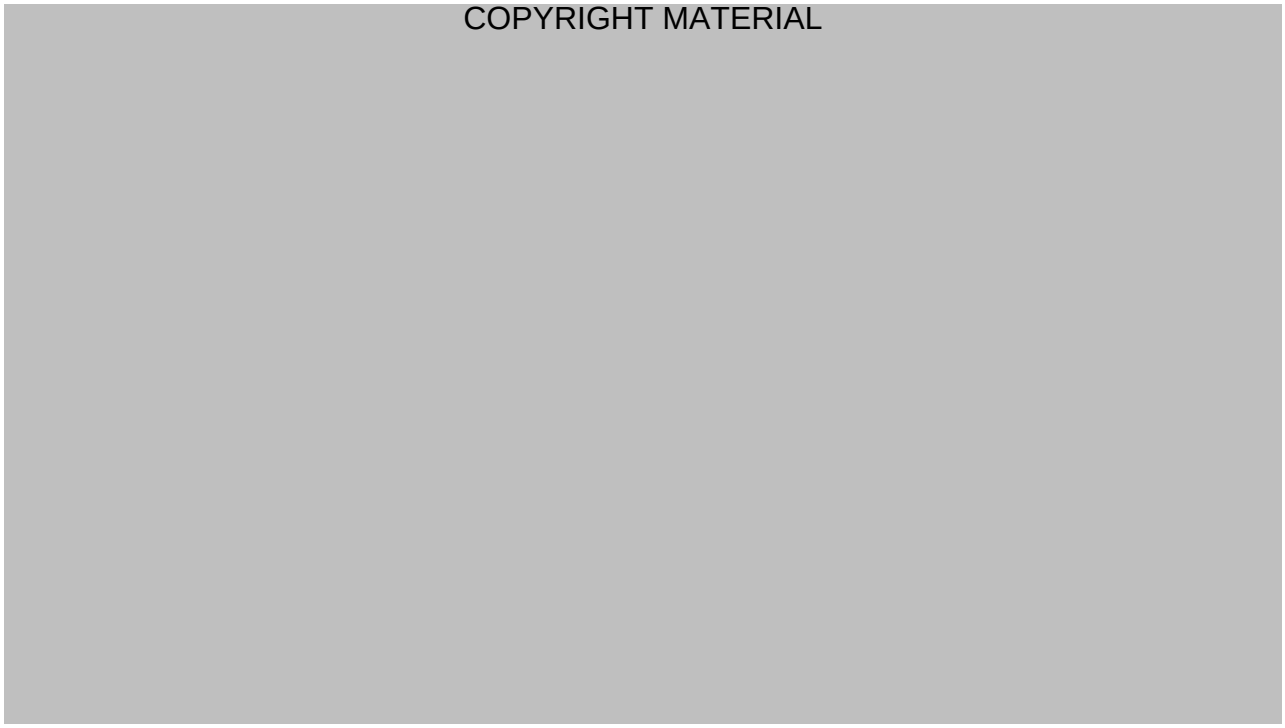
Salmonella typhimurium Mutagenicity Test

Methods
Testing was performed as reported by Zeiger et at. (1987, see above study). Carisoprodol was sent as a coded aliquot from Radian Corporation (Austin, TX) and was incubated with the Salmonella typhimurium tester strains TA98, TA100, TA1535, and TA1537 either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroc1or 1254-induced male Sprague-Dawley rat or Syrian hamster liver) for 20 minutes at 37° C. Top agar supplemented with L-histidine and d-biotin was added, and the contents of the tubes were mixed and poured onto the surfaces of minimal glucose agar plates. Histidine-independent mutant colonies arising on these

plates were counted following incubation for 2 days at 37° C. Each trial consisted of triplicate plates of concurrent positive and negative controls and of five doses of carisoprodol. The high dose was limited by study design to 10,000 µg/plate. All trials were repeated.

In this assay, a positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in anyone strain/activation combination. An equivocal response was defined as an increase in revertants that was not dose related, not reproducible, or not of sufficient magnitude to support a determination of mutagenicity. A negative response was obtained when no increase in revertant colonies was observed following chemical treatment. There was no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

Results
Carisoprodol at doses up to 10,000 µg/plate was not mutagenic in any of four strains of Salmonella typhimurium, with or without S9 metabolic activation. This is the same data that was presented in the previously described study (Ziegler et al., 1987).



Mouse Lymphoma Mutagenicity Test

Methods

The experimental protocol is presented in detail by Myhr et at. (1985). Carisoprodol was supplied as a coded aliquot by Radian Corporation. The high dose of 1,000 µg/mL was determined by its' toxicity. L5178Y mouse lymphoma cells were maintained at 37ºC as suspension cultures in supplemented Fischer's medium; normal cycling time was approximately 10 hours. To reduce the number of spontaneously occurring cells resistant to trif1uorothymdine (TFT) , subcultures were exposed to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day; to medium containing thymidine, hypoxanthine, and glycine for 1 day; and to normal medium for 3 to 5 days. For cloning, the horse serum content was increased and Noble agar was added. All treatment levels within an experiment, except 300 µg/mL with S9 activation, were replicated, including concurrent positive and solvent controls. Treated cultures contained 6 x 10^6 cells in 10 mL medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with carisoprodol continued for 4 hours, at which time the medium plus carisoprodol was removed, and the cells were resuspended in fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, cells were plated in medium and soft agar supplemented with TFT for selection of TFT - resistant cells, and cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37ºC in 5% CO_2 for 10 to 12 days. The test was initially performed without S9. Because a clearly positive response was not obtained, the test was repeated using freshly prepared S9 from the livers of Aroclor 1254-induced male F344 rats.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Caspary et al. (1988). All data were evaluated statistically for trend and peak responses. Both responses had to be significant ($P<0.05$) for carisoprodol to be considered positive, i.e. capable of inducing TFT resistance. A single significant response led to a "questionable" conclusion, and the absence of both a trend and peak response resulted in a "negative" call.

Results

In the L5178Y mouse lymphoma cell assay, small dose-related increases of approximately 2-fold in the number of mutant colonies were observed in thee of four trials conducted in the absence of exogenous metabolic activation (-S9). However, with metabolic activation (+S9), no mutagenic activity was observed. Relative total growth, although depressed at the mutagenic active concentrations, remained at acceptable levels.

Summary of the L5178Y mouse lymphoma cell assay (reviewer created table)

Compound	Concentration* (µg/mL)	Average Mutant Frrequency			
		Trial 1	**Trial 2**	**Trial 3**	**Trial 4**
Without S9					
Ethanol (negative control)		34	42	31	28
Methyl methanesulfonate (positive control)	5	**198**	**608**	**255**	**282**
Carisoprodol	250	30	-	-	-
	300	-	46	26	-
	375	31	-	-	-
	400	-	**65**	40	-
	500	29	**98**	**50**	**50**
	550				42
	600	-	lethal	**63**	**59**
	650	-	-	**-**	**70 (n=1),** (lethal n=1)
	700	-	-	38	**62**
	750	42	-	-	-
	1000	lethal	-	-	-
With S9					
Ethanol (negative control)		62	49		
Methyl cholanthrene (positive control)	2.5	**345**	**437**		
Carisoprodol	200	47	-		
	300	-	49 (n=1)		
	400	39	72		
	500	34	53		
	600	45	29		
	700	49	51		
	800	60 (lethal, n=1)	lethal		
	1000	lethal			

* different doses were used in the individual trials

-, concentration not tested

Bold numbers: positive response ($p \leq 0.05$) versus the solvent control

Chinese Hamster Ovary Cell Cytogenetics: Sister Chromatid Exchange Test

Method

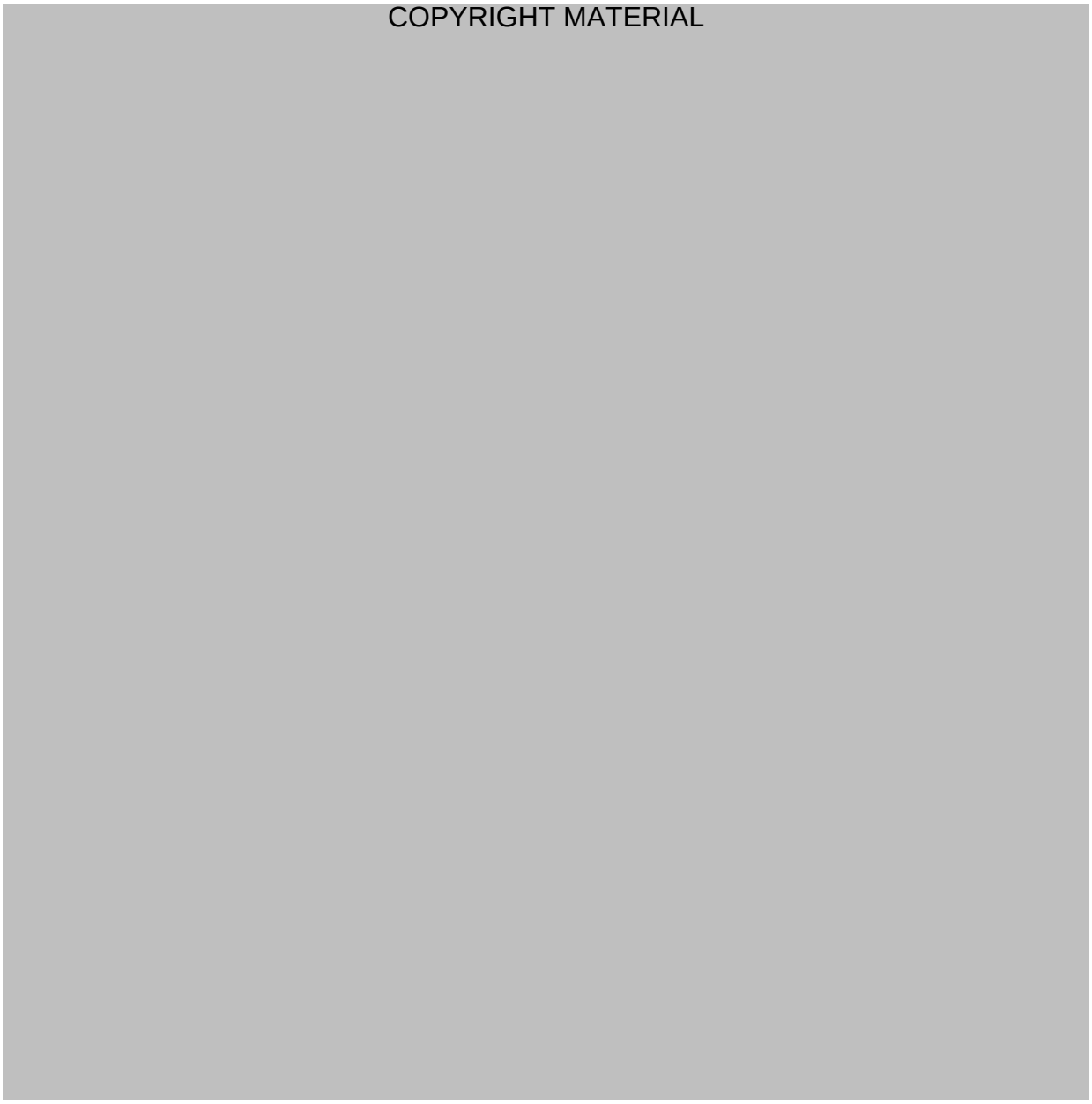
Testing was performed as reported by Galloway et al. (1987). Carisoprodol was sent to the laboratory as a coded aliquot by Radian Corporation. It was tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCE) and chromosomal aberrations (Abs), both in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least four doses of carisoprodol; the high dose was limited by toxicity. A single flask per dose was used.

In the SCE test without S9, CHO cells were incubated for 26 hours with carisoprodol in supplemented McCoy's 5A medium. Bromodeoxyuridine (BrdU) was added 2 hours after culture initiation. After 26 hours, the medium containing carisoprodol was removed and replaced with fresh medium plus BrdU and Colcemid, and incubation was continued for 2 hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with carisoprodol, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no carisoprodol. Incubation proceeded for an additional 27 hours, with Colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells were scored for frequency of SCEs/cell from each dose level. Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points (Galloway et at., 1987).

An SCE frequency 20% above the concurrent solvent control value was conservatively chosen as a statistically positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01, and the probabilty for such a chance occurrence at two dose points is less than 0.001. An increase of 20% or greater at any single dose was considered weak evidence of activity; increases at two or more doses resulted in a determination that the trial was positive. A statistically significant trend ($P<0.005$) in the absence of any responses reaching 20% above background led to a call of equivocal effect.

Results

Results of the sister chromatid exchange test with carisoprodol in cultured Chinese hamster ovary cells were considered equivocal with and without S9.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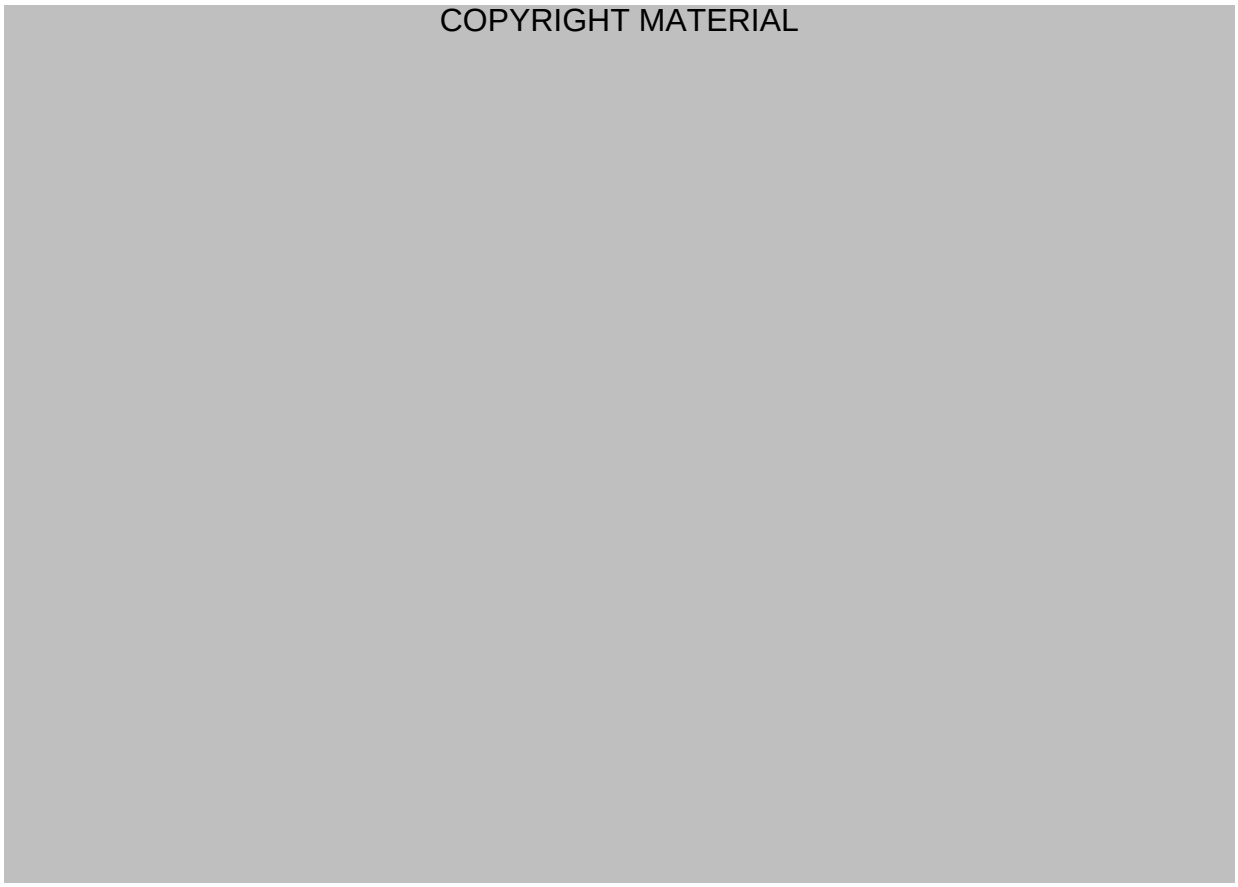


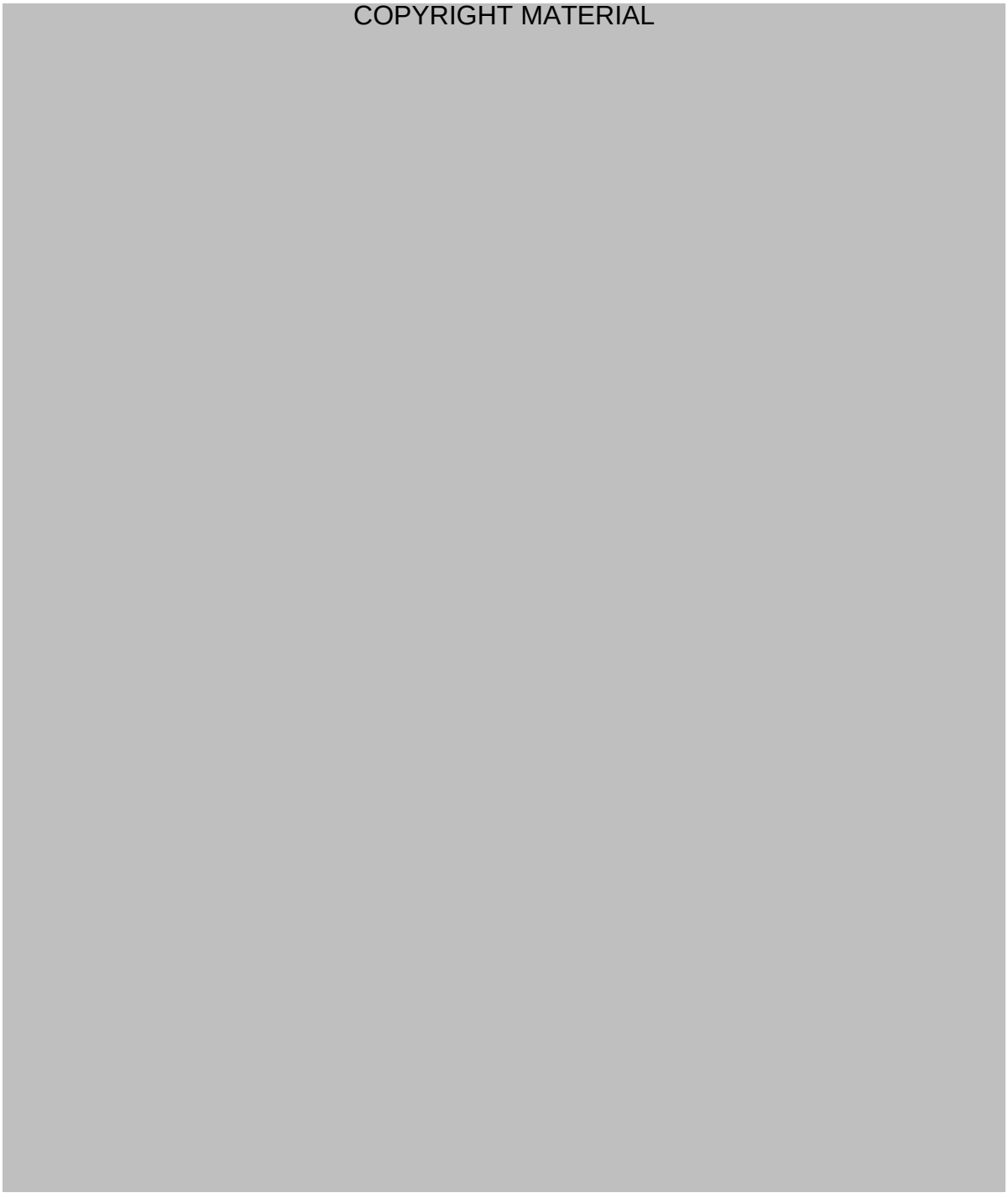
Chinese Hamster Ovary Cell Cytogenetics: Chromosomal Aberrations Test:

Methods

In the chromosomal aberration test without S9, cells were incubated in McCoy's SA medium with carisoprodol for 10 hours; Colcemid was added and incubation continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the test with S9, cells were treated with carisoprodol and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with Colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9. The harvest time was based on the cell cycle information obtained in the SCE test. Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. One hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despira1ized chromosomes, and cells containing 10 or more aberrations). Chromosomal aberration data are presented as percentages of cells with aberrations. To arrive at a statistical call for a trial, analyses were conducted on both the dose response curve and individual dose points. For a single trial, a statistically significant ($P<0.05$) difference for one dose point and a significant trend ($P<0.015$) were considered weak evidence for a positive response; significant differences for two or more doses indicated the trial was positive. A positive trend test in the absence of a statistically significant increase at anyone dose

resulted in an equivocal call (Galloway et al., 1987). Ultimately, the trial calls were based on a consideration of the statistical analyses as well as the biological information available to the study director.

Results
Chromosomal aberrations in cultured Chinese hamster ovary cells were increased by carisoprodol treatment, particularly in the presence of S9.



Mouse Peripheral Blood Micronucleus Test

Methods

A detailed discussion of this assay is presented by MacGregor et al. (1990). At the end of the 13-week toxicity study of carisoprodol in com oil, peripheral blood samples were obtained from male and female mice. Smears were immediately prepared and fixed in absolute methanol. The methanol-fixed slides were stained with a chromatin-specific fluorescent dye mixture of Hoechst 33258/pyronin Y (MacGregor et at., 1983) and coded. Slides were scanned to determine the frequency of micronuclei in 2,000 polychromatic erythrocytes (PCEs) and 10,000 normochromatic erythrocytes (NCEs) in up to 10 animals per dose group. Log transformation of the NCE data, testing for normality by the Shapiro-Wilk test, and testing for heterogeneity of variance by Cochran's test were performed before statistical analyses. The frequency of micronucleated cells among NCEs was determined by analysis of variance with the SAS GLM procedure. The NCE data for each dose group were compared with the concurrent solvent

control by Student's t-test. The frequency of micronucleated cells among PCEs was analyzed by the Cochran-Armitage trend test, and individual dose groups were compared to the concurrent solvent control by Kastenbaum-Bowman's binomial test.

Evaluation Protocol
The basic guidelines for arriving at an overall assay result for assays performed by the National Toxicology Program include both statistical and biological factors. For an individual assay, the statistical procedures for data analysis have been described in the preceding protocols. There have been instances, however, in which multiple aliquots of a chemical were tested in the same assay, and differing results were obtained among aliquots and/or among laboratories. Results from more than one aliquot or from more than one laboratory are not simply combined into an overall result. Rather, all the data are critically evaluated, particularly with regard to pertinent protocol variations, in determining the weight of evidence for an overall conclusion of chemical activity in an assay. In addition to multiple aliquots, the in vitro assays have another variable that must be considered in arriving at an overall test result. In vitro assays are conducted with and without exogenous metabolic activation. Results obtained in the absence of activation are not combined with results obtained in the presence of activation; each testing condition is evaluated separately.

Results
No significant increases in the frequency of micronucleated erythrocytes were observed in peripheral blood samples from male and female mice administered carisoprodol by gavage for 13 weeks.
Reviewer Comment: There was no positive control for genotoxic effects.

Study title: Transformation of BALB/c-3T3 cells: IV. Rank-ordered potency of 24 chemical responses detected in a sensitive new assay procedure

Matthews, E.J.; Spalding, J.W.; Tennant, R .W. 1993.
Environ Health Perspect 101(Suppl. 2):319-345.
NDA 11-792, SE2 S-041, Vol. 6, p. 130
GLP: no

Key findings: Carisoprodol was inactive in the inducing morphological transformation of 1-13 clone of A31 BALB/c-3T3 cells.

Methods
Carisoprodol was one of 24 compounds studied in this improved method of detecting chemical-induced morphological transformation of the 1-13 clone of A31 BALB/c-3T3 cells. This procedure used an increased target cell population to assess chemical-induced damage by increasing the initial seeding density and by delaying the initiation time of chemical treatment. Furthermore, a newly developed co-culture clonal survival assay was used to select chemical doses for the transformation assay. This assay measured the relative cloning efficiency (RCE) of chemical treatments in high-density cell cultures. In addition, transformation assay sensitivity was enhanced through the use of improved methods to solubilize many chemicals. (The BALB/c-3T3 cell transformation assay is generally considered to have low sensitivity for detecting carcinogenic chemicals).

Carisoprodol was dissolved in dimethyl sulfoxide and than diluted in medium supplemented with a noncytotoxic, non ionic surfactant pluronic F68 at 1.25% w/v. The final concentration of the solvent vehicles applied to cell cultures was low and limited to ≤ 0.2% v/v organic solvent and 0.25% w/v pluronic F68.

The positive control for each assay was benzo(a)pyrene (BaP) and it was tested at doses of 0.200 and 0.0633 µg/mL to assess the reproducibilty of dose-related increases of BaP-induced cytotoxic and transforming activities. A total of three to six test chemicals were included in each transformation experiment, and each chemical was tested at four treatment doses in two or more independent trials. The four doses were chosen based on chemical-induced cytotoxic activities detected in the co-culture clonal survival assay. These doses attempted to cover a range of cytotoxic responses of 10-l00% RCE. Test chemical, positive control, and solvent control treatments of cell cultures were performed as described for the standard clonal survival assay. Transformation assay culture vessels were fed biweekly with minimal culture media a total of seven times over 3.5 weeks, and the assays were terminated after a total culture period of 28 days.

The transformation assays in this investigation also included additional components to extend the information obtained from each experiment. Each transformation experiment had concomitant standard and co-culture clonal survival assays. In addition, the transformation assay included seeding density controls (NC-2 and NC-3) of 1.0×10^4 cells/vessel and 3.2×10^3 cells/vessel, respectively. These controls were used to detect crowding effects and preexisting transformed variants that were occasionally detected in transformation assays using wildtype (WT) BALB/c-

3T3 cells. Finally, because each chemical was tested in two or more trials, one active test chemical was used as a second positive control for each experiment and tested along with test chemicals of unknown activity.

A test chemical's activity in a single transformation experiment was evaluated as having one of four possible transformation responses: suffcient positive (SP), limited activity (LA), suffcient negative (SN), and limited negative (LN). An SP transformation response required that a test chemical response was statistically signifcant at two or more consecutive treatment doses. One of the two doses must have been significant at the 99% confidence level ($p \leq 0.01$), but the second dose could have been significant at either the 99% or the 95% confidence level ($0.05 \leq p \leq 0.01$). In addition, the SP response must have included a dose-related increase in activity relative to the experiment solvent control. In contrast to the SP response, a LA transformation response required that a test chemical response was statistically significant at either one treatment dose alone at the 99% confidence level or at two consecutive doses at the 95% confidence level. An SN transformation response required that a test chemical response did not have a statistically significant increase in transformation responses at any of the four treatment doses. Furthermore, one or more of the chemical treatment doses induced a significant cytotoxic response. A significant cytotoxic response is a test chemical treatment dose that resulted in 50% RCE detected in the co-culture clonal survival assay. The cytotoxic responses of chemicals were compared using the concentration in millimoles that resulted in 50% RCE of chemical-treated cells relative to untreated cultures. This LD_{50} treatment dose was extrapolated from graphs of dose-related changes in cytotoxic responses of the chemical detected in the co-culture and the standard clonal survival assays.

An LN transformation response occurred under two different circumstances. First, the four test chemical treatment doses did not induce a statistically significant transformation response; however, in contrast to an SN transformation response, the test chemical treatments did have significant cytotoxic responses. Therefore, higher concentrations of the test chemical could have induced a significant cytotoxic response, and this could have resulted in a statistically significant transformation response. Second, the test chemical had the equivalent of an SN transformation response; however, the positive control for the transformation experiment was inactive and did not induce a statistically significant response.

Spontaneous and BaP-induced transformation responses of this clone of BALB/c-3T3 cells have been shown to include a continuum of type I, II, and III foci of different sizes. The number of type III foci were identified microscopically according to published criteria. Type III foci ≥ 2 mm in diameter had three phenotypic properties, including pilling and overlapping of cells, disorientation of cells at the periphery of the focus, and invasion of transformed cells into a contact-inhibited monolayer of WT cells. Type I and II foci of BALB/c-3T3 cells were also recorded and appeared in many different sizes, but they lacked the combination of three phenotypic properties previously noted for the type III transformed focus. This report presented only the type III focus data for the test chemicals.

Results

Carisoprodol was a moderately cytotoxic chemical with an average LD_{50} of 3.33 mM. The statistical sensitivities of trials 1 and 2 were 88 and 34/110, respectively; the detection sensitivities for BaP of trials 1 and 2 were 77 and 45/110, respectively. Carisoprodol was evaluated as inactive in the transformation assay. For other compounds, all the positive responses were detected in the absence of an exogenous activation system and exhibited significant activity at two or more consecutive doses.

MEPROBAMATE STUDIES

Study title: Detection of chemical mutagens by the dominant lethal assay in the mouse
Epstein, S.S.;Arnold, E.; Andrea, J.; Bass,W .; Bishop, Y. 1972.
Toxicol Appl Pharmacol 23:288-325.
NDA 11-792, SE2 S-041, Vol. 5, p. 215
GLP: no, (conducted before GLP was established)

Key findings: In the dominant lethal assay in mice, there was no significant effect of meprobamate at intraperitoneal doses of 80 or 400 mg/kg.

Methods
This study examined the effects of 174 compounds, including the carisoprodol metabolite meprobamate, in mice in a modified dominant lethal assay.

Background: The genetic basis for dominant lethality is mainly the induction of structural and numerical chromosomal anomalies such as translocations and aneuploidies that may induce preimplantation losses of nonviable zygotes, early fetal deaths and sterility and semisterility in F_1 progeny. In the dominant lethal assay, male mice are dosed singly with subtoxic concentration of the test substance. Then, they are mated during sequential weekly periods with groups of untreated virgin females. Matings in weeks 1-3, 4-5 and 6-8 following treatment in male mice represent samplings of postmeiotic, meiotic and premeiotic stages of spermatogenesis, respectively. Female mice are inspected daily for vaginal plugs and on day 12 or 13 of pregnancy, scored for corpora lutea and for total implants, comprising early and late fetal deaths and living fetuses.

Meprobamate was administered IP at 80 mg/kg to 7 male mice (ICR/Ha Swiss) and 400 mg/kg to 9 male mice. They were mated for 8 weeks. In the modified assay used here, daily vaginal plug inspection and corpora luteal counts were eliminated, and the total implants were compared between groups of treated and control animals.

Results
There were no deaths. There were no significant effects of meprobamate at intraperitoneal doses of 80 or 400 mg/kg on reproductive parameters examined.

Results of the assay for each compound were compared the concurrent controls. For the controls, the mean weekly pregnancy rate was 66% and exceeded 30% in 99% of all weeks; the distribution of weekly mean total implants per pregnancy was symmetrical around a peak of 11.5-11.9 and was never less than 8; mean early fetal deaths per pregnancy were <0.95 in 99.6% of weeks and their distribution was highly asymmetrical. Less than 10% of all agents tested were unequivocally mutagenic as determined directly by increased early fetal deaths per pregnancy and in some instances, also indirectly by reduction in total implants per pregnancy; the majority of these were known alkylating agents. About 5% of all compounds tested yielded data which fell beyond control limits and which were significantly at <5% by analysis of variance, but which however require further replication because of internal inconsistencies.

Reviewer's Comment: There was no data for meprobamate presented. It was not clear if meprobamate was administered as a solution in distilled water or in tricaprylin. This is not considered an adequate test of genotoxicity, without additional information such as its concentration within the blood-testis barrier. Without this information, a negative test

Study title: Formation of nitroso compounds and mutagens from tranquilizers by drug/nitrite interaction

Takeda,Y.; Kanaya, H . 1981.
Cancer Lett 12:81-86.
NDA 11-792, SE2 S-041, Vol. 7, p. 143
GLP: no

Key findings: Meprobamate reacted with nitrite to form 0.8 mole percent of nitroso compounds (lowest yield of the 14 compounds tested). In mutagenicity tests of the nitrosation product, it was equivocal in assays with TA98 and TA100 with or without metabolic activation. The parent compound meprobamate was not mutagenic at concentrations of 0.8-8 µmol/plate.

Methods
The formation of nitroso compounds and mutagens by drug/nitrite interaction was screened for 14 tranquilizers. Mutagenicity of the reaction product and parent was then tested by the Ames assay using *Salmonella typhimurium* strains TA98 and TA100.

The pulveried pharmaceutical preparation containing 0.1 mmol of the drug and 1.0 mmol of sodium nitrite was added to 2 ml of water. The final concentration of the drug was 0.05 M and that of nitrite was 0.5 M. 3.0-3.5 by the addition of diluted hydrochloric acid, the tube was stoppered and shaken in a 37°C water bath for 4 h. After the tube was placed in an ice bath, 0.5 ml of 2 M ammonium sulfamate was added to the reaction mixture in order to decompose the residual nitrite. After standing for 10 min in an ice bath, no residual nitrite was detected in the reaction mixture by Griess reagent. An aliquot of the reaction mixture (0.5 ml) was taken for the determination of nitroso compounds. The remainder was centrifuged (3000 rev./min, 10 min) and the supernatant (aqueous extract) was pipetted off. The precipitate was extracted with 1 ml of dimethylsulfoxide (DM80 extract).

Strains/species/cell line:
The Griess reagent-positive substance formed by the treatment with hydrogen bromide in glacial acetic acid was determined colorimetrically according to the method of Eisenbrand and Preussmann (3). Results were converted to N-nitrosodimethylamine equivalents and the yields of nitroso compounds based on the parent drugs were shown as mole per cent (Nnitrosodimethylamine equivalents).

Mutagenicity of the reaction product and parent was then tested by the Ames assay using Salmonella typhimurium strains TA98 and TA100 in the plate-incorporation method. The sample (aqueous extract or DMS0 extract) and 0.1 ml of tester strain suspension were mixed with 0.5 ml of S9 Mix or 0.2 M phosphate buffer (pH 7.4). The mixture was incubated for 20 min at 37°C, before addition of the soft agar.

Mutagenicity of the sample, assayed in a range of 0.8-8 µmol parent drug/plate, was evaluated from the slope of the linear portion of a dose response curve and represented by the number of revertant colonies per 1 µmol of the parent drug.

Results
Meprobamate reacted with nitrite to form 0.8 mole percent of nitroso compounds (lowest yield of the 14 compounds tested). The number of spontaneous revertant colonies of negative controls are indicated in the table below. The parent drug was not mutagenic in a range of 0.8-8 µmol/plate. The nitrosation product from reaction with meprobamate was equivocal (indicated as '±' in the data Table 2 of the article).

Negative control values

Salmonella typhimurium strain	Metabolic activation	Number of revertant colonies
TA98	-S9	15
	+S9	30
TA100	-S9	110
	+S9	120

Reviewer's Comment: Only the negative control data was presented, no data was presented for meprobamate or its nitrosation product.

2.6.6.5 Carcinogenicity

No carcinogenicity studies were conducted by the Sponsor or found in the literature. A 2-year carcinogenicity study, C56235C, was listed for study on the NTP website under carisoprodol studies, but is was apparently cancelled. Carisoprodol will be labeled for short-term use, less than 3 weeks duration.

The Sponsor's proposed carcinogenicity labeling:

(b) (4)

Reviewer's Comment: The above is based on chronic toxicology studies. This does not address the carcinogenic potential, which is most often apparent during the second year of the lifetime (2-year) continuous treatment in rodent studies. The recommendation is therefore to replace the above label with: "The carcinogenic potential of carisoprodol has not been studied."

2.6.6.6 Reproductive and developmental toxicology

Study title: Final Report on the Reproductive Toxicity of Carsoprodol (Cas No. 78-44-4) in CD-1 Swiss Mice

Key Findings: Overall, the NOAEL for reproductive and general toxicity in F_0 animals was 750 mg/kg/day, based on mild reproductive and developmental toxicity observed at 1200 mg/kg/day including decreased pup weight and alterations in the estrus cycle. In the F_1 animals, the NOAEL was 300 mg/kg/day based on decreased postnatal survival and weight gain noted at 750 and 1200 mg/kg/day. A mating trial to determine the fertility and reproductive competence of the F_1 generation showed no effect of carisoprodol on indices of mating, pregnancy, or fertility, the proportion of F_2 pups born alive, the sex ratio of live F_2 pups, live F_2 pup weight, or gestation length. However, decreased live litter size and weight were also noted for litters of the high-dose F_1 generation.

NTP (National Toxicology Program) 1991
Research Triangle Inst.; Research Triangle Park, NC. (PB92-128404; DART/TER/94000390).
NDA 11-792, SE2 S-041, Vol. 6, p. 168
GLP: yes

Grizzle et al., study directors associated with the NTP 1991 study, published the following article using the NTP 1991 data:

Grizzle TB, George JD, Fail PA, Heindel JJ. 1995.
Carisoprodol: Reproductive assessment by continuous breeding in Swiss mice.
Fundam Appl Toxicol 24(1):132-139.
NDA 11-792, SE2 S-041, Vol. 5, p. 269

Some of the data presented in the NTP 1991 report are summarized in more concise tables than in NTP 1991 report and are presented here.

OVERALL STUDY DESIGN

Carisoprodol was evaluated for reproductive toxicity in CD-1 (Swiss) mice using the Reproductive Assessment by Continuous Breeding Protocol which consisted of 4 segments (or "tasks", the term used in the published articles) as indicated here:

1) a dose range-finding phase (optional)
2) a F_0 cohabitation and lactation phase
3) a crossover mating trial for the F_0 generation (conducted if F_0 reproductive performance is affected),
4) a final phase assessing fertility of the F_1, generation (born and reared during the F_0 lactation phase),

Drug:

Carisoprodol, Lot 58764, Purity 99.5%; (CAS No. 78-44-4, from Carter Wallace, Inc., New York. NY)
Vehicle: Mazola corn oil

Doses were administered once daily by oral gavage at 10 mL/kg
There was no discernible change in purity during the study.
Carisoprodol in the stock solutions ranged between 92 and 129% of the expected level.

Animals

CD-1 (ICR)BR outbred Swiss albino mice, 6 weeks old at arrival

DOSE RANGING STUDY

Methods

A dose ranging study was conducted to determine dose levels for the main study. In the dose ranging study, mice (8/sex/group, 8 weeks of age) were administered carisoprodol by oral gavage for 2 weeks at doses of 0, 100, 300, 600, 900, or 1,200 mg/kg/day. Animals were cohabited during the 2nd week of dosing and females were checked daily for vaginal copulatory plugs. At the end of week 2 all animals were terminated with no further data collection.

Results

There were no treatment-related deaths. Initially, clinical signs included transient sedation at the 900 and 1200 mg/kg/day doses within 5 to 10 minutes of dosing and lasting for several hours. By the second week of exposure only high-dose animals exhibited transient sedation and for a much shorter duration.

There was no effect on the time to mating (detected by presence of vaginal copulatory plug). There were no changes in body weight. Male food consumption during week 1 and combined water consumption during week 2 tended to increase with dose (up to 50% for food and 34% for water). Based on these effects, the maximum tolerated dose was initially estimated to be 1,500 mg/kg/day.

TASK 2: CONTINUOUS F_0 COHABITATION AND LACTATION PHASE

Methods

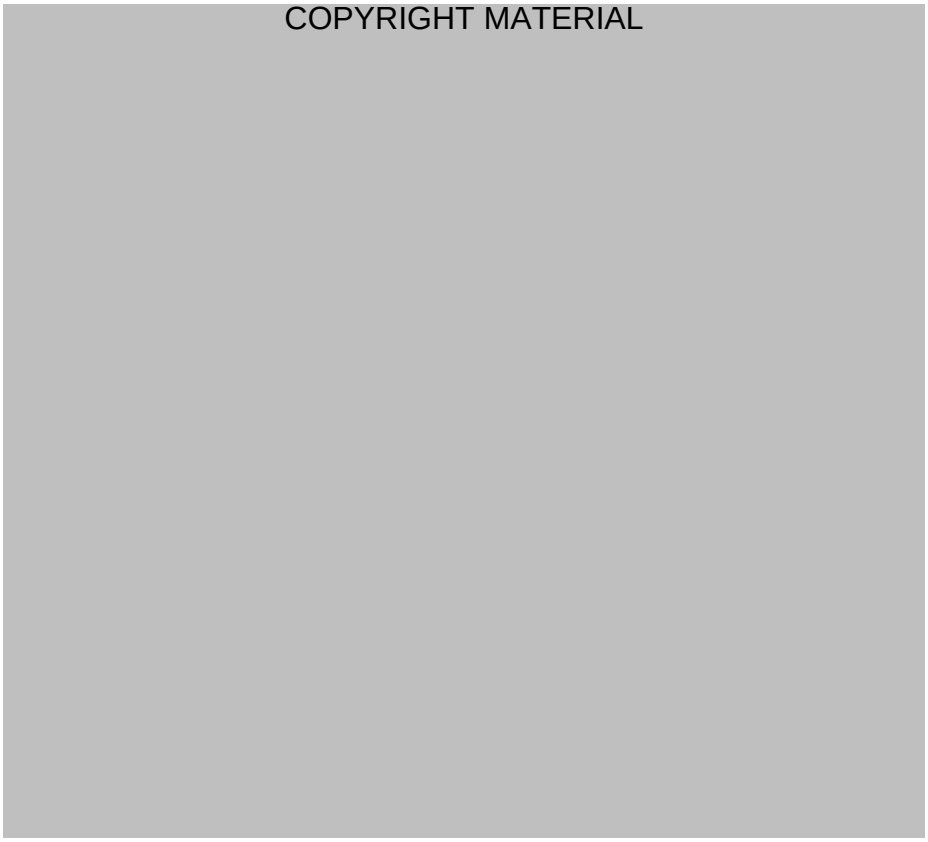
Mice (n=40 for vehicle or 20 for carisoprodol/sex/dose, 11 weeks of age) were administered daily doses of 0, 300, 750, and 1500 mg/kg/day. After the first administration of the 1500 mg/kg dose, excessive lethality 7/40 of undetermined causes and sedation 10/33 occurred. Dead mice were replaced and the high dose was reduced to 1200 mg/kg/day for the duration of the study. Feed and water consumption was monitored during treatment weeks 1, 3, 5, 9, 13, and l8. During week 1, the sexes were segregated and housed two per cage by dose group. During weeks 2 through 15, animals were housed in breeding pairs within dose groups, and newborn litters were euthanized immediately after evaluation. Starting at week 16, the breeing pairs were separated, and F_0 females were allowed to deliver and rear the final litter until Postnatal Day (PND) 21. On PND 0, 4, 7, 14, and 21, pups were sexed, counted, and weighed. On PND 21, up to 4 randomly selected F_1 pups (two males and two females) from each litter were weaned and housed in same sex pairs by dose and reared for the F_1 fertility assessment phase. Low- and mid-dose F_0 females were humanely killed shortly after the litters were weaned, and F_0 males from these dose groups were humanely killed during week 17.

Results
Mortalities and their cause during the entire study, if determined, are indicated in the reviewer's table below.

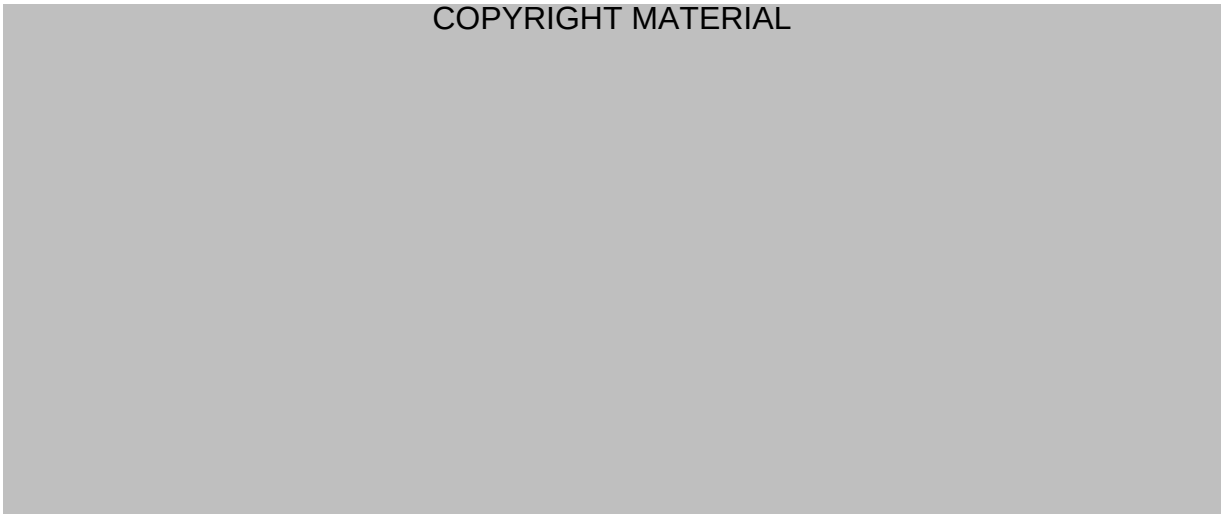
Mortalities

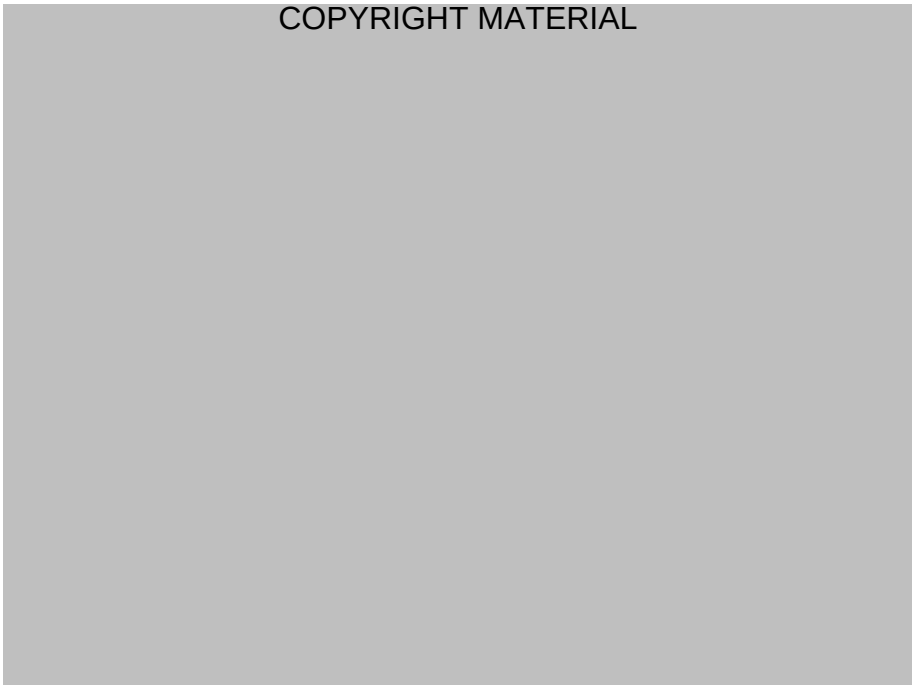
Dose (mg/kg/day)	**0**		**300**		**750**		**1200**	
Gender	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
N	**40**	**40**	**20**	**20**	**20**	**20**	**20**	**20**
F_0 Mortality (29 weeks) known causes indicated (n)	1 (2%)	3 (7.5%) Dystocia (1) Coronary hemorrhage (1)	0 (0%)	1 (5%)	1 (5%)	1 (5%)	9 (45%) Urinary obstruction (1)	4 (20%).
Removed from study due to gavage injuries , cagemate trauma, flooded cages	12		2		8		8	
F_1 Mortality (PND 21 to day 74 ± 10) Unknown cause	2		2		4		5	
Removed from study due to gavage injuries	15		13		7		8	

Indications of generalized toxicity in the F_0 animals included sedation or lethargy, primarily in the 1200 mg/kg/day group during the first 3 to 4 weeks of dosing, after which the incidence and severity of this effect abated. Females in the 1200 mg/kg/day group had reduced body weights (up to 17%) from weeks 3 through week 18, and males had a decreasing linear trend of weight loss.



During 14 weeks of cohabitation, there was no effect of carisoprodol treatment on estrous cyclicity or the ability of the F_0 animals to produce litters. However, in the 1200 mg/kg dose group, there was a decreased proportion of pups born alive (4%) and absolute (5%) and adjusted live pup weight (7%) compared to controls. There was no effect on fertility, number of litters per pair, number of live pups/litter, sex ratio of pups, or the cumulative days to litter. During the lactation period, there was reduced postnatal survival in the 750 and 1200 mg/kg dose groups and decreasing linear trend for survival at PND 4, 7, 14, and 21. Pup weights were also decreased at all carisoprodol dose groups during the lactation period.





Examination at necropsy at the end of the 27 week period, indicated no effect of the 1200 mg/kg/day dose on sperm concentration, motility, or morphology, although epididymis weight was greater than the control. Males in the 1200 mg/kg dose also had greater liver weights. Females at this dose had decreased absolute but not relative kidney/adrenal weight than controls. However, there was no histopathological findings in the kidney, liver, or reproductive organs in either males or females in the 1200 mg/kg/day dose group.

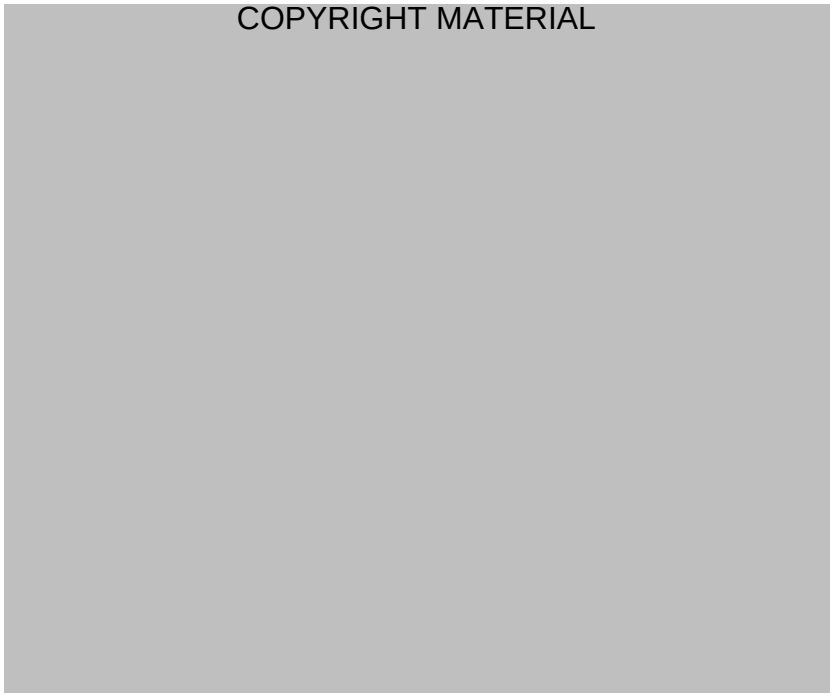
TASK 3: CROSSOVER MATING TRIAL FOR THE F_0 GENERATION

Methods

Since a small effect on reproductive function was deteced during the F_0 cohabitation phase, a crossover mating trial (to determine the affected sex) was performed during Week 23 of treatment on parental animals from the control and 1200 mg/kg groups. Three breeding groups were created: control male x control female, control male x 1200 mg/kg female, and 1200 mg/kg male x control female. During the 1-week mating trial, carisoprodol was not administered. After collection of litter data, at week 27 of carisoprodol exposure, vaginal smears were collected from F_0 females for 12 days. At Week 29, immediately following CO_2 asphyxiation, F_0 males and females were weighed and necropsied. Weights from liver, paired kidney with attached adrenal, right testes, right epididymis, prostate, seminal vesicles with coagulating glands (glandular secretions not removed), and right ovary with attached oviduct were weighed. Evaluations of right epididymis sperm included motility, concentration, and morphology. Spermatids were evaluated in the right testes after the tunica albuguinea was removed and tesis homogenized in ice cold phosphate buffered saline. Histopathologcal evaluations of the control and 1200 mg/kg mice were conducted on all livers, right and left kidneys and adrenals, the right tesis and epididymis, prostate, seminal vesicles, ovary, uterus, and any gross lesions noted during the necropsy.

Results
Evaluation of the control and 1200 mg/kg/day dose groups in the crossover mating segment (to identify the affected sex), found no effect of carisoprodol on any measure of reproductive function.

After 27 weeks of dosing, evaluation of the 12 days of vaginal smears revealed that carisoprodol at the 1200 mg/kg/day dose increased the proportion of time spent in proestrus and estrus compared to controls, but total estrus cycle length was unaffected.



Examination of the F_0 mice at necropsy during week 29 (40 weeks of age) slightly reduced 1200 mg/kg male body weight (7%). Males in the 1200 mg/kg dose also had greater liver weights (23%) than the control. There was also no effect of the 1200 mg/kg/day dose on sperm concentration, motility, or morphology, although right epididymis weight was greater (12%) than the control. Females at this dose also had reduced body weight (8%) and decreased absolute but not relative kidney/adrenal weight compared to controls. However, there were no histopathological findings in the kidney, liver, or reproductive organs in either males or females in the 1200 mg/kg/day dose group.

TASK 4: FERTILITY OF THE F_1 GENERATION

Methods
This was a trial to determine the fertility and reproductive competence of the second generation (F_1 animals). It was conducted with the final offspring of all groups.

At weaning (PND 21), randomly selected F_1 pups from all dose groups were housed 2 per cage by sex within dose group. Carisoprodol was administered by oral gavage on PND 22 and continued until necropsy (119 ± 10 days of age). At 74 ± 10 days of age, 20 males and 20 females per dose group were cohabited as nonsibling breeing pairs until a vaginal copulatory plug was observed or for 1 week, whichever occurred first. Litter data resulting from the F_1 cohabitation were collected. After delivery of the F_2 litters, vaginal smears were collected for 12 days. Feed and water consumption were measured at 77 ± 10 (mating), 84 ± 10, 91 ± 10, and 98 ± 10 (gestation) days of age during the F_1 fertilty assessment period.

At the necropsy (119 ± 10 days of age), following CO2, ashyxiation, F_1 males and females were weighed and data collected as previously described for F_0 animals. Histopathological evaluations were conducted on all livers, right and left kidneys and adrenals, the right testis and epididymis, ovary, uterus, and any gross lesions noted during the necropsy.

Results
The number of F_2 pups per litter was reduced by 22% in the 1200 mg/kg group. F_2 pup weights, when adjusted for litter size, were reduced (8%) in the high-dose group compared to controls.

PND 0 dam weights were decreased in the low- (6%) and high-dose (7%) groups. High-dose feed consumption was increaed for both males (up to 21%) and females (up to 16%) at all time points except mid-gestation for females, whereas mid-dose feed consumption was transiently increased for males (up to 11%) and females (up to 13%). Mid- and high-dose water consumption was transiently increased (up to 14%) in males. Evaluation of 12 days of vaginal smears collected immediately prior to necropsy showed no significant differences between contro and carisorprodol treated females.

At the F_1 necropsy (119 ± 10 days of age), 300 mg/kg females and 750 and 1200 mg/kg females and males reduced body weights (<10%). Increased relative liver weights occurred in females of all dose groups (up to 18%) and in males of the the mid and high doses (up to 23%). Spermatid counts in whole testis homogenates were reduced (up to 21%) in all 3 dose groups. However, epididymal sperm evaluation of motility, morphology, and concentration were not affected. There were no effects on testis weight and histopathology.

TERATOLOGY STUDY IN RATS

In 2 separate studies, Wistar rats were administered carisoprodol in water by oral gavage every 4 hours during the day cycle of Days 7 through 13 of presumed gestation for total doses of 0, 20, 200, or 400 mg/kg/day (Blicharski et al., 2001, 2002). Dams were terminated and caesarean sections were performed on Day 21. In one study (Blicharski et al., 2001), fetuses were evaluated for soft tissue alterations; in the other study (Blicharski et aI., 2002) fetuses were evaluated for skeletal alterations. The results indicated no significant developmental abnormalities of soft or skeletal tissues. There were no effects on the dams in the skeletal study, while effects on dams were not specified in the other study.
Reviewer's Comment: There was little data presented in these studies, one of which was just an abstract. The dams were not likely dosed to the maximum tolerated dose since no effects on the

dams were observed in one of the studies. There is insufficient information provided for these teratology studies to be used in labeling.

Blicharski, T.; Burdan, F.; Maelkiewicz, J.; Piechota, G. 2001.
Histological examination of visceral organs in rat foetuses exposed in utero to carisoprodol.
Front Fetal Health 3(11&12):286 [Abstract No. P-6].
NDA 11-792, SE2 S-041, Vol. 5, p. 136
GLP: no

Method
Pregnant females rats (n=10/dose) were orally administered, every 4 hours from day 7 to day 13, carisoprodol at doses of 0 (distilled water) mg/kg/24h, 20 mg/kg/24h, 200 mg/kg/24h, or 400 mg/kg/24h. The body weight gain of the dams was monitored on day 1, 8, 15, and 21 of pregnancy. The dams were sacrificed and caesarean sections were performed on day 21 of gestation. The number of implantations, living and dead fetuses were counted. Fetuses were separated from placenta and macroscopically examined for external malformation. The evaluation of birth defects of internal organs was carried out with serial histological slice examination after hematoxylin and eosin, PAS and Masson staining. The data were analyzed statistically by Mann-Whitney test.

Result
There were no developmental abnormalities of soft tissues.

***Reviewer's comment*:** In this abstract, no data was presented.

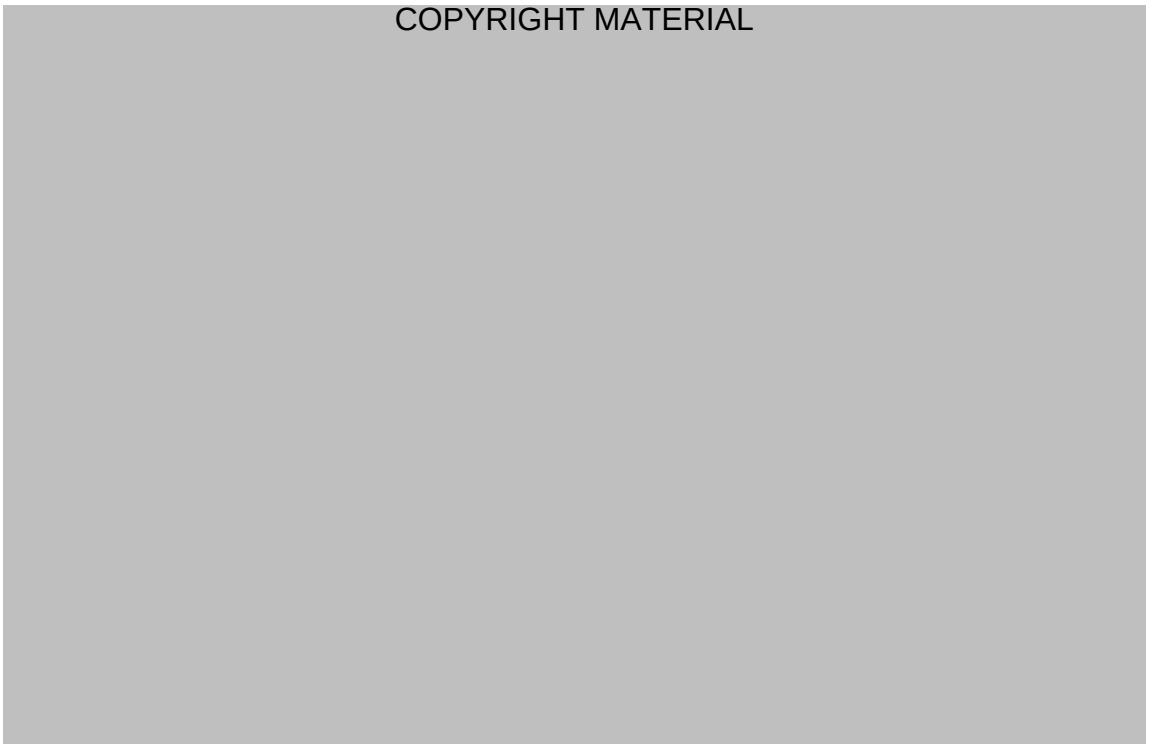
Blicharski, T.; Burdan, F.; Malkiewicz, J.; Piechota, G. 2002.
Blockade of reticular formation activity, due to carisoprodol maternal administration, and its effects on rat skeleton development.
Ann Univ Mariae Curie Sklodowska [Med] 57(1):143-149.
NDA 11-792, SE2 S-041, Vol. 5, p. 138
GLP: no

Method
Carisoprodol was administered to Wistar rats (n=10/dose group) three times a day(every 4 hours, diluted in distilled water) by stomach tube from day 7 to day 13 of pregnancy at doses of 0 (distilled water)/mg/kg/24 h, 20 mg/kg/24h, 200 mg/kg/24h, or 400 mg/kg/24h. The fetuses obtained on day 21 of gestation were counted and macroscopically examined. Placental and fetal weight, fetal and tail length were examined and measured. After fixation in 95% ethanol the fetuses were stained under single alizarin red and examined.

Results
The macroscopic examination of 407 fetuses did not revealed any malformations in drug treated and control groups, except for an insignificant number of subcutaneous haematomas, which were found on interscapular region in group 200 and 400 mg/kg/24h dose groups. Morphological

examination revealed no major malformations. No statistical differences between carisoprodol-exposed groups and control one in fetal parameters such as body weight, body length, tail length were noted. A number of subcutaneous ecchymoses and various skeleton anomalies were observed, but there were no significant differences between treatment groups. Thus at these doses, carisoprodol did affect skeleton development.

The examination of alizarin-stained specimens showed insignificant number of reduction of ossification in crania-facial bones, as well as the other skeleton anomalies. The ribs, especially the last pair were the most often malformed part of the fetal skeleton. The wavy 13th ribs were observed in all the examined groups, including the control one. However, the shorter 13th rib was seen only in fetus from control and 400 mg/kg/24h group. Single bud or short extra lumbar unilateral ribs occurred in control group as well as in the 20 mg/kg/24h group. Missing, rudimentary, cleaved, and bifurcated distal end form of sternebrae were seen in drug-treated and control groups. Occasionally missing and reduced alizarin staining of metacarpal and metatarsal bones were found in carisoprodol-treated as well as control groups. Different degrees of phalanges classification were also noted. No other anomalies of appendicular skeleton formation were seen.



***Reviewer's Comment*:** Both of these tetratology studies are inadequate to support product labeling, lacking appropriate data and analysis.

Reproductive and Developmental Toxicology

Study (Reference)	Species	Dose (mg/kg/day)	Findings / (comments)
NTP, 1988	Mouse, B6C3F$_1$ Rats, 344/N Males and females 5/sex/dose	0, 75, 150, 300, 600, 1200 mg/kg; oral gavage; for 90 days rats: 0, 600, 1200, 1600 mg/kg	No effect on female reproductive parameters Relative right testis weight was decreased at 75. 180. 300. and 1200 mg/kg/day Body weight gain was significantly greater than controls in the male mice receiving 150 and 300 mg/kg/day and in female mice receiving 150, 300. and 600 mg/kg/day. Relative liver weight was increased in both male at doses >300 and female mice >150 mg/kg/day
Fertility and early embryonic development---Dose ranging study			
NTP, 1991 (GLP) Grizzle et al., 1995 (same study as NTP, 1991) Heindel et al., 1997 (summary of the NTP 1991 study)	Mouse (Swiss CD-1) (8/sex/group)	0, 100, 300, 600, 900, 1200 oral gavage; daily for 2 weeks; 1 week premating and 1 week cohabitation Vehicle: corn oil	Prelim study Max tolerated dose 1500 mg/kg lowered after 1 dose to 1200 mg/kg Initially, clinical signs included transient sedation at the 2 highest doses within 5 to 10 minutes of dosing and lasting for several hours. By the 2nd week of exposure only high-dose animals exhibited transient sedation and for a much shorter duration. (the authors that tolerance developed to the sedative effects due to faster metabolism to meprobamate and/or of meprobamate).
Embryofetal development and Prenatal and postnatal development combined study			
NTP, 1991 (GLP) Grizzle et al., 1995 (same study as NTP, 1991) Heindel et al., 1997 (summary of the NTP 1991 study)	Mouse (Swiss CD-1) 8/sex/dose Housed in breeding pairs during weeks 2 to 15 Newborn litters were terminated immediately after evaluation. At week 16, the pairs were segregated and the Fo females were allowed to deliver and rear the final litter	F_0 and F_1: 0, 300, 750, 1200 oral gavage; Vehicle: corn oil Control and high-dose groups dosed daily from 11 weeks of age for 29 weeks; low- and mid-dose females were terminated shortly after the litters were weaned and low- and mid-dose males were terminated during Week 17; F1: treated from postnatal day 22	Overall, the NOAEL for reproductive and general toxicity in F_0 animals was 750 mg/kg/day, based on mild reproductive and developmental toxicity observed at 1200 mg/kg/day including decreased pup weight and alterations in the estrus cycle. In the F_1 animals, the NOAEL was 300 mg/kg/day based on decreased postnatal survival and weight gain noted at 750 and 1200 mg/kg/day. Decreased live litter size and weight were also noted for litters of the high-dose F_1 generation. See detailed description below.

	until post-natal day (PND) 2	until 119 (± 10) days of age	

During the 29 weeks of study with the animals there were
F_0 deaths observed as follows:
4 control; 1 300 mg/kg/day; 2 750 mg/kg/day; and 14 1200 mg/kg/day
causes of death were dystocia (1 control), coronary hemorrhage (l control female), urinary obstruction (l high-dose male), or indeterminate causes. Twelve controls, 2 low-, 8 mid-, and 8 high-dose animals were removed from the study due to gavage-related injuries, cage mate inflicted fatal trauma, or flooded cages.

Carsoprodol resulted in:
Transient sedation in the 1200 mg/kg/day group for the first 3 to 4 weeks of dosing, after which the incidence and severity of this effect abated.
Reduced body weights (up to 17%) in high-dose females from week 3 through 18
Increased feed and water consumption in the high-dose animals (up to 18% for feed and 17% for water)
Reduced dam weight at delivery in the high dose females was reduced at the fourth and fifth litters (by 6 and 7%, respectively).
7% reduction in pup weight adjusted for litter size.
Decreased proportion of total pups born alive and the combined and adjusted live pup weights in the 1200 mg/kg/day group
No effect on fertility, the number of litters per pair, the number of live pups per litter, the sex ratio of pups, or the cumulative days to litter.

During the lactation period:
Reduced average postnatal survival for mid- and high-dose groups, decreasing linear trend at PND 4, 7, 14, and 21
Transiently decreased pup weights (up to 14% for males and 15% for females) in all 3 dose groups

The crossover mating trial:
No effect on any measure of reproductive performance
High dose females spend more time in proestrus and estrus (based on vaginal smears) , **but did not altered total estrus cycle length**

F_0 necropsy, week 29:
Males:
increased liver weights (23%)
increased right epididymis weight relative to body weights (11 %)
Females:
reduced body weight in high dose (16%)
reduced absolute kidney/adrenal weights in high dose
No treatment-related histopathology was observed for either sex.

F_1 maturation period and ferilty assessment:
Deaths: 2 control, 2 low-, 4 mid-, and 5 high-dose animals; indeterminate causes.
gavage incidents: removal of 15 control, 13 low-, 7 mid-, and 9 high-dose animals
Feed and water consumption by the F_1 adults was increased by 12 to 20% in the middle and high dose groups, respectively.
F_1 pups per litter was reduced by 22% in the high-dose group
F_1 pup weights, when adjusted for litter size, were reduced (8%) in the high-dose group

Adult F_1 necropsy,

	Female body weights were reduced by 5, 6, and 8% (low to high dose levels), respectively Relative liver weights were increased by 8, 13, 18%, respectively. Male body weights were reduced in the middle and high dose groups by 6 and 9%, respectively. Adjusted liver weights in those same groups of males were increased by 10 and 20%, respectively **Right testis weight was reduced by 12% at the high dose level.** **Spermatid counts in whole testis homogenates were reduced (up to 21%) in all 3 dose groups**. No other sperm parameters were affected. **F_2**: F_2 pups were reared by their dams until weaning, when they began receiving the same dose of CAR administered to their parents. During the nursing period, there was **increased mortality of female pups in the middle dose group only**, to a maximum of 13% loss of pups. **Body weight at weaning was reduced by 11 % (all treated females) and 12% (high dose males).**		
Teratology			
Blicharski et al. 2001, 2002	Rat (Wistar), females	0, 20, 200, 400 total daily dose; oral gavage; (dosed every 4 hours); gestation day 7 through 13 Vehicle: water	Day 21 ceasarean section and fetal analysis: No soft tissue or skeletal alterations (no effect on dams in skeletal study of 2002; not mention effects on dams in soft tissue study of 2001) (**Not dosed to max tolerated dose: no maternal toxicity**)

2.6.6.7 Local tolerance

No information submitted

2.6.6.7 Local tolerance

No information submitted

2.6.6.8 Special toxicology studies

No information submitted

2.6.6.9 Discussion and Conclusions

Many of the toxicological studies were conducted prior to the implementation of GLP. Due to the known genotoxic and embryotoxicity of other carbamate containing compounds and the potential abuse potential of these drugs, the National Toxicology Program started a series of studies with carisoprodol in 1988, followed by a more complete reproductive study in 1991, and additional toxicology and genetic toxicology studies in 2000. Early in carisoprodol development, it was noted that high doses of carisoprodol (>1,000 mg/kg) produced a reversible, flaccid paralysis of voluntary muscles that may cause death due to respiratory paralysis. Three month repeated oral dose studies in mice and rats identified the liver and kidney as target organs. High doses caused increased liver weights with minimal to mild centrilobular hypertrophy, probably due to induction of metabolizing enzymes. Increased kidney weights and nephropathy in male and female rats were also observed. Decreased testis weights and sperm motility were observed in male mice, but not rats, administered 1,200 mg/kg/day. Clinical signs included dose-related lethargy, ataxia, tremors convulsions, and prostration. The no-observed-adverse-effect levels (NOAELs) were 75 and 100 mg/kg/day in mice and rats, respectively. Similar clinical signs were observed in repeated dose studies in dogs, and as in rodents, these signs attenuated after a few weeks, as tolerance and/or metabolism of carisoprodol became more efficient.

Genetic toxicology

Carisoprodol was mutagenic in the *in vitro* mouse lymphoma cell assay at concentrations of 400 to 1,000 μg/mL in the absence of metabolizing enzymes. Carisoprodol was clastogenic in the *in vitro* chromosomal aberration assay using Chinese hamster ovary cells at the highest concentration tested (1,250 μg/mL) with or without the presence of metabolizing enzymes.

Carisoprodol was not mutagenic in the *in vitro* mouse lymphoma cell assay in the presence of metabolizing enzymes or in the Ames reverse mutation assay using *S. typhimurium* strains (E. coli strains were not tested) with or without incubation with metabolizing enzymes. Carisoprodol was not clastogenic in an *in vivo* mouse micronucleus assay of circulating blood cells. This was conducted with peripheral blood samples obtained from mice at the end of a 13-week oral carisoprodol administration toxicology study. The genotoxic potential of the primary metabolite, meprobamate, has not been adequately studied, although it is an approved drug that has been marketed since 1957.

Carcinogenicity toxicology

No carcinogenicity studies were conducted by the Sponsor or found in the literature. A 2-year carcinogenicity study (# C56235C) was listed for study on the NTP website under carisoprodol studies, year unknown, but it was apparently cancelled. Carisoprodol will be labeled for (b) (4)

Reproductive toxicology

Carisoprodol was evaluated for reproductive toxicological effects in mice and rats. The Sponsor presented articles from the National Toxicology Program (NTP) which conducted studies using the Reproductive Assessment by Continuous Breeding protocol in mice in 1991. The Sponsor did not reference the 1988 studies also performed by the NTP. Another 13-week toxicology study was conducted by the NTP in 2000. Both the 1988 and 2000 general toxicology studies found some evidence of reproductive toxicity, reduced testes weight and reduced sperm motility in male mice, but not in rats. There was no sign of reproductive toxicity in female reproductive organs.

In the 3-month study (NTP, 1988), carisoprodol at 0, 75, 150, 300, 600, and 1200 mg/kg, p.o., was administered to $B6C3F_1$ mice. Body weight gain was significantly greater than controls in the male mice receiving 75-300 mg/kg/day and in female mice receiving 150. 300, and 600 mg/kg/day. At necropsy, 1200 mg/kg males had reduced testis weights. Also, 150, 300, and 1200 mg/kg animals, but not 600 mg/kg, had decreased testis/body weight ratios when compared to controls. Sperm motility was decreased only in the 150 mg/kg/day group but there were no changes in sperm concentrations. There was no gonadal toxicity noted for female mice. In F344/N rats, daily carisoprodol administration for 13 weeks at doses of 100 to 1600 mg/kg failed to produce any significant changes in the reproductive system of males or females.

In a later 3-month studies (NTP, 2000), the reproductive effects observed previously were confirmed, but only in contrast to the 1988 study, only carisoprodol dosed at 1200 mg/kg resulted in decreased testis weight and decreased epididymal spermatozoa motility in $B6C3F_1$ mice. These effects were absent in F344/N rats and there were no effect on vaginal cytology or female organ weights in rats or mice.

In the NTP 1991 study, the Reproductive Assessment by Continuous Breeding protocol was used to study carisoprodol in Swiss CD-1 mice. In this protocol, the F_0, and F_1 generations are continuously administered carisoprodol. After a few cycles of F_2 litters, the study is terminated. Carisoprodol was administered by oral gavage at doses of 0, 300, 750, or 1,200 mg/kg/day. The maternal reproductive NOAEL was 750 mg/kg/day, based on small decrease in viable offspring, and an increase in time spent in estrus, at the 1200 mg/kg/day dose. Males at this dose had decreased testicular spermatid concentrations. The developmental NOAEL was 300 mg/kg/day based on 750 mg/kg/day dose findings of decreased postnatal survival and decreased F_1 weight gain at equal to or greater than 750 mg/kg/day as well as decreased live litter size (22% fewer live pups per litter) and weight (8% less) than that of the controls noted for litters of the high dose F_1 generation.

Teratogenic effects were not examined in the NTP studies. No teratogenic effects of carisoprodol were observed in the one study in rats dosed up to 400 mg/kg/day, but the data presented was inadequate to support labeling.

2.6.6.10 Tables and Figures

Refer to relevant sections

2.6.7 TOXICOLOGY TABULATED SUMMARY

Refer to relevant sections

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

This supplement is for approval of a lower dose, 250 mg tablet, of SOMA. The 350 mg tablet was originally approved in 1959 and subsequent DESI reviews. The purpose of this review was to update the label to comply with the prescription drug labeling. The Sponsors performed no pharmacological or toxicological studies with SOMA, but provided articles from the published literature and some historical documents from their predecessor company, Wallace Pharmaceuticals, the originator of this NDA. Overall, they provided a poor integation, but an adequate summary of the nonclinical aspects of SOMA development. They did not include a number of studies, especially newer publication of the pharmacology and metabolism of carisoprodol and its metabolite, meprobamate.

Many of the toxicological studies were conducted prior to the implementation of GLP. Due to the known genotoxicity and embryotoxicity of other carbamate containing compounds and the potential abuse potential of these drugs, the National Toxicology Program started a series of studies with carisoprodol in 1988, followed by a more complete reproductive study in 1991, and additional toxicology and genetic toxicology studies in 2000.

Genetic Toxicology
Carisoprodol was mutagenic in the *in vitro* mouse lymphoma cell assay at concentrations of 400 to 1,000 µg/mL 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 at the highest concentration tested (1,250 µg/mL) with or without the presence of metabolizing enzymes.

Carisoprodol was not mutagenic in the Ames reverse mutation assay using *S. typhimurium* strains (E. coli strains were not tested) with or without incubations with metabolizing enzymes. Carisoprodol was not clastogenic in an *in vivo* mouse micronucleus assay of circulating blood cells obtained from mice at the end of a 13-week oral carisoprodol administration toxicology study. The genotoxic potential of the primary metabolite, meprobamate, has not been adequately studied, although mebrobamate, itself is an approved and marketed drug since 1957.

Reproductive Toxicology

Carisoprodol was evaluated for reproductive toxicological effects in mice and rats. The Sponsor presented articles from the studies conducted by the National Toxicology Program (NTP) in 1991 and 2000. The Sponsor did not reference the 1988 studies also performed by the NTP. Both of the 1988 and 2000 NTP general toxicology studies found that carisoprodol treatment at 1200 mg/kg for 3 months resulted in reduced testes weight and reduced sperm motility in $B6C3F_1$ mice compared to controls, but had no effect in rats. Also there were no indicators of reproductive toxicity in female reproductive organs.

In the NTP 1991 study in Swiss CD-1 mice, the Reproductive Assessment by Continuous Breeding protocol was used to more thoroughly examine potential reproductive toxicological effects. In this protocol, the F_0, and F_1 generations were continuously administered carisoprodol. Carisoprodol was administered by oral gavage at doses of 0, 300, 750, or 1,200 mg/kg/day. After a few F_2 litters are produced, the study was terminated. The maternal reproductive NOAEL was 750 mg/kg/day, based on small decrease in viable offspring, and an increase in time spent in estrus, at the 1200 mg/kg/day dose. Males at this dose had decreased testicular spermatid concentrations. The developmental NOAEL was 300 mg/kg/day based on 750 mg/kg/day dose findings of decreased postnatal survival and decreased F_1 weight gain at equal to or greater than 750 mg/kg/day as well as decreased live litter size (22% fewer live pups per litter) and weight (8% less) than that of the controls noted for litters of the high dose F_1 generation.

Teratogenic effects were not examined in the NTP studies. No teratogenic effects of carisoprodol were observed in the one rat study with dosing up to 400 mg/kg/day, but the data presented was inadequate to support labeling.

Safety Margin Table for Reproductive Toxicity

	Dose[1]	**mg/day**[1]	**C_{max} (ng/mL)**	**AUC_{0-24} (ng-h/mL)**		
Approved Human Dose	350 mg qid **= 5.8 mg/kg**	1400 mg/day= **23.3 mg/kg/day**	**1771**	**6941**		
Proposed Human Dose	250 mg qid **= 4.2 mg/kg**	1000 mg/day= **16.7 mg/kg/day**	**1241**	**4461**		
Meprobamate (Metabolite Concentration)			2458 1841	44081 31056	**Human Equivalent Dose Safety Margin***	
REPRODUCTIVE STUDIES		**NOAEL**			**250 mg**	**350 mg**
F_0 mice (altered duration of estrus cycle stages,mouse testes weight, sperm motility)		**750 mg/kg/day**	No Toxicokinetic data		**3.6X**	**2.6X**
F_1 mice (reduced fetal weights, reduced postnatal weight gain, reduced survival)		**300 mg/kg/day**			**1.5X**	**1X**

[1] based on 60 kg subject

* based on body surface area

Unresolved toxicology issues (if any):

There is a lack of information concerning the toxicology of the impurites, genotoxic potential of the major metabolite, meprobamate, the teratogenic potential of carisoprodol, and the neurochemical interactions related to carisoprodol's mechanism of action. Carisoprodol has a long history of use since its approval and marketing in 1959 (meprobamate in 1957), followed by approval under the DESI program. There has been no widespread safety concerns during this time, except for its abuse liability. Therefore, these are only useful areas of study for which safety information is inadequate. The clinical impact from this lack of information is not documented and is unknown.

Recommendations:

Approve

Suggested labeling:

See labeling suggestion in the Executive Summary section.

Signatures (optional):

Reviewer Signature _____
L.S. Leshin, DVM, PhD

Supervisor Signature _____ Concurrence Yes ___ No ___
A. Wasserman, PhD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lawrence Leshin
8/26/2007 07:32:35 PM
PHARMACOLOGIST

Adam Wasserman
8/27/2007 11:18:01 AM
PHARMACOLOGIST
I concur with Dr. Leshin's recommendation that the supplement may be Approved with changes to labeling as described in his review. Final label will be negotiated with the Sponsor.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA Number: **11-792** Applicant: **MedPointe Pharmceuticals** Stamp Date: **Nov 13, 2006**
SE2 S-041
Drug Name: **Soma**

IS THE PHARM/TOX SECTION OF THE APPLICATION FILABLE? Yes [X] No [ ]

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameters	Yes	No	Comment
1	On its face, is the Pharmacology/Toxicology section of the NDA organized in a manner to allow substantive review to begin?	X		
2	Is the Pharmacology/Toxicology section of the NDA indexed and paginated in a manner to allow substantive review begin?	X		
3	On its face, is the Pharmacology/Toxicology section of the NDA legible so that substantive review can begin?	X		
4	Are ALL required* and requested IND studies completed and submitted in this NDA (carcinogenicity, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, ocular toxicity studies*, acute adult studies*, chronic adult studies*, maximum tolerated dosage determination, dermal irritancy, ocular irritancy, photocarcinogenicity, animal pharmacokinetic studies, etc)?	X		published scientific studies comprise the PharmTox section, there are 5 non-English papers submitted, 4 in French and 1 in German The Sponsor will be asked to submit copies translated into English.
5	If the formulation to be marketed is different from that used in the toxicology studies, has the sponsor made a appropriate effort to either repeat the studies with the to be marketed product or to explain why such repetition should not be required?			unknown
6	Are the proposed labeling sections relative to pharmacology appropriate (including human dose multiples expressed in mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?		X	The labeling is inadequate for current requirements.
7	Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions?	X		
8	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	X		
9	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable
10	Has the sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?			Not applicable
11	From a pharmacology perspective, is this NDA fileable?	X		

Note:

Reviewing Pharmacologist: L.S. Leshin

Date: Dec 8, 2006

Team Leader: A Wasserman

Date: Dec 8, 2006

cc:
Original NDA
HFD-170/Division File
HFD-170/Pharm-Tox/
HFD-170/Pharm-ToxTL/
HFD-170/MO
HFD-170/PM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lawrence Leshin
12/15/2006 05:19:32 PM
PHARMACOLOGIST

Adam Wasserman
12/15/2006 05:44:06 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

Stability Study – Updated Data

NDA/SERIAL NO.:	11-792/Supplement 041/Amendment 16
DRUG NAME:	Soma (carisoprodol), 250 mg Tablets
INDICATION:	Relief of Discomfort Associated with Acute, Painful Musculoskeletal Conditions
SPONSOR:	MedPointe Pharmaceuticals
DATE RECEIVED BY CENTER:	August 16, 2007
REVIEW PRIORITY:	Standard
DOCUMENTS REVIEWED:	Stability Report and Stability Data
STATISTICAL REVIEWERS:	Roswitha Kelly, M.S. (OTS/OB/DB6)
CONCURRING REVIEWER:	Yi Tsong, Ph.D. (OTS/OB/DB6)
CHEMISTRY REVIEWER:	Donald Klein, Ph.D. (OPS/ONDQA/DPE)
CHEMISTRY BRANCH CHIEF:	James Vidra, Ph.D. (OPS/ONDQA/DPE)
PROJECT MANAGER:	Sharon Turner-Rinehardt (OND/ODEII/DAARP)

Keywords: Stability, Shelf life.

Distribution: NDA 11792-Soma 250 mg
OND/ODEII/DAARP/S. Turner-Rinehardt
ONDQA/DPE/D. Klein, Ph.D., J. Vidra, Ph.D.
OTS/OB/DB6/Roswitha Kelly, M.S., Yi Tsong, Ph.D.,
Stella Machado, Ph.D., Ms. S. Tinku
OTS/OB/R. O'Neill, Ph. D., L. Patrician, M.S.

File Directory: RKelly: *C:\Data\N11792_updated_stab_f1.doc*

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

In Supplement 041 the sponsor requested a 36 month shelf life based on 12 month data for Soma 250 mg tablet. The statistical reviewer had concluded based on the analysis of potency and dissolution data that an extrapolated shelf life was supported. However, the length of the extrapolation should follow ICH guidelines, i.e. be not more than 12 months beyond the amount of actual data.

By Agency request the sponsor submitted updated stability data which contained the 18 month data points. The sponsor continues to maintain that the expiry for Soma 250 mg tablets should be 36 months as these tablets are made from the same (b) (4) as Soma 350 mg tablets, which have a 90 months shelf life. Stability batches of Soma 350 mg tablets have data between 0.9 and 8.7 years.

The reviewer could duplicate the sponsor's statistical consultant's findings and agrees that the updated assay results of Soma 250 mg tablets estimate an extrapolated shelf life beyond 60 months. The reviewer also analyzed individual dissolution data which also estimated expiries longer than 60 months. However, following ICH guidelines, the maximum extrapolated shelf life would be 30 months until the 24 month stability data confirm the stability patterns currently observed.

1.2 Overview of the Submission

The sponsor submitted Amendment 16 via email, which contained their report, the updated stability data, and the analysis report by their consultant, (b) (4) In addition, the stability data were submitted as Excel and as SAS transport files.

1.3 Principle Findings

1.3.1 Sponsor's Results and Conclusions

The sponsor had the updated (18 month) stability data statistically analyzed by (b) (4), a well-known expert in this field. He concluded based on the analyses of the assay data that shelf lives of at least 60 months are supported. The sponsor maintained their previous position that a 36 month shelf life is warranted based on the stability observed for the 250 mg tablets and the established shelf life (90 months) for the 350 mg

tablets. The two strengths are based on the same (b) (4) and differ only in size and minor features of the packaging.

1.3.2 Reviewer's Results and Conclusions

The reviewer confirmed the findings the sponsor's consultant had obtained for assay. She also analyzed the individual dissolution data which also estimated shelf lives of at least 60 months. However, following ICH recommendations, the reviewer concludes that only a 30 month expiry is appropriate at this point for the 250 mg tablets, as the maximum extrapolation beyond actual data is 12 months.

1.3.3 Extent of Evidence in Support of Requested Extension of Expiry

Following ICH guideline, the sponsor needs 24 month actual stability data before a 36 month expiry should be granted. The evaluation of the 18 month stability data points to a stable product and a 36 month shelf life is likely to be achieved with the next evaluation.

1.3.4 Statistical Issues

There are no statistical issues. The only point of disagreement is whether to follow ICH guidelines which recommend an extrapolation of no more than 12 months beyond the amount of actual stability data whereas the sponsor argues for a 36 month expiry as the 250 mg tablets come from the same (b) (4) as do the 350 mg tablets which have an approved 90 month expiry.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

The review of the sponsor's 12 month stability data was completed on June 1, 2007. Though the data extrapolated well, the reviewer concluded that at most a 24 month shelf life should be granted as ICH guidelines recommend an extrapolation of no more than 12 months. Thereupon the sponsor was requested to submit a stability update which is the subject of this review.

2.2 Overview of Stability Study

The sponsor has three registration batches (one full size, two 1/3 size each) of the 250 mg tablets on stability at 25°C/60%RH. In addition, the 350 mg tablets which are made from the same (b) (4) have an approved shelf life of 90 months and actual data of up to 8.7 years.

2.3 Data Analyzed and Sources

The reviewer statistically analyzed the 18 month stability data of the 250 mg tablet batches which the sponsor submitted as Excel and as SAS transport files on Aug. 16, 2007. The assay data from these files were also statistically evaluated by the sponsor's consultant, (b) (4)

2.4 The Stability Study

2.4.1 Sponsor's Analyses, Results, and Conclusions

(b) (4) an expert in the field, evaluated the sponsor's assay data for the bottles and the unit-dose pouches. He truncated the extrapolation of the shelf life at 60 months and found that both data sets estimated a shelf life of at least that length.

The sponsor notes that this stability update was submitted at the request of the Agency and that they have not changed their position, namely that the shelf life for the 250 mg tablets should be 36 months. They base their conclusion on the observed stability pattern of these tablets and on the fact that the 250 mg tablets are different from the 350 mg tablets only in size, i.e. they are made from the same (b) (4). The 350 mg tablets have an approved shelf life of 90 months and actual data of up to 8.7 years.

2.4.2 Reviewer's Analyses, Results, and Conclusions

The reviewer independently confirmed the sponsor's consultant's results for assay. It is noted that (b) (4) reported the slope estimates per year whereas the reviewer's estimates are per month (see Appendix, Tables and Figures 1 and 2). Otherwise, the results are identical to several significant digits.

The reviewer also analyzed individual dissolution data. For each package type the extrapolated shelf life is beyond 60 months (see Appendix, Tables and Figures 3 and 4).

ICH guidelines recommend that a shelf life estimate should not be extrapolated by more than 12 months beyond the actual data. Taking these recommendations into account, a 30 month expiry is supported based on the evaluation of the 18 month assay and dissolution

data of the 250 mg tablets. Once the 24 month stability data are available, a 36 month shelf life will likely be estimated.

2.5 Statistical and Technical Issues

With respect to the sponsor's statistical analysis of the assay data, there are no issues. As the sponsor, the reviewer did not analyze impurities data as many observations were below the level of detection. The reviewer did analyze the dissolution data, which the sponsor hat not, but the analyses and results were straight forward.

The only technical issue is that the sponsor maintains that a 36 month shelf life is warranted based on the observed stability of the 250 mg tablets and their relationship (same (b) (4) to the 350 mg tablets which have a 90 month shelf life. As ICH guidelines recommend no more than a 12 month extension beyond actual data, a 36 month expiry would go against these guidelines. However, the actual granting of a shelf life lies within the purview of the reviewing chemist.

2.6 Statistical Evaluation of Collective Evidence

The reviewer did not take the stability profile (90 months) of the 350 mg tablets into account but based her conclusions strictly on the results of the statistical analyses of the assay and dissolution data available for the 250 mg tablets. The impurities data did not lend themselves to statistical analyses since most points were LOQ.

2.7 Conclusions and Recommendations

The reviewer independently estimated expiries based on assay and individual dissolution data. Both attributes supported shelf lives extension well beyond the available 18 month data. Relying on ICH guidelines, these findings would support a shelf life of 30 months. However, the sponsor considers a shelf life of 36 months as appropriate, as the 250 mg tablets are made from the same (b) (4) as the 350 mg tablets which have a 90 month shelf life. There are also minor differences in some packaging components between the two strengths which according to the sponsor have no impact on the stability of the 250 mg tablets. Again, the actual granting of the shelf life is left to the expertise of the reviewing chemist.

3. APPENDIX

Table 1: Shelf Life Evaluation for Assay of Soma 250 mg Tablets in 100 ct Bottles

Source	SS	DF	MS	F-Statistic	P-Value
A	3.9105	4	0.9776	3.7618	0.0260
B	3.7181	2	1.8590	7.1534	0.0066
C	0.1924	2	0.0962	0.3702	0.6968
RESIDUAL	3.8982	15	0.2599		

Fitted Line	R-Square	Batch	Estimated Expiry Period
Y = 99.6599 + 0.0077 x Time	0.4791	27-02-03S	200
Y = 100.2314 + 0.0077 x Time	0.4791	27-02-04S	200
Y = 100.6885 + 0.0077 x Time	0.4791	27-02-05S	200
	.	~MIN~	200

Figure 1: Shelf Life for Assay of Batch 270203s in 100 ct Bottles

Table 2: Shelf Life Evaluation for Assay of Soma 250 mg Tablets in CR Pouches

Source	SS	DF	MS	F-Statistic	P-Value
A	6.7065	4	1.6766	5.1449	0.0082
B	6.0467	2	3.0233	9.2773	0.0024
C	0.6599	2	0.3299	1.0124	0.3869
RESIDUAL	4.8883	15	0.3259		

Fitted Line	R-Square	Batch	Estimated Expiry Period
Y = 100.0828 - 0.0158 x Time	0.5289	27-02-03S	197
Y = 101.2971 - 0.0158 x Time	0.5289	27-02-04S	200
Y = 101.1257 - 0.0158 x Time	0.5289	27-02-05S	200
	.	~MIN~	197

Figure 2: Shelf Life for Assay of Batch 270203s in CR Pouches

Table 3: Shelf Life Evaluation for Individual Dissolution of Soma 250 mg Tablets in 100 ct Bottles

Source	SS	DF	MS	F-Statistic	P-Value
A	13.2656	4	3.3164	0.8633	0.4882
B	4.9683	2	2.4841	0.6466	0.5256
C	8.2973	2	4.1487	1.0799	0.3429
RESIDUAL	461.0072	120	3.8417		

Fitted Line	R-Square	Batch	Estimated Expiry Period
Y = 98.8804 - 0.0190 x Time	0.0034	POOLED	200
	.	~MIN~	200

Figure 3: Shelf Life for Dissolution of the Pooled Batches of Soma 250 mg in 100 ct Bottles

Table 4: Shelf Life Evaluation for Individual Dissolution of Soma 250 mg Tablets in CR Pouches

Source	SS	DF	MS	F-Statistic	P-Value
A	24.8043	4	6.2011	1.6116	0.1758
B	19.8571	2	9.9286	2.5803	0.0800
C	4.9472	2	2.4736	0.6429	0.5276
RESIDUAL	461.7415	120	3.8478		

Fitted Line	R-Square	Batch	Estimated Expiry Period
Y = 98.4678 - 0.0123 x Time	0.0421	27-02-03S	200
Y = 97.7535 - 0.0123 x Time	0.0421	27-02-04S	200
Y = 98.6821 - 0.0123 x Time	0.0421	27-02-05S	200
	.	~MIN~	200

Figure 4: Shelf Life for Dissolution of Batch 270203s in CR Pouches

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation
Clinical Studies

NDA/Serial Number:	NDA 11-792 /S41
Drug Name:	SOMA (carisoprodol)
Indication(s):	SOMA is a skeletal muscle relaxant indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions
Applicant:	MedPointe Pharmaceuticals
Date(s):	Applicant's package insert date: November 10, 2006 Review completion date:
Review Priority:	Standard
Biometrics Division:	Biometrics Division 2
Statistical Reviewer:	Ted Guo, Ph.D., Biometrics Division 2
Concurring Reviewers:	Dionne Price, Ph.D., Acting Team Leader, Biometrics Division 2
Medical Division:	Division of Anesthesia Analgesia and Rheumatology Products (OND II)
Clinical Team:	Eric Brodsky, M.D., Medical Officer (OND II)
Project Manager:	Sharon Turner-Rhinehardt (OND II)
Keywords:	NDA review, clinical studies

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Executive Summary

Recommendations

MedPointe Pharmaceuticals proposes SOMA 250 mg for the relief of discomfort associated with acute, painful musculoskeletal conditions. Patients receiving SOMA 250 mg experienced greater relief from back pain compared to patients receiving placebo. In addition, values representing the global impression of change were higher for patients randomized to SOMA 250 mg than placebo. The most common adverse events (AEs) among patients randomized to SOMA included somnolence, dizziness, headache and nausea. Based on my evaluation of the application, I conclude that SOMA 250 mg is effective in relieving discomfort associated with acute, painful musculoskeletal conditions. Moreover, I recommend that the most common adverse events appear in the label.

Brief Overview of Clinical Studies

SOMA is a skeletal muscle relaxant. SOMA 350 mg is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions. The sponsor submitted the results of two Phase-3 clinical studies, MP502 and MP505, to confirm the effectiveness and safety of SOMA 250 mg. Both studies were randomized, double-blind, placebo-controlled, parallel group, 7-day studies. The primary endpoints were the patient-rated global impression of change (GIC) and the patient-rated relief from starting backache (RSB) at Day 3. The primary efficacy analysis for both studies was based on the comparison between SOMA 250 mg and placebo. Safety was evaluated by monitoring AEs and other lab indicators.

Table 1 Studies reviewed

Study	Objective	Design	Evaluated
MP502	Efficacy and safety	Phase 3 randomized, double-blind, placebo-controlled, parallel group	Efficacy and safety
MP505	Efficacy and safety	Same as above	Same as above

Statistical Findings

Efficacy

An analysis of variance (ANOVA) model was used to analyze the data and included terms for treatment and center. In order for the study to be considered positive, the primary efficacy comparisons for both efficacy variables had to be statistically significant at the 0.025 level at Day 3. A last observation carried forward (LOCF) strategy was used to impute missing data. The results of the primary efficacy analyses for Studies MP502 and MP505 demonstrated that SOMA 250 mg was superior to placebo (See Table 2).

Additional analyses showed that SOMA 350 mg was also superior to placebo based on GIC and RSB. The difference between SOMA 350 and 250 mg groups appeared to be small.

Table 2 Efficacy findings based on Day-3 patient-rated global impression of change (GIC) and patient-rated relief from starting backache (RSB) from Studies MP502 and MP505

Treatment	Comparator	Study	Primary efficacy variable	LS mean Diff.	P value	95% confidence interval
SOMA 250 MG	**Placebo**	**MP502**	GIC	0.22	<0.025	0.07, 0.37
			RSB	0.35	<0.025	0.17, 0.53
		MP505	GIC	0.52	<0.025	0.37, 0.67
			RSB	0.69	<0.025	0.50, 0.87

Source: ADGC3, ADPR3 (ITT patients, LOCF for missing values)

Safety

Based on the numbers and percentages of AEs found in at least 2% of the patients, the most commonly reported AEs were found to be somnolence, dizziness, headache and nausea (See Table 3).

Table 3 AEs in 2%+ patients (Studies MP502 and MP505)

AEs	Study	Treatment						N	%
		Placebo		SOMA 250mg		SOMA 350mg			
		N	%	N	%	N	%		
SOMNOLENCE	MP502	18	6.69	34	12.88	46	16.85	98	12.16
	MP505	13	4.68	38	14.13	N/A	N/A	51	9.32
DIZZINESS	MP502	2	0.74	16	6.06	19	6.96	37	4.59
	MP505	9	3.24	27	10.04	N/A	N/A	36	6.58
HEADACHE	MP502	7	2.60	16	6.06	9	3.30	32	3.97
	MP505	4	1.44	10	3.72	N/A	N/A	14	2.56
NAUSEA	MP502	7	2.60	4	1.52	12	4.40	23	2.85
	MP505	8	2.88	2	0.74	N/A	N/A	10	1.83

Source: AE2 (AEs in 2%+ of patients)

The number of patients on SOMA 250 or 350 mg experiencing somnolence or dizziness was two times greater than the number of patients on placebo. The number of patients on SOMA 250 mg experiencing headaches was also two times greater than the number of patients on placebo, but the number of patients on SOMA 350 mg experiencing headaches was not much different from the number of patients with headaches on placebo. The number of patients on SOMA 350 mg having nausea was a little less than twice the number of patients on placebo, while the number of patients on SOMA 250 mg having nausea was smaller than the number of patients on placebo.

Overall, patients treated with SOMA (250 or 350 mg) had more reported episodes of somnolence, dizziness and headache than those on placebo. This trend was observed in both Studies MP502 and MP505. These AE findings, in my opinion, can be helpful to the review team for labeling comments.

Introduction

Overview

SOMA is a skeletal muscle relaxant indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions. The currently approved dose for SOMA is 350 mg, four times per day with a total daily dose of 1400 mg. Drowsiness and other adverse effects of the central nervous system are the most common AEs associated with SOMA 350 mg tablets. According to the sponsor, lower doses may still maintain clinical effectiveness with fewer incidences of AEs compared with the currently recommended 350 mg dosage (page 25, Sec. 7, Clinical Study Report MP502). Thus, the purpose of this NDA is to demonstrate that the SOMA 250 mg tablet is safe and effective.

The clinical development of SOMA 250 mg was introduced to the Division of Anesthesia, Analgesia, and Rheumatology Products via IND 71,218. The study design, inclusion/exclusion criteria, sample size, duration, endpoints, and analyses were discussed at a Type B meeting on February 7, 2005. Subsequently, the sponsor submitted a special protocol on March 4, 2005. The Division did not agree on several aspects of the protocol and revised protocols were submitted. The statistical reviewer, Dr. Yongman, Kim, reviewed the protocols and commented,

> The statistical aspect of the protocol is acceptable, in general. However, we recommend that you investigate the sensitivity of the results to the procedure for handling missing data using conservative approaches such as a continuous responder analysis and a baseline observation carried forward (BOCF) analysis.

Scope of Statistical Review

To confirm that SOMA is efficacious, the sponsor submitted two Phase 3 clinical studies: Studies MP502 and MP505. These studies had nearly the same design except that the former included an additional treatment arm of SOMA 350 mg. For simplicity, only MP502 is mentioned in the following text, unless otherwise specified.

Study MP502 was a randomized, double-blind, placebo-controlled, parallel group 7-day study. The planned statistical comparisons were the following:

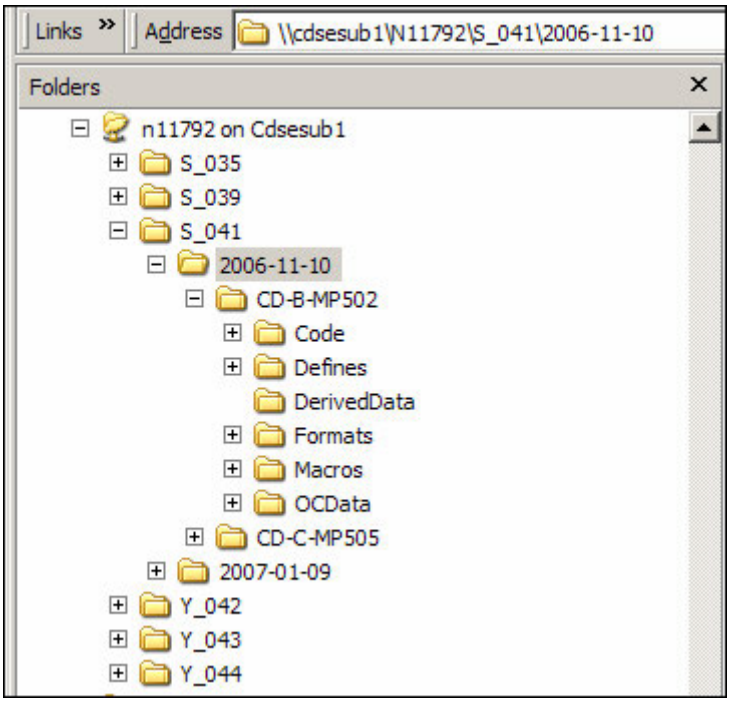
SOMA 250 mg (four times daily) vs. placebo	(The primary analysis)
SOMA 350 mg (four times daily) vs. placebo	(A secondary analysis)

The primary efficacy endpoints were **patient-rated relief from starting backache (RSB)** and **patient-rated global impression of change (GIC)**, both evaluated at Day 3 of the study.

Data Sources

The sponsor submitted study reports in hard copy and data in electronic format to the FDA Electronic Document Room (EDR). All the data are in SAS v.5 transport format. The organization of the submitted data is shown in Table 4.

Table 4 Data Source:



Statistical Evaluation

Evaluation of Efficacy

Study Designs and Endpoints

Following the screening day (Day 1) when inclusion and exclusion criteria were applied to all participants, eligible patients were randomized in a 1:1:1 (1:1 for MP505) ratio to seven days of double-blind treatment with SOMA 350 mg (arm not included in MP505), SOMA 250 mg, or placebo. For the analyses, each dose of SOMA was compared to placebo.

Efficacy measurements: Assessments were made twice daily, 6-9 AM and 6-9 PM, for the previous 12 hours and recorded in a dairy. The primary outcomes were measured on a 0–4 scale as shown below.

- Measurement of patient-rated relief from starting backache (RSB):

0	No relief
1	A little relief
2	Some relief
3	A lot of relief
4	Complete relief

- Measurement of patient-rated global impression of change (GIC):

0	Worsening
1	No change
2	Mild improvement
3	Moderate improvement
4	Marked improvement

Measurement scales for the secondary outcomes were provided on page 27 of the Study Report. The scales are not provided in this review.

Primary efficacy variables were:

- Patient-rated relief from starting backache (RSB) – analyzed for Day 3
- Patient-rated global impression of change (GIC) – analyzed for Day 3

Secondary efficacy variables included:

- Patient functional assessment using Roland-Morris Disability Questionnaire (RMDQ) – analyzed for Days 1, 3, and 7

- Assessment of range of motion – analyzed for Days 1, 3, and 7
- Patient-rated medication helpfulness – analyzed for Days 3 and 7
- Time to symptom improvement, defined as the first time point the patient reported moderate or marked improvement based on global impression of change (page 26, Sec. 9.1, Clinical Study Report MP)

Patients returned to the clinic for evaluations on Days 3 and 7. Patients were questioned regarding AEs on the Day 7 visit.

Analysis Patient Populations

The following table summarizes the number of study participants randomized and the number included in the analysis populations.

Table 5 Number of patients for Studies MP502 and MP505

Study	Patient population	SOMA 250 mg	SOMA 350 mg	Placebo	Total
MP502	Randomized: all patients randomized to study medication	271	281	276	828
	ITT: (randomized patients) who received at least one dose of medication and had at least one post-baseline efficacy assessment	264	273	269	806
	Per Protocol: ITT patients with complete diary data, who took at least 70% of required medication at Day 3, and completed the study according to the protocol	234	232	221	687
MP505	Randomized	277		285	562
	ITT	269		278	547
	Per Protocol	244		246	490

Source: Page 51-52, Sec. 11.1, Clinical Study Report MP502; page 45, Sec. 11.1, Clinical Study Report MP505

Patient Distributions of Demographic and Baseline Characteristics

Study MP502

This section describes patient disposition, demographic characteristics, protocol compliance, and reasons for early withdrawal from Study MP502.

There were 806 patients in the intent-to-treat (ITT) population for Study MP502. The ITT population included all randomized patients who received study medication and had at least one post-baseline assessment. There was a single observation (sometimes called score, value, or number) for the **patient-rated global impression of change (GIC)** and the **patient-rated relief from starting backache (RSB)** per patient visit day. For some visits, observations for either variable were missing. These observations were not

included in the sponsor's analyses. Table 6 shows the numbers and percentages of GIC present and missing by treatment and day for Study MP502. Table 7 shows the same numbers for RSB. Of note, an imputation strategy was used to handle missing data in the primary analysis.

Table 6 Numbers and percentages of GIC present and missing by treatment and day based on efficacy data ADGC (Study MP502)

Treatment	Day	Total N	N	% Present	% Missing
Placebo	**1**	269	269	100%	0%
	3	269	251	93%	7%
	7	269	202	75%	25%
250mg	**1**	264	264	100%	0%
	3	264	250	95%	5%
	7	264	224	85%	15%
350mg	**1**	273	273	100%	0%
	3	273	255	93%	7%
	7	273	209	77%	23%

Source: ADGC2 (based on ADGC and DEMO)

Table 7 Numbers and percentages of RSB present and missing by treatment and day based on efficacy data ADPR (Study MP502)

Treatment	Day	Total N	N	% Present	% Missing
Placebo	1	269	269	100%	0%
	3	269	250	93%	7%
	7	269	200	74%	26%
250mg	1	264	264	100%	0%
	3	264	249	94%	6%
	7	264	223	84%	16%
350mg	1	273	273	100%	0%
	3	273	254	93%	7%
	7	273	201	74%	26%

Source: ADPR2 (based on ADPR and DEMO)

Table 8**Error! Reference source not found.** shows the reasons for discontinuation for all randomized patients presented by the sponsor. This reviewer also produced this table (provided in the appendix) based on the ITT population.

Table 8 Reason for discontinuation based on study report (Study MP502)

Reason for discontinuation	SOMA 250 n=271	SOMA 350 n=281	Placebo n=276
Lost to follow-up	10	11	12
Unsatisfactory treatment effect	2	7	20
AE	3	15	10
Withdrawal consent	5	6	2
Abnormal testing procedure results	1	1	1

Reason for discontinuation	SOMA 250 n=271	SOMA 350 n=281	Placebo n=276
Protocol violation	1	1	3
Other	4	1	2
Total	26	42	48

Source: Sponsor's Table 10-1, page 49 of the study report, MP502

Table 9 and Table 10 are populated by the numbers and percentages of ITT patients by treatment and by race and sex. Approximately 73% of the study participants were Caucasian. Males accounted for 44% of all ITT patients. The average patient age was 41 years old (Table 11). The age variation among the treatment groups appeared to be small. The treatment groups were considered to be balanced, based on the demographic measures.

Table 9 Number of patients by treatment and race (Study MP502)

Race	Treatment						Total	
	Placebo		250mg		350mg			
	N	%	N	%	N	%	N	%
Asian	25	9	22	8	16	6	63	8
Black	50	19	45	17	42	15	137	17
Caucasian	188	70	191	72	208	76	587	73
Native American					3	1	3	0
Other	6	2	6	2	4	1	16	2
Total	269	100	264	100	273	100	806	100

Source: DEMO

Table 10 Number of patients by treatment and sex (Study MP502)

Sex	Treatment						Total	
	PLACEBO		250MG		350MG			
	N	%	N	%	N	%	N	%
Female	163	61	138	52	152	56	453	56
Male	106	39	126	48	121	44	353	44
Total	269	100	264	100	273	100	806	100

Source: DEMO

Table 11 Analysis of patient-age distribution by treatment (Study MP502)

Treatment	N	Mean	Min	Max	Lower quartile	Upper quartile
Placebo	269	41	18	75	30	50
250mg	264	41	19	71	31	49
350mg	273	41	18	74	30	50
Total	806	41	18	75	31	50

Source: DEMO

Study MP505

This section describes patient disposition, demographic characteristics, protocol compliance, and reasons for early withdrawal from Study MP505.

In Study MP505, there were 547 patients in the ITT population Similar to Study MP502, there was a single observation (sometimes called score, value, or number) for variables **patient-rated global impression of change (GIC)** or **patient-rated relief from starting backache (RSB)** per patient visit day.

Table 12 shows the numbers and percentages of GIC present and missing by treatment and day for Study MP505. Table 13 shows the same numbers for RSB.

Table 12 Numbers and percentages of GIC present and missing by treatment and day based on efficacy data ADGC (Study MP505)

Treatment	Day	Total N	N	% Present	% Missing
Placebo	**1**	278	278	100%	0%
	3	278	263	95%	5%
	7	278	212	76%	24%
250mg	**1**	269	269	100%	0%
	3	269	258	96%	4%
	7	269	214	80%	20%

Source: ADGC2 (based on ADGC and DEMO)

Table 13 Numbers and percentages of RSB present and missing by treatment and day based on efficacy data ADPR (Study MP505)

Treatment	Day	Total N	N	% Present	% Missing
Placebo	**1**	278	278	100%	0%
	3	278	262	94%	6%
	7	278	210	76%	24%
250mg	**1**	269	269	100%	0%
	3	269	258	96%	4%
	7	269	212	79%	21%

Source: ADPR2 (based on ADPR and DEMO)

Table 14 shows the disposition of all of the randomized patients. This reviewer additionally explored the disposition of patients included in the ITT population, and the table is included in the appendix.

Table 14 Reason for discontinuation based on study report (Study MP505)

Reason for discontinuation	SOMA 250mg n=277	Placebo N=285
Loss to follow-up	7	4
Unsatisfactory treatment effect	8	19
AE	8	5
Withdrawal consent	6	7
Protocol violation	1	2
Other	1	6
Total	31	43

Source: Sponsor's Table 10-1, page 42 of the study report, MP505

Table 15 and Table 16 are populated by the numbers and percentages of ITT patients by treatment and by race and sex. Approximately 76% of the study participants were Caucasian. Males accounted for 48% of all ITT patients. The average patient age was approximately 40 years old (Table 17). The age variation among the treatment groups appeared to be small. The treatment groups were considered to be balanced, based on these demographic measures.

Table 15 Number of patients by treatment and race (Study MP505)

Race	Treatment				Total	
	PLACEBO		250MG			
	N	%	N	%	N	%
Asian	28	10	28	10	56	10
Black	33	12	39	14	72	13
Caucasian	215	77	199	74	414	76
Native American	1	0	2	1	3	1
Other	1	0	1	0	2	0
Total	278	100	269	100	547	100

Source: DEMO

Table 16 Number of patients by treatment and sex (Study MP505)

Sex	Treatment				Total	
	PLACEBO		250MG			
	N	%	N	%	N	%
Female	153	55	131	49	284	52
Male	125	45	138	51	263	48
TOTAL	278	100	269	100	547	100

Source: DEMO

Table 17 Analysis of patient-age distribution by treatment (Study MP505)

Treatment	N	Mean	Min	Max	Lower quartile	Upper quartile
Placebo	278	41	19	71	33	50
250mg	269	39	18	72	30	47
Total	547	40	18	72	31	49

Source: DEMO

Efficacy Analysis and Results

Study MP502

The primary statistical analysis was based on a comparison between SOMA 250 mg and placebo. The sponsor stated, "Comparisons of the 350 mg carisoprodol group to the other two treatment groups were confirmatory only." In order for the study to be considered positive, the comparisons for both primary efficacy variables had to be statistically significant at a 0.025 level for Day 3. The significance tests were two-sided tests. The primary statistical analysis was conducted on the ITT population. Analyses based on the per protocol population were considered secondary (page 44, Sec. 9.7.1.7, Clinical Study Report MP502).

For the primary efficacy analysis, an analysis of variance (ANOVA) model was used to test for mean treatment differences in daily values of GIC and RSB at Day 3. The ANOVA model included fixed effects for **treatment** and **center**. The treatment-by-center interaction was tested at a 0.1 level and would be removed from the model if it was found not to be significant. The sponsor did not explain what steps would be taken if the test of interaction was not significant.

Missing data at Day 3 were imputed using the following procedures:

1. If Day 2 data were available, use the Day 2 data (i.e. last observation carried forward)
2. Otherwise, if Day 4 data were available, use Day 4 data

For analyses of endpoints beyond Day 3, the mean daily value from the last available evaluation was used. Details of the strategy to handle missing data were provided on page 43, Sec. 9.7.1.7, Clinical Study Report MP502.

This reviewer verified the sponsor's analyses and results. The results are provided in Table 18, Table 19, and Table 22. The SAS program producing the results is included in Table 39 of the Appendix. Of note, a positive difference indicated more favorable responses among patients randomized to the study medication. Additionally, there were 22 patients without LOCF estimates for GIC. According to the sponsor, "Patients who had missing data for either global impression of change or patient-rated relief from starting backache were excluded for the analysis."

Table 18 Day 3 GIC and RSB for ITT patients (Study MP502)

Treatment	N	Median	Mean	Std	Min	Max
Patient-rated global impression of change						
Placebo	269	2.00	1.96	0.91	0.00	4.00
250mg	264	2.00	2.19	0.91	0.00	4.00
350mg	273	2.50	2.21	0.86	0.00	4.00
Total	806	2.00	2.12	0.90	0.00	4.00
Patient-rated relief from starting backache						
Placebo	269	2.00	1.44	1.12	0.00	4.00
250mg	264	2.00	1.81	1.07	0.00	4.00
350mg	273	2.00	1.87	1.00	0.00	4.00
Total	806	2.00	1.71	1.08	0.00	4.00

Source: ADGCPR (LOCF)

ANOVA of GIC (Study MP502)

Table 19 Comparisons between treatments for GIC (Study MP502)

Treatment comparison Applying LOCF (variable LGICAVGN used)		**Estimate**	**Standard Error**	**P-Value**	**Lower CL**	**Upper CL**
250mg	**350mg**	-0.04	0.078	0.61	-0.19	0.11
***250mg**	**Placebo**	0.22	0.078	0.0001	0.07	0.37
350mg	**Placebo**	0.26	0.077	0.0008	0.11	0.41
Using available data (variable OGICAVGN used)						
250mg	**350mg**	-0.07	0.079	0.35	-0.23	0.081
***250mg**	**Placebo**	0.20	0.079	0.01	0.04	0.35
350mg	**Placebo**	0.27	0.078	0.0006	0.12	0.42

Source: ADGC3

*: Primary comparison.

ANOVA of RSB (Study MP502)

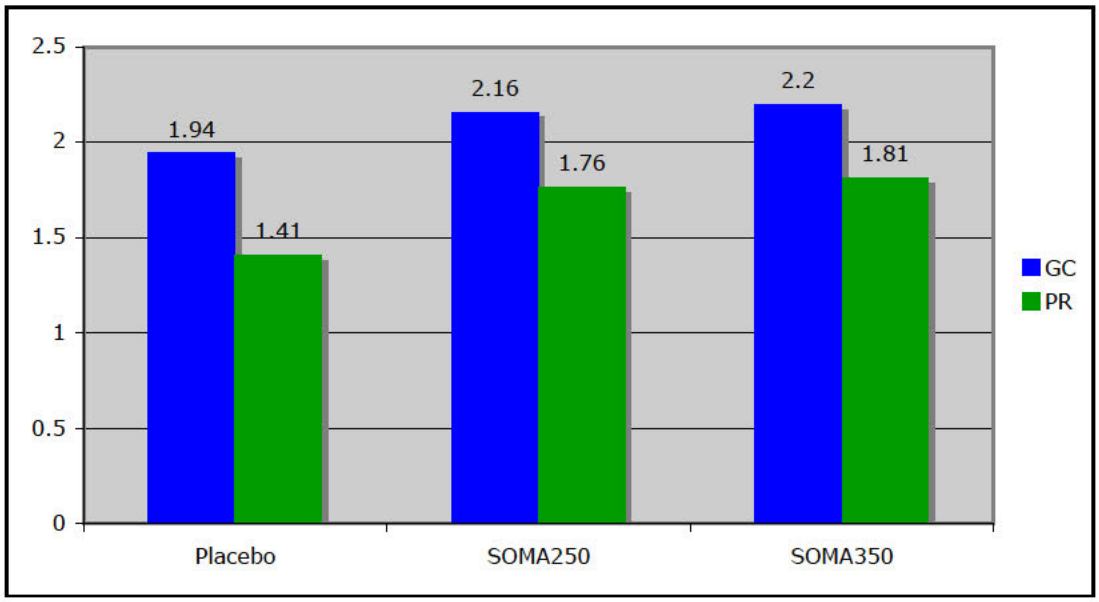
Table 20 Comparisons between treatments for RSB (Study MP502)

Treatment comparison Applying LOCF (variable LPRAVGN used)		**Estimate**	**Standard Error**	**P-Value**	**Lower CL**	**Upper CL**
250mg	**350mg**	-0.07	0.093	0.44	-0.26	0.11
***250mg**	**Placebo**	0.35	0.093	0.0002	0.17	0.53
350mg	**Placebo**	0.42	0.092	<.0001	0.24	0.60
Using available data (variable OPRAVGN used)						
250mg	**350mg**	-0.11	0.094	0.24	-0.30	0.073
***250mg**	**Placebo**	0.32	0.094	0.0007	0.14	0.51
350mg	**Placebo**	0.43	0.094	<.0001	0.25	0.62

Source: ADPR3
*: Primary comparison.

SOMA 250mg was superior to placebo based on the analyses of the primary efficacy variables and using the alpha level of 0.025. In addition, SOMA 350 was also superior to placebo. The magnitude of the difference between SOMA 250 and SOMA 350 was small. The results based on the observed data were consistent with the primary analysis.

Figure 1 LS means of GIC and RSB (Study MP502)



The sponsor also provided tables summarizing the frequencies of the various categories denoting the patients' global impression of change and the patient-rated relief from starting backache. The frequencies for Day 3 and Day 7 are shown below. The sponsor calculated the percentages using the available patients in each treatment group.

Table 21 Frequencies of Global Impression of Change: ITT Population

Time Interval	SOMA 250 mg N=264		SOMA 350 mg N=273		Placebo N=269	
Day 3 – morning						
Marked improvement	20	8%	24	9%	14	5%
Moderate improvement	58	22%	53	19%	52	19%
Mild improvement	110	42%	128	47%	97	36%
No change	55	21%	43	16%	81	30%
Worsening	6	2%	4	1%	4	1%
Missing	3	1%	11	4%	5	2%
Day 3 – evening						
Marked improvement	30	11%	27	10%	18	7%
Moderate improvement	58	22%	71	26%	56	21%
Mild improvement	106	40%	111	41%	90	33%
No change	48	18%	36	13%	75	28%
Worsening	3	1%	5	2%	4	1%
Missing	7	3%	13	5%	10	4%
Day 7 – morning						
Marked improvement	64	24%	74	27%	51	19%
Moderate improvement	74	28%	69	25%	57	21%
Mild improvement	55	21%	47	17%	45	17%
No change	26	10%	13	5%	45	17%
Worsening	5	2%	4	1%	4	1%
Missing	6	2%	12	4%	13	5%
Day 7 – evening						
Marked improvement	43	16%	41	15%	32	12%
Moderate improvement	33	13%	39	14%	33	12%
Mild improvement	33	13%	28	10%	33	12%
No change	14	5%	8	3%	22	8%
Worsening	2	1%	2	1%	2	1%
Missing	104	39%	101	37%	93	35%

Source: Table 11-8, Clinical Study Report

Table 22 Frequencies of Patient-rated Relief from Starting Backache

Time Interval	SOMA 250 mg N=264		SOMA 350 mg N=273		Placebo N=269	
Day 3 – morning						
Complete relief	7	3%	11	4%	6	2%
A lot of relief	56	21%	50	18%	39	14%
Some relief	93	35%	108	40%	77	29%
A little relief	50	19%	54	20%	58	22%
No relief	43	16%	28	10%	67	25%
Missing	3	1%	12	4%	6	2%
Day 3 – evening						
Complete relief	14	5%	13	5%	8	3%
A lot of relief	62	23%	73	27%	53	20%
Some relief	86	33%	88	32%	71	26%
A little relief	50	19%	55	20%	49	18%
No relief	33	13%	20	7%	62	23%
Missing	7	3%	14	5%	10	4%
Day 7 – morning						
Complete relief	48	18%	46	17%	34	13%
A lot of relief	76	29%	76	28%	69	26%
Some relief	53	20%	49	18%	38	14%
A little relief	24	9%	16	6%	26	10%
No relief	21	8%	12	4%	33	12%
Missing	8	3%	20	7%	15	6%
Day 7 – evening						
Complete relief	33	13%	27	10%	23	9%
A lot of relief	35	13%	45	16%	40	15%
Some relief	31	12%	27	10%	26	10%
A little relief	11	4%	12	4%	12	4%
No relief	14	5%	7	3%	20	7%
Missing	105	40%	101	37%	94	35%

Source: Table 11-10, Clinical Study Report

Analyses of secondary efficacy variables (Study MP502)

The sponsor's analyses of the secondary efficacy variables were based on RMDQ, range of motion, and patient-rated medication helpfulness. Note that in comparing the two SOMA dose groups with placebo, a significant level of 0.025 was used to adjust for multiple comparisons between SOMA 250 and placebo and between SOMA 350 and placebo. Comparisons for Days 3 and 7, as well as for the four different secondary efficacy variables, were made separately and no adjustments for multiplicity were applied.

With the exception of the analysis of Range of Motion, the other three analyses showed that SOMA dose groups were superior to placebo. For these analyses, this reviewer did not reanalyze the sponsor's data.

Study MP505

Because of the similarity between this study, Study MP505, and Study MP502, explanations of the analyses in this section are excluded. The same statistical analyses were conducted for both studies. Only statistical results are shown here with remarks.

This reviewer analyzed GIC (variable `LGICAVGN`) and RSB (variable `LPRAVGN`). Results from analyses of the global impression of change and patient-rated relief from starting backache are shown in the following tables.

Table 23 Day 3 GIC and RSB for ITT patients (Study MP505)

Treatment	N	Median	Mean	Std	Min	Max
Patient-rated global impression of change (GIC)						
Placebo	278	2.00	1.77	0.89	0.00	4.00
250mg	269	2.50	2.30	0.90	0.00	4.00
Total	547	2.00	2.03	0.93	0.00	4.00
Patient-rated relief from starting backache (RSB)						
Placebo	278	1.50	1.22	1.09	0.00	4.00
250mg	269	2.00	1.93	1.14	0.00	4.00
Total	547	2.00	1.57	1.17	0.00	4.00

Source: ADGCPR (LOCF)

ANOVA of GIC (Study MP505)

Table 24 Comparisons between treatments for GIC (Study MP505)

Treatment comparison Applying LOCF (variable LGICAVGN used)		Estimate	Standard Error	P-Value	Lower CL	Upper CL
250mg	**Placebo**	0.52	0.076	<.0001	0.37	0.67
Using available data (variable OGICAVGN used)						
250mg	**Placebo**	0.50	0.077	<.0001	0.35	0.65

Source: ADGC3

ANOVA of RSB (Study MP505)

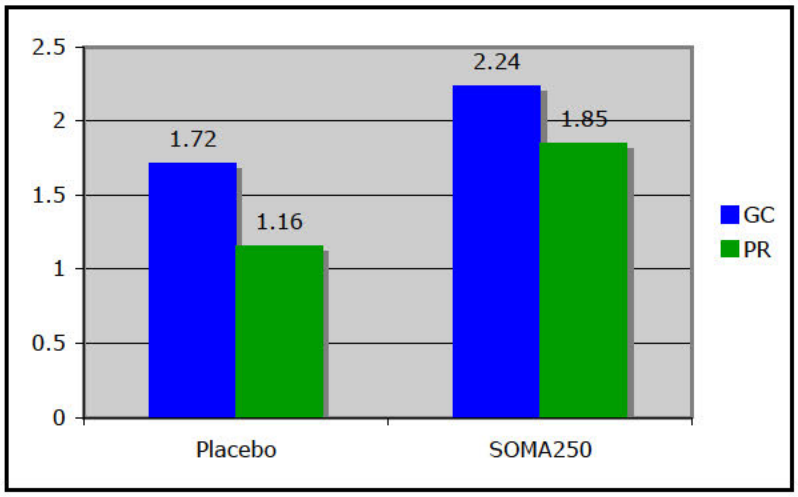
Table 25 Comparisons between treatments for RSB (Study MP505)

Treatment comparison Applying LOCF		Estimate	Standard Error	P-Value	Lower CL	Upper CL
250mg	**Placebo**	0.69	0.095	<.0001	0.50	0.87
Using available data						
250mg	**Placebo**	0.67	0.095	<.0001	0.48	0.85

Source: ADPR3

Based on the results shown in Table 24and Table 25, SOMA 250 mg was superior to placebo for both primary efficacy variables, using an alpha level of 0.025 (Figure 2 depicts the superiority of SOMA 250 to placebo). In addition, the results based on the observed data and those using LOCF estimation were consistent.

Figure 2 LS means of GIC and RSB (Study MP505)



The sponsor also provided tables summarizing the frequencies of the various categories denoting the patients' global impression of change and the patient-rated relief from starting backache. The frequencies for Day 3 and Day 7 are shown below. The sponsor calculated the percentages using the available patients in each treatment group.

Table 26 Frequencies of Global Impression of Change: ITT Population

Time Interval	SOMA 250 mg N=269		Placebo N=278	
Day 3 – morning				
Marked improvement	21	8%	9	3%
Moderate improvement	70	26%	39	14%
Mild improvement	118	44%	105	38%
No change	45	17%	93	33%
Worsening	3	1%	17	6%
Missing	4	1%	2	1%
Day 3 – evening				
Marked improvement	33	12%	13	5%
Moderate improvement	80	30%	42	15%
Mild improvement	98	36%	106	38%
No change	38	14%	77	28%
Worsening	4	1%	8	3%
Missing	8	3%	19	7%
Day 7 – morning				
Marked improvement	71	26%	46	17%
Moderate improvement	74	28%	59	21%
Mild improvement	46	17%	53	19%
No change	21	8%	50	18%
Worsening	2	1%	3	1%
Missing	12	4%	7	3%
Day 7 – evening				
Marked improvement	38	14%	23	8%
Moderate improvement	37	14%	32	12%
Mild improvement	17	6%	23	8%
No change	16	6%	28	10%
Worsening	1	0%	2	1%
Missing	114	42%	108	39%

Source: Table 11-7, Clinical Study Report

Table 27 Frequencies of Patient-rated Relief From Starting Backache

Time Interval	SOMA 250 mg N=269		Placebo N=278	
Day 3 – morning				
Complete relief	14	1%	4	1%
A lot of relief	64	10%	27	10%
Some relief	96	29%	77	28%
A little relief	41	22%	58	21%
No relief	41	35%	93	33%
Missing	5	2%	6	2%
Day 3 – evening				
Complete relief	22	3%	7	3%
A lot of relief	74	14%	39	14%
Some relief	83	26%	70	25%
A little relief	42	23%	62	22%
No relief	32	26%	71	26%
Missing	8	6%	16	6%
Day 7 – morning				
Complete relief	58	12%	32	12%
A lot of relief	82	23%	61	22%
Some relief	37	18%	48	17%
A little relief	15	8%	22	8%
No relief	20	17%	45	16%
Missing	14	4%	10	4%
Day 7 – evening				
Complete relief	28	6%	17	6%
A lot of relief	45	12%	32	12%
Some relief	10	6%	17	6%
A little relief	11	6%	15	5%
No relief	13	10%	28	10%
Missing	116	40%	108	39%

Source: Table 11-9, Clinical Study Report

Analyses of secondary efficacy variables (Study MP505)

The sponsor's analyses of the secondary efficacy variables were based on RMDQ, range of motion, and patient-rated medication helpfulness. Comparisons for Days 3 and 7, as well as for the four different secondary efficacy variables were made separately and no adjustments for multiplicity were applied.

With the exception of the analysis of the range of motion, the other three analyses showed that SOMA dose groups were superior to placebo. For these analyses, this reviewer did not reanalyze the sponsor's data.

Evaluation of Safety

Table 28 and Table 29 show the numbers and percentages of AEs using **Dictionary-Derived Terms** reported in more than 2% of the patients for Study MP502 and MP505, respectively. For complete lists of AEs, see Table 41 and Table 42 in the Appendix. The method by which AEs were classified and counted were provided on page 46, Clinical Study Report of MP502; page 38, Clinical Study Report for MP505.

It was not clear how the sponsor defined "Dictionary-Derived Terms" for AEs.

Table 28 Selected AE findings (Study MP502)

AEs presented as: DICTIONARY-DERIVED TERM; Group totals: 269,264,273	**Treatment**						**N**	**%**
	Placebo		**SOMA 250mg**		**SOMA 350mg**			
	N	**%**	**N**	**%**	**N**	**%**		
SOMNOLENCE	18	6.69	34	12.88	46	16.85	98	12.16
DIZZINESS	2	0.74	16	6.06	19	6.96	37	4.59
HEADACHE	7	2.60	16	6.06	9	3.30	32	3.97
NAUSEA	7	2.60	4	1.52	12	4.40	23	2.85

Source: AE2

Table 29 Selected AE findings (Study MP505)

AEs presented as: DICTIONARY-DERIVED TERM; Group totals: 278,269	**Treatment**				**N**	**%**
	Placebo		**250mg**			
	N	**%**	**N**	**%**		
SOMNOLENCE	**13**	**4.68**	**38**	**14.13**	**51**	**9.32**
DIZZINESS	**9**	**3.24**	**27**	**10.04**	**36**	**6.58**
HEADACHE	**4**	**1.44**	**10**	**3.72**	**14**	**2.56**
NAUSEA	**8**	**2.88**	**2**	**0.74**	**10**	**1.83**

Source: AE2

The number of patients on SOMA 250 or 350 mg experiencing somnolence or dizziness was two times greater than the number of patients on placebo. The number of patients on SOMA 250 mg experiencing headaches was also two times greater than the number of patients on placebo, but the number of patients on SOMA 350 mg experiencing headaches was not much different from the number of patients with headaches on placebo. The number of patients on SOMA 350 mg having nausea was a little less than twice the number of patients on placebo, while the number of patients on SOMA 250 mg having nausea was smaller than the number of patients on placebo.

Overall, patients treated with SOMA (250 or 350 mg) had more reported episodes of somnolence, dizziness and headache than those on placebo. This trend was observed in both Studies MP502 and MP505. These AE findings, in my opinion, can be helpful to the review team when reviewing the proposed label.

An additional evaluation of the safety profile was also conducted by Dr. Eric Brodsky.

Findings in Special/Subgroup Populations

Study MP502

The purpose of the following subgroup analyses is to show consistency of the treatment effect across groups of selected demographic characteristics. Such analyses are of exploratory nature. Based on GIC, SOMA 250 appears to perform better than placebo in patients under 66, among females, and among whites. Based on RSB, SOMA 250 appears to perform better than placebo in patients under 66, among both gender groups, and among non-black patients. Table 30 shows results from the subgroup analyses. The SAS program producing results of the ANOVA can be found in Table 40 of the Appendix.

Table 30 Subgroup analyses by selected demographic characteristics for GIC (Study MP502)

Subgroup	Differences of Least Squares Means						
	Trt1	Trt2	Estimate	Std Err	p-value	Lower Bound of 95% CI	Upper Bound of 95% CI
Age							
≤ 65 yrs N=799	**250mg**	**350mg**	-0.04	0.08	0.5865	-0.20	0.11
	250mg	**Placebo**	0.21	0.08	0.0061	0.06	0.37
	350mg	**Placebo**	0.26	0.08	0.0009	0.11	0.41
Gender							
Female	**250mg**	**350mg**	0.01	0.1125	0.9020	-0.21	0.24
	250mg	**Placebo**	0.35	0.1099	0.0014	0.14	0.57
	350mg	**Placebo**	0.34	0.1079	0.0018	0.13	0.55
Male	**250mg**	**350mg**	-0.04	0.12	0.7577	-0.27	0.20
	250mg	**Placebo**	0.15	0.12	0.2088	-0.09	0.40
	350mg	**Placebo**	0.19	0.12	0.1229	-0.05	0.44
Race							
White	**250mg**	**350mg**	-0.07	0.09	0.4369	-0.25	0.11
	250mg	**Placebo**	0.20	0.09	0.0334	0.02	0.38
	350mg	**Placebo**	0.27	0.09	0.0034	0.09	0.45
Black	**250mg**	**350mg**	-0.11	0.22	0.6093	-0.54	0.32
	250mg	**Placebo**	0.07	0.22	0.7574	-0.36	0.49
	350mg	**Placebo**	0.18	0.21	0.3928	-0.23	0.59
Other	**250mg**	**350mg**	-0.05	0.26	0.8571	-0.58	0.48
	250mg	**Placebo**	0.42	0.25	0.0977	-0.08	0.93
	350mg	**Placebo**	0.47	0.26	0.0769	-0.05	0.99

Source: ADGC3

Table 31 Subgroup analyses by selected demographic characteristics for RSB (Study MP502)

Subgroup	Differences of Least Squares Means						
	Trt1	Trt2	Estimate	Std Err	p-value	Lower	Upper
Age							
≤ 65 yrs N=799	**250mg**	**350mg**	-0.07	0.09	0.4518	-0.25	0.11
	250mg	**Placebo**	0.35	0.09	0.0002	0.17	0.53
	350mg	**Placebo**	0.42	0.09	<.0001	0.24	0.60
Gender							
Female	**250mg**	**350mg**	-0.01	0.13	0.9494	-0.27	0.26
	250mg	**Placebo**	0.50	0.13	0.0002	0.24	0.76
	350mg	**Placebo**	0.51	0.13	<.0001	0.26	0.76
Male	**250mg**	**350mg**	-0.09	0.14	0.5236	-0.37	0.19
	250mg	**Placebo**	0.30	0.15	0.0388	0.02	0.59
	350mg	**Placebo**	0.39	0.15	0.0079	0.10	0.68
Race							
White	**250mg**	**350mg**	-0.10	0.11	0.3430	-0.31	0.11
	250mg	**Placebo**	0.33	0.11	0.0025	0.12	0.55
	350mg	**Placebo**	0.43	0.11	<.0001	0.22	0.65
Black	**250mg**	**350mg**	-0.11	0.24	0.6440	-0.58	0.36
	250mg	**Placebo**	0.16	0.24	0.4952	-0.31	0.63
	350mg	**Placebo**	0.27	0.23	0.2345	-0.18	0.72
Other	**250mg**	**350mg**	-0.17	0.33	0.6177	-0.83	0.50
	250mg	**Placebo**	0.79	0.32	0.0154	0.16	1.42
	350mg	**Placebo**	0.95	0.33	0.0051	0.30	1.61

Source: ADPR3

Study MP505

The purpose of the following subgroup analyses is to show consistency of treatment effect across groups of selected demographic characteristics. Based on GIC and RSB, SOMA 250 appears to perform better than placebo in patients under 66, among both gender groups, and among non-black patients. Table 32 shows results from the subgroup analysis. The SAS program producing results of the ANOVA can be found in Table 40 of the Appendix.

Table 32 Subgroup analyses by selected demographic characteristics for GIC (Study MP505)

Subgroup	Estimate	Std Err	p-value	Lower	Upper
Age					
≤ 65 yrs N=541	0.51	0.08	<.0001	0.36	0.66
Gender					
Female	0.76	0.11	<.0001	0.53	0.98
Male	0.46	0.10	<.0001	0.26	0.67
Race					
White	0.57	0.09	<.0001	0.40	0.75
Black	0.07	0.23	0.7522	-0.38	0.53
Asian	1.10	0.21	<.0001	0.67	1.53

Source: ADGC3 (LOCF)

Table 33 Subgroup analyses by selected demographic characteristics for RSB (Study MP505)

Differences in Least Squares Means					
Subgroup	**Estimate**	**Std Err**	**p-value**	**Lower**	**Upper**
Age					
≤ 65 yrs N=541	0.68	0.10	<.0001	0.49	0.87
Gender					
Female	0.96	0.14	<.0001	0.69	1.24
Male	0.65	0.13	<.0001	0.38	0.91
Race					
White	0.73	0.11	<.0001	0.51	0.95
Black	0.34	0.31	0.2789	-0.28	0.96
Asian	1.36	0.26	<.0001	0.84	1.89

Source: ADPR3 (LOCF)

Summary and Conclusions

Statistical issues and Collective Evidence

Prior to the submission of this application, the Agency recommended the sponsor conduct sensitivity analyses. The Advice letter of 7/12/2006 (IND 71,218) stated, "The statistical aspect of the protocol is acceptable, in general. However, we recommend that you investigate the sensitivity of the results to the procedure for handling missing data using conservative approaches such as a continuous responder analysis and a baseline observation carried forward (BOCF) analysis."

The sponsor did not perform any conservative sensitivity analyses as recommended. The Division's recommendation was based on a general concern that patients who demonstrated improvement in pain but discontinued because of adverse events might possibly be assigned favorable outcomes. The endpoints of interest were highly

significant. In this reviewer's opinion, a conservative imputation strategy (i.e. imputing the worse possible value) would not have likely altered the overall conclusions.

Conclusions and Recommendations

Efficacy

Patients receiving SOMA 250 mg experienced greater relief from back pain after three days compared to patients receiving placebo. In addition, values representing the global impression of change after three days were higher for patients randomized to SOMA 250 mg than placebo. Additional analyses showed that SOMA 350 mg was also superior to placebo based on GIC and RSB. The difference between SOMA 350 and 250 mg groups appeared to be small.

Safety

Patients treated with SOMA (250 or 350 mg) had more reported episodes of somnolence, dizziness and headache than patients treated with placebo. The trend was observed in both Studies MP502 and MP505.

COMMENTS ON LABELING

This reviewer evaluated the sponsor's package insert of 6/13/2007 by verifying selected statistics presented in the areas of **Adverse Reactions** and **Clinical Studies** in the package insert.

Adverse Reactions

Table 34 Adverse reactions

Percent of Patients with Adverse Reactions in Controlled Studies			
Event	**SOMA 250mg (n=548)**	**SOMA 350 mg (n=279)**	**Placebo (n=560)**
Drowsiness	13	17	6
Dizziness	8	7	2
Headache	5	3	2

(b) (4)

Source: Sec. 6.1 of package insert

I have confirmed the accuracy of the percentages presented in Table 34, above, and concluded that the sponsor's numbers are acceptable. However as suggested by the medical reviewer, it is more desirable to present AEs as Table 35, below.

Table 35 Numbers and Percentages of Patients with Adverse Reactions

Numbers and Percentages of Patients with Adverse Reactions in the Low Back Pain Trials			
Adverse Reaction	**Placebo (n=547) n (%)**	**SOMA 250 mg (n=533) n (%)**	**SOMA 350 mg (n=273) n (%)**
Drowsiness	31 (6)	72 (14)	46 (17)
Dizziness	11 (2)	43 (8)	19 (7)
Headache	11 (2)	26 (5)	9 (3)

Source: AECOMB

The sponsor stated in the package insert, (b) (4)

I evaluated the data and found 2% of the patients on SOMA 250mg, 5.5% of the patients on SOMA 350mg, and 2.5% of the patients on placebo discontinued due to AEs. These numbers calculated by this reviewer are very similar to those in the package insert. Thus, this reviewer concludes that the sponsor's numbers are acceptable.

Clinical Studies

Table 36 Sponsor's Summary of Primary Efficacy Analysis (Intent-to-Treat

(b) (4)

Source: Sec. 14 of package insert

The statistics in the sponsor's summary have been verified by this reviewer. This reviewer concludes that the sponsor's numbers based on primary efficacy variables are acceptable. However, results from one of the sponsor's secondary efficacy variables are also presented in the table. This endpoint was one of many explored by the applicant without any adjustment for multiplicity. In general, we do not recommend inclusion of arbitrary endpoints and/or inclusion of endpoints without appropriate multiplicity adjustments.

APPENDIX

Table 37 shows the reasons for discontinuation based on the ITT-patient data.

Table 37 Reason for discontinuation based on sponsor's data (ITT, Study MP502)

Reported Term For The Disposition Event	Treatment						Total	
	Placebo		250mg		350mg			
	N	%	N	%	N	%	N	%
–Dropout–								
Abnormal test procedure result(s)	1	0.4	1	0.4	1	0.4	3	0.4
Adverse event(s)	9	3.3	3	1.1	15	5.5	27	3.3
Lost to follow-up	6	2.2	4	1.5	4	1.5	14	1.7
Other: his pain was much better 2/20/06, so he decided to discontinue his study medication			1	0.4			1	0.1
Other: non compliant with visits			1	0.4			1	0.1
Other: subject stopped taking study medication because subject felt better	1	0.4	1	0.4			2	0.2
Other: subject stopped taking study medication because subject had no pain					1	0.4	1	0.1
Other: subject stopped taking study medication because subject was fine and had no pain			1	0.4			1	0.1
Other: subject stated when back pain cleared he decided to stop taking study drug	1	0.4					1	0.1
Other: subject stopped taking study drug because it was too strong & he felt like he no longer needed it	1	0.4					1	0.1
Subject withdrew consent	2	0.7	4	1.5	5	1.8	11	1.4
Protocol violation			1	0.4	1	0.4	2	0.2
Unsatisfactory therapeutic effect	20	7.4	2	0.8	7	2.6	29	3.6
–Stay on trial–	228	84.8	245	92.8	239	87.5	712	88.3
Total	269	100.0	264	100.0	273	100.0	806	100.0

Source: DEMO1 (DEMO1 created based on DEMO, BASE, DISP2 where ITT=Y)

Table 38 shows the reasons for discontinuation based on the ITT-patient data.

Table 38 Reason for discontinuation based on ITT-patient data (Study MP505)

Reported Term for the Disposition Event	Treatment				Total	
	Placebo		250mg			
	N	%	N	%	N	%
–Dropout–						
Adverse event(s)	5	1.8	8	3.0	13	2.4
Lost to follow-up	1	0.4	2	0.7	3	0.5
Other: e/t subject left town on emergency	1	0.4			1	0.2
Other: subject stopped taking study medication because subject did not have pain			1	0.4	1	0.2
Other: subject stopped taking study medication because subject felt better	1	0.4			1	0.2
Other: pt missed day 3 visit	1	0.4			1	0.2
Other: pt unable to comply with day 3 visit	1	0.4			1	0.2
Other: subject unable to return at day 7 final visit done at day 5	1	0.4			1	0.2
Subject withdrew consent	4	1.4	4	1.5	8	1.5
Protocol violation	2	0.7			2	0.4
Unsatisfactory therapeutic effect	19	6.8	8	3.0	27	4.9
–Stay on Trial--	242	87.1	246	91.4	488	89.2
Total	278	100.0	269	100.0	547	100.0

Source: DEMO1 (DEMO1 created based on DEMO, BASE, DISP2 where ITT=Y)

The sponsor's efficacy data sets, ADGC and ADPR (xpt) were restructured (named ADGC3 and ADPR3) to fit my review tool.

Table 39 SAS program for ANOVA

```
%let std=2;   /*2 5    */
%let v=GC;    /*GC PR  */
%let dv=GIC;  /*GIC PR */
%let ds=L;    /*L O    */
options mstored sasmstore=sasuser fmtsearch=(n117920&std);
ods select Nobs ClassLevels Tests3 LSMeans Diffs;
proc mixed data=n117920&std..AD&v.3(where=(visitnum=3));
class treatment center;
model &ds.&dv.AVGN=treatment center/e3;
lsmeans treatment/cl diff alpha=0.05;
```

Table 40 SAS program for subgroup analysis

```
%let std=2;    /*2 5           */
%let v=PR;     /*GC PR         */
%let dv=PR;    /*GIC PR        */
%let bv=race;  /*agegrp sex race*/
options mstored sasmstore=sasuser fmtsearch=(n117920&std);
data temp;
set n117920&std..AD&v.3;
if trim(left(agegrp))^='>65' then agegrp='<66';
if trim(left(race))^='CAUCASIAN' and trim(left(race))^='BLACK'
/* if study mp505 use this: and trim(left(race))^='ASIAN'*/
then race='OTHER';
proc sort;
by &bv;
%freq(&bv,distinct=subject,libref=,memname=temp);
proc print data=out1; run;
ods select Nobs ClassLevels Tests3 LSMeans Diffs;
proc mixed data=temp(where=(visitnum=3));
by &bv;
class treatment center ;
model L&dv.AVGN=treatment center/e3;
lsmeans treatment/cl diff alpha=0.05; quit;
```

Table 41 AE findings (MP502)

AEs presented as: DICTIONARY-DERIVED TERM; Group totals: 269,264,273	Treatment						N	%
	Placebo		250mg		350mg			
	N	%	N	%	N	%		
SOMNOLENCE	18	6.69	34	12.88	46	16.85	98	12.16
DIZZINESS	2	0.74	16	6.06	19	6.96	37	4.59
HEADACHE	7	2.60	16	6.06	9	3.30	32	3.97
NAUSEA	7	2.60	4	1.52	12	4.40	23	2.85
BLOOD CREATINE PHOSPHOKINASE INCREASED	4	1.49	2	0.76	2	0.73	8	0.99
DIARRHOEA	3	1.12	4	1.52	1	0.37	8	0.99
FATIGUE	2	0.74	4	1.52	2	0.73	8	0.99
ABDOMINAL PAIN UPPER			3	1.14	4	1.47	7	0.87
STOMACH DISCOMFORT	4	1.49	2	0.76	1	0.37	7	0.87
VOMITING	2	0.74	1	0.38	3	1.10	6	0.74
RASH	1	0.37	1	0.38	2	0.73	4	0.50
DRY MOUTH			1	0.38	2	0.73	3	0.37
SEDATION			2	0.76	1	0.37	3	0.37
APATHY			1	0.38	1	0.37	2	0.25
ARTHRALGIA	1	0.37			1	0.37	2	0.25
ASTHENIA	1	0.37			1	0.37	2	0.25
BACK PAIN	1	0.37			1	0.37	2	0.25
BLOOD TRIGLYCERIDES INCREASED	2	0.74					2	0.25
BLOOD URINE PRESENT	1	0.37	1	0.38			2	0.25
CONSTIPATION	1	0.37	1	0.38			2	0.25
DISORIENTATION					2	0.73	2	0.25
DYSPEPSIA			1	0.38	1	0.37	2	0.25
HYPOREFLEXIA	1	0.37			1	0.37	2	0.25
INSOMNIA	2	0.74					2	0.25
MUSCLE SPASMS	1	0.37			1	0.37	2	0.25
PRURITUS	1	0.37			1	0.37	2	0.25
PYREXIA	1	0.37			1	0.37	2	0.25
RED BLOOD CELLS URINE	1	0.37	1	0.38			2	0.25
SINUSITIS	1	0.37			1	0.37	2	0.25
THIRST	1	0.37			1	0.37	2	0.25
URINARY TRACT INFECTION			2	0.76			2	0.25
ABNORMAL DREAMS	1	0.37					1	0.12
ALANINE AMINOTRANSFERASE INCREASED					1	0.37	1	0.12
ANAEMIA			1	0.38			1	0.12
ANOREXIA			1	0.38			1	0.12
AREFLEXIA	1	0.37					1	0.12
ASPARTATE AMINOTRANSFERASE INCREASED					1	0.37	1	0.12
ASTHMA			1	0.38			1	0.12
BACK INJURY	1	0.37					1	0.12
BLOOD POTASSIUM INCREASED			1	0.38			1	0.12
CARBON DIOXIDE DECREASED			1	0.38			1	0.12
COGNITIVE DISORDER					1	0.37	1	0.12
COUGH					1	0.37	1	0.12
DEPRESSION			1	0.38			1	0.12
DERMAL CYST	1	0.37					1	0.12
DYSMENORRHOEA					1	0.37	1	0.12

AEs presented as: DICTIONARY-DERIVED TERM; Group totals: 269,264,273	Treatment						N	%
	Placebo		250mg		350mg			
	N	%	N	%	N	%		
EUPHORIC MOOD					1	0.37	1	0.12
FALL	1	0.37					1	0.12
FEELING ABNORMAL					1	0.37	1	0.12
FEELING DRUNK	1	0.37					1	0.12
FEELING JITTERY	1	0.37					1	0.12
FLUSHING			1	0.38			1	0.12
FOOD POISONING	1	0.37					1	0.12
GAMMA-GLUTAMYLTRANSFERASE INCREASED					1	0.37	1	0.12
GASTROENTERITIS VIRAL	1	0.37					1	0.12
GLOSSITIS			1	0.38			1	0.12
HYPOAESTHESIA					1	0.37	1	0.12
INCREASED APPETITE					1	0.37	1	0.12
INTERVERTEBRAL DISC PROTRUSION					1	0.37	1	0.12
IRRITABILITY			1	0.38			1	0.12
JOINT DISLOCATION	1	0.37					1	0.12
LETHARGY					1	0.37	1	0.12
LIMB INJURY			1	0.38			1	0.12
LIP DRY	1	0.37					1	0.12
MUSCULOSKELETAL STIFFNESS					1	0.37	1	0.12
NASOPHARYNGITIS			1	0.38			1	0.12
NEPHROLITHIASIS					1	0.37	1	0.12
NEUROLOGICAL EXAMINATION ABNORMAL					1	0.37	1	0.12
NIGHTMARE	1	0.37					1	0.12
PAIN	1	0.37					1	0.12
PAIN IN EXTREMITY	1	0.37					1	0.12
PALPITATIONS					1	0.37	1	0.12
PARAESTHESIA					1	0.37	1	0.12
POLLAKIURIA	1	0.37					1	0.12
POLYMENORRHOEA			1	0.38			1	0.12
PROTEIN URINE PRESENT			1	0.38			1	0.12
RESTLESSNESS	1	0.37					1	0.12
RHINORRHOEA			1	0.38			1	0.12
SEASONAL ALLERGY	1	0.37					1	0.12
SHOULDER PAIN					1	0.37	1	0.12
SKIN PAPILLOMA					1	0.37	1	0.12
STRESS					1	0.37	1	0.12
TOOTH ABSCESS					1	0.37	1	0.12
TOOTH DISORDER			1	0.38			1	0.12
TREMOR			1	0.38			1	0.12
UPPER RESPIRATORY TRACT INFECTION	1	0.37					1	0.12
VERTIGO	1	0.37					1	0.12
WHITE BLOOD CELLS URINE POSITIVE	1	0.37					1	0.12

Source: AE2

Table 42 AE findings (MP505)

AEs presented as: DICTIONARY-DERIVED TERM; Group totals: 278,269	Treatment				N	%
	Placebo		250mg			
	N	%	N	%		
SOMNOLENCE	13	4.68	38	14.13	51	9.32
DIZZINESS	9	3.24	27	10.04	36	6.58
HEADACHE	4	1.44	10	3.72	14	2.56
NAUSEA	8	2.88	2	0.74	10	1.83
DRY MOUTH	4	1.44	2	0.74	6	1.10
STOMACH DISCOMFORT	2	0.72	4	1.49	6	1.10
DIARRHOEA	3	1.08	1	0.37	4	0.73
FATIGUE			3	1.12	3	0.55
INSOMNIA	3	1.08			3	0.55
ABDOMINAL DISTENSION			2	0.74	2	0.37
BACK PAIN	1	0.36	1	0.37	2	0.37
CONSTIPATION	1	0.36	1	0.37	2	0.37
IRON DEFICIENCY ANAEMIA	1	0.36	1	0.37	2	0.37
IRRITABILITY			2	0.74	2	0.37
UPPER RESPIRATORY TRACT INFECTION	2	0.72			2	0.37
ABDOMINAL DISCOMFORT			1	0.37	1	0.18
ABDOMINAL PAIN UPPER	1	0.36			1	0.18
ACUTE TONSILLITIS			1	0.37	1	0.18
CARBON DIOXIDE INCREASED	1	0.36			1	0.18
CLUMSINESS			1	0.37	1	0.18
DISORIENTATION			1	0.37	1	0.18
DRUG HYPERSENSITIVITY			1	0.37	1	0.18
DRY EYE	1	0.36			1	0.18
DYSMENORRHOEA	1	0.36			1	0.18
DYSPEPSIA			1	0.37	1	0.18
FLATULENCE	1	0.36			1	0.18
GROIN PAIN	1	0.36			1	0.18
HEART RATE INCREASED			1	0.37	1	0.18
INCREASED APPETITE			1	0.37	1	0.18
INTERVERTEBRAL DISC PROTRUSION			1	0.37	1	0.18
JOINT RANGE OF MOTION DECREASED			1	0.37	1	0.18
JOINT SWELLING			1	0.37	1	0.18
LETHARGY			1	0.37	1	0.18
LIMB INJURY			1	0.37	1	0.18
LIP ULCERATION			1	0.37	1	0.18
MEMORY IMPAIRMENT			1	0.37	1	0.18
MUSCLE SPASMS	1	0.36			1	0.18
NECK PAIN	1	0.36			1	0.18
NEUROLOGICAL EXAMINATION ABNORMAL			1	0.37	1	0.18
PAIN IN EXTREMITY			1	0.37	1	0.18
PALPITATIONS			1	0.37	1	0.18
PNEUMONIA	1	0.36			1	0.18
PSYCHOMOTOR HYPERACTIVITY			1	0.37	1	0.18
RASH	1	0.36			1	0.18
SINUS HEADACHE			1	0.37	1	0.18
SINUSITIS			1	0.37	1	0.18
SPINAL FRACTURE	1	0.36			1	0.18
TENSION HEADACHE	1	0.36			1	0.18

AEs presented as: DICTIONARY-DERIVED TERM; Group totals: 278,269	Treatment				N	%
	Placebo		250mg			
	N	%	N	%		
URINARY TRACT INFECTION	1	0.36			1	0.18
VESSEL PUNCTURE SITE HAEMORRHAGE			1	0.37	1	0.18
VISION BLURRED	1	0.36			1	0.18
VOMITING	1	0.36			1	0.18
WATER INTOXICATION	1	0.36			1	0.18

Source: AE2

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/s/

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Dionne Price
7/27/2007 07:50:05 AM
BIOMETRICS

STATISTICAL REVIEW AND EVALUATION

Stability Study

NDA/SERIAL NO.:	11-792/Supplement 041
DRUG NAME:	Soma (carisoprodol), 250 mg Tablets
INDICATION:	Relief of Discomfort Associated with Acute, Painful Musculoskeletal Conditions
SPONSOR:	MedPointe Pharmaceuticals
DATE RECEIVED BY CENTER:	October 11, 2006
REVIEW PRIORITY:	Standard
DOCUMENTS REVIEWED:	Stability Report and Stability Data
STATISTICAL REVIEWERS:	Roswitha Kelly, M.S. (OTS/OB/DB6)
CONCURRING REVIEWER:	Yi Tsong, Ph.D. (OTS/OB/DB6)
CHEMISTRY REVIEWER:	Donald Klein, Ph.D. (OPS/ONDQA/DPE)
CHEMISTRY BRANCH CHIEF:	James Vidra, Ph.D. (OPS/ONDQA/DPE)
PROJECT MANAGER:	Sharon Turner-Rinehardt (OND/ODEII/DAARP)

Keywords: Stability, Shelf life.

Distribution: NDA 11792-Soma 250 mg
OND/ODEII/DAARP/S. Turner-Rinehardt
ONDQA/DPE/D. Klein, J. Vidra
OTS/OB/DB6/Roswitha Kelly, M.S., Yi Tsong, Ph.D.,
Stella Machado, Ph.D., Ms. S. Tinku
OTS/OB/R. O'Neill, Ph. D., L. Patrician, M.S.

File Directory: RKelly: *C:\Data\N11792_Soma_stab_f1.doc*

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor requested a 36-month shelf life based on 12 month stability data from one full-scale and two one-third-scale registration batches of the 250 mg product and the product history of Soma 350 mg tablets.

In the reviewer's opinion, an extrapolated shelf life of 24 months is supported based on the assay and dissolution data of the 250 mg product. An extrapolation to 36 months can be investigated once the 250 mg product has been stored for at least 24 months.

The sponsor relied on the approved 90-month shelf life of the 350 mg product to support a longer extrapolation for the 250 mg product. The sponsor's description of differences in the manufacture of the two strengths is sparse. The evaluation of their potential impact on the stability of the 250 mg product is left to the expertise of the reviewing chemist.

The impurities data could not be analyzed as submitted. The reviewer decided against modeling these data because of potential validity issues which will be addressed by the reviewing chemist and because these data are not likely to be stability limiting.

The sponsor's statistical model to declare independence of the product's stability from the packaging was considered flawed. In addition, the reviewer's analyses of the dissolution data did not support such a conclusion.

The reviewer recommends that three, not one, production batches will be put on stability when they become available because the current data are only from registration batches and the production batches will be packaged into pouches with the modified (b) (4) component.

1.2 Overview of the Submission

The sponsor submitted a desk copy of Supplement 041, Amendment 4, on March 2, 2007. The reviewer's desk copy contained the sponsor's stability report for the 250 mg tablets, the comparison report for the change in a packaging component, the stability data sheets for the 250 mg tablet, and the sponsor's data analyses. In addition, the sponsor's report (b) (4) dealt with the 350 mg product and Attachment 3 gave the editorial changes and corrections.

1.3 Principal Findings

1.3.1 Sponsor's Results and Conclusions

The sponsor analyzed assay data with a stability program that had been provided by FDA in 1992 and estimated a shelf life of 84 months. In addition, they concluded that the stability of the 250 mg tablets was independent of packaging. They described the range of the observed dissolution data but did not analyze them statistically. They concluded that impurities data could not be statistically analyzed. Based on these findings and conclusions and relying on the long term stability of the marketed 350 mg tablets which are made from the same (b) (4) the sponsor requested an extrapolated shelf life of 36 months.

1.3.2 Reviewers' Results and Conclusions

Using basically the same program the sponsor had employed, the reviewer analyzed both the assay and dissolution data and estimated an extrapolated shelf life of 54 months.

Most impurity data were recorded as non-numeric and as such were not amenable to statistical analysis. It was determined that modeling these data would not be necessary as they were not likely stability limiting. Any potential issues with the validity of the method will be addressed by the reviewing chemist.

An analysis of the dissolution data showed that the stability of the 250 mg tablets was not independent of packaging.

The reviewer concluded that an extrapolated 24-month shelf life was supported for the 250 mg tablets but did not agree with the sponsor that a 36-month extrapolated shelf life was appropriate.

The reviewer suggests that the sponsor put three, not one, production batches on stability when they become available, as this shelf life will be based on registration batches only, two of which are only 1/3 scale, and because the production batches will be packaged into the modified pouches.

1.3.3 Extent of Evidence in Support of Requested Extension of Expiry

The sponsor submitted 12-month stability data from one full-scale and from two one-third-scale registration batches which were stored at 25°C/60%RH. These data would be sufficient to support a shelf life extension to 24 months if proper statistical analyses would lead to such a conclusion.

The sponsor relied on the stability of the 350 mg product, which has an approved shelf life of 90 months, to request a 36-month shelf life. Both tablets are made from the same

(b) (4) and differ only in tablet weight and a minor component in the pouch film. However, potential differences in stability due to tablet weight have not been addressed adequately and in general a shelf life extrapolation is limited to at most 12 months beyond the actual long-term data.

1.3.4 Statistical Issues

The sponsor requested a 36-month shelf life based on a statistical analysis of the assay data and a reliance on the stability of the 350 mg tablet which is made from the same (b) (4) This represents a 24-month extrapolation beyond the 12-month observed long-term stability data of the 250 mg product. Though the 250 mg tablets appeared stable based on the analyses of potency and dissolution data, an extension of shelf life by more than 12 month does not follow ICH guidelines.

The sponsor did not analyze dissolution data to estimate a shelf life based on this attribute. However, the reviewer's analyses supported an extrapolated shelf life.

The impurities data presented challenges as most data were recorded as non-numeric. However, as it is not likely that these data will become stability limiting, no attempt was made to model the data. The evaluation of the potential lack of validity of the method is left to the expertise of the reviewing chemist

The sponsor claimed that the stability of the 250 mg tablets was independent of packaging. This conclusion was not supported by an analysis of the dissolution data.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

Dr. Donald Klein, OPS/ONDQA/DPE, requested the Division of Biometrics 6 on April 16, 2007, to evaluate the sponsor's supplement of March 2, 2007. The supplement contained the sponsor's stability report and data and the analyses of the 12-month assay data of the 250 mg tablet. In addition, the differences between the 250 mg tablets and the approved 350 mg tablets were described. The 350 mg tablets have an approved shelf life of 90 months.

2.2 Overview of Stability Study

The sponsor submitted 12-month stability data from three 250 mg registration batches stored at 25°C/60%RH with a request for a 36-month shelf life. One registration batch was full scale, the other two were at 1/3 scale. The sponsor plans to put at least one

production batch on stability when they become available. In addition, Attachment F contained stability reports and data from the marketed 350 mg tablets as additional support.

2.3 Data Analyzed and Sources

The desk copy of March 2, 2007, contained the stability data as hard copy. Upon request, the sponsor provided the stability data for assay and individual dissolution of the 250 mg tablets as Excel data sheets in an email to the project manager, Ms. Sharon Turner-Rinehardt. The reviewer converted these Excel sheets to SAS data sets and applied the in-house stability program to assay and individual dissolution data by package type. Additional analyses were performed to assess potential stability differences between package types.

2.4 The Stability Study

2.4.1 Sponsor's Analyses, Results, and Conclusions

The sponsor analyzed only the assay data collected from the 250 mg product packaged into promotional unit-dose (b) (4) pouches or into 100-count HDPE bottles and stored at room temperature. Each batch was tested initially and at 1.5, 3, 6, 9, and 12 months. They used a stability program which had been made available to industry by the Office of Biostatistics in 1992. They estimated an 84-month extrapolated shelf life.

The sponsor wished to show that the product's stability is independent of packaging. They used the assay data from both package types in one model which allowed each package type to have an individual intercept and slope. The data could be pooled to estimate a common slope and the sponsor concluded that the stability of Soma 250 mg is independent of packaging.

The sponsor noted that the 250 mg tablet is made from the same (b) (4) as the 350 mg tablet which has an approved shelf life of 90 months. Reasoning that the lower tablet weight of the 250 mg tablet should not affect stability, they requested a 24-month shelf life extrapolation beyond the 12 month actual data.

2.4.2 Reviewers' Analyses, Results, and Conclusions

The reviewer analyzed the potency data with internal software (eStable) that relies on the same program the sponsor used. She obtained numerically identical results for the assay data of the 250 mg tablets when packaged in 100-count bottles or in unit-dose CR pouches. The sponsor did not provide the individual intercepts of the parallel regression lines, but the ANCOVA tables and the common slope estimates were identical between

the sponsor and the reviewer. The reviewer's software allowed for potentially longer extrapolation than what the sponsor had used. Based on this feature she obtained 194 and 95 months of extrapolated shelf lives for bottles and pouches respectively.

The sponsor did not provide analysis results for dissolution. The reviewer analyzed the individual dissolution values as provided by the sponsor in an email to Ms. Turner-Rhinehardt (May 10, 2007). The data from the three batches packaged into 100 count bottles could not be pooled. However, the six replications per time point resulted in the confidence limit being close to the regression line which in turn resulted in extrapolated shelf lives of at least 54 months. The dissolution data obtained from the unit-dose pouches pooled to a common slope but different intercepts. For this package type, the shortest extrapolated shelf life was 78 months despite an apparent poor linear fit. As can be seen from Figures 3 and 4 (Appendix), there were unusually low readings at Month 3 for both the bottles and pouches. Still, if the data are valid, the product can be expected to meet the criterion of at leas (b) (4) percent dissolution for 54 months.

The reviewer's detailed analysis results are given in the Appendix. It is noted that the R^2's are fairly low for some models. R^2 gives a measure of how good the linear fit is, but is also dependent on the slope estimate. If the slope estimate is almost zero, so will be R^2 regardless of how good the fit is. Taking both aspects (linearity and slope estimate) into account, the reviewer concluded that the linear regression models fitted these data adequately and that the estimated shelf lives are appropriate.

Most individual and total impurities were recorded as below the level of quantitation (LOQ) or as not detected (ND). Table 1 gives the impurities above LOQ per batch and package type. Batch 27-02-05s did not have a single impurities' measurement that was above LOQ. Batch 27-02-04s had a single measurable (b) (4) reading in both the bottle and the pouch, but not at the same time. Batch 27-02-03s had a single (b) (4) reading at month 6 when packaged in bottles and two (b) (4) readings and one (b) (4) reading at various months when packaged in pouches. In general, Total Impurities is the sum of the impurities listed here, except for batch 27-02-03s in bottles where a single unknown impurity also contributed to the Total. The challenge of determining a potential analysis of these data was two-fold. One was related to whether the data could be considered valid, as impurities were measured at the occasional time point but fell below the level of quatitation again at subsequent time points. This issue will be addressed by the reviewing chemist. The second challenge was, if the data were deemed valid, which numeric values to assign to '<LOQ' or 'ND'. One approach could be to assign random numbers between zero and the value given for the limit of quantitation for each of the impurities. However, such an approach would lead to long shelf life estimates as the assignment of random numbers would result in slopes close to zero and little variation around the regression lines. The actual observed levels of impurities (those greater than LOQ) would change these slopes by little. Hence there is no need of such an analysis. In general, if the data are valid, they are not likely to become stability limiting and no further attempt to evaluate them was made.

Table 1: Summary of Measurable Impurities for Soma 250 mg in Bottle or Pouch

Batch	Package	(b) (4)
27-02-03s	Bottle	
27-02-03s	Pouch	
27-02-04s	Bottle	
27-02-04s	Pouch	
27-02-05s	Bottle	
27-02-05s	Pouch	

The reviewer concluded that an extrapolation of the shelf life beyond the actual 12-month data is supported by the statistical analyses. The sponsor's request for a 24-month extrapolation seems inconsistent with ICH guidelines, whereas a 12-month extension seems warranted based on the analyses of both the assay and dissolution data obtained from the three registration batches stored at room temperature.

The reviewer is aware that the 250 mg and 350 mg strengths are made from the same (b) (4) The different strengths are achieved through (b) (4) different tablet weights. The 350 mg strength has an approved shelf life of 90 months. The sponsor stated 'Since carisoprodol 250 mg tablets are manufactured using the same formula and (b) (4) as the Soma 350 mg tablets but (b) (4), it is expected that they will exhibit the same stability profile as the parent Soma 350 mg product.' The sponsor did not submit any further details or data in support of this reasoning and hence the reviewer leaves the decision as to its appropriateness to the expertise of the reviewing chemist. If there is any doubt as to whether the (b) (4) has stability as good as the 350 mg tablet, in the reviewer's opinion three production batches, not one, should be put on stability when they become available.

The sponsor will change (b) (4) component of the pouch when manufacturing production batches. The decision of any potential impact of the change in the (b) (4) component of the pouch material is left to the expertise of the reviewing chemist. The reviewer would suggest that the sponsor put three, not one, production batch on stability.

The sponsor had concluded that the stability of the 250mg tablet is independent of packaging. The reviewer re-analyzed the assay data with the ANCOVA model given in

(1), i.e. including batch and package type and their interaction into the model. The sponsor had analyzed a model with package and time only, i.e. had not included batch in this model. Following rules for reducing the model proposed by Tsong et al.[1], the reviewer's final model (see (2)) included a common slope but different intercepts for batch and package type, i.e. there was not enough evidence to conclude a different loss of potency (over time) between the two package types. The model fit was acceptable at 62 percent of the total variation. However, this conclusion is based on only 12 month data from three registration batches and the study was likely to have had low power to conclude a significant difference between the stability patterns of the product packaged in bottles versus pouches. The dissolution data did not support a model with a common slope for the packages. In fact, the model could not be reduced at all because the slope term for the batch by package interaction was significant at α=0.25. As there were six times as many data points for dissolution as there were for assay, observing a significant difference between the slopes of batches and package types is not surprising. Overall, one cannot conclude that the stability of Soma 250mg is independent of packaging.

$$y = \mu + b + p + bp + bt + pt + bpt + \varepsilon \quad (1)$$

$$y = \mu + b + p + t + \varepsilon \quad (2)$$

Details of the analyses discussed above are given in the Appendix.

2.5 Statistical and Technical Issues

Most data for impurities (b) (4) and for Total Impurities were recorded as below the level of quantitation or as not detectable. Hence the data as submitted were not amenable to statistical analysis. The reviewer considered assigning random numbers between zero and the level of quantitation but decided against such an analysis. Such an approach would likely result in long shelf life estimates (slopes close to zero and little variability around the regression lines) but mask the inconsistency of the reported data, namely recording measurable impurities at some time points which are no longer detectable at later time points. From a statistical point of view, the impurities are not likely to be stability limiting. The validity of the method will be addressed by the reviewing chemist.

As noted above, an extrapolated shelf life is supported by the assay and dissolution data. However, the length of the extrapolation should follow ICH guidelines, i.e. not be more than 12 months beyond the data.

The sponsor stated that the stability of the Soma 250 mg was independent of packaging. The reviewer agreed with the sponsor that the slopes of the two package types could be

[1] Y. Tsong et al: 'Stability Studies of Pharmaceuticals' in *Statistics in the Pharmaceutical Industry*, 3rd edition, Buncher and Tsay Editors, 2005.

pooled for the assay data though she used a more detailed initial ANCOVA model. It needs to be kept in mind that the observed finding may be due to lack of power for this comparison and not necessarily imply an identical stability pattern for the two package types. For the dissolution data, the full model could not be reduced at all, indicating significant differences in the slopes for packages and batches. The power for this test is much higher than it was for the assay data because there are six times as many data points for dissolution. Overall, one cannot conclude that the stability of Soma 250 mg is independent of packaging.

2.6 Statistical Evaluation of Collective Evidence

The sponsor provided 12-month stability data from three 250 mg registration batches stored at 25°C/60%RH. An extrapolated shelf life is supported based on the assay and dissolution data submitted. The submitted impurities data showed un-interpretable results. Most data points were listed as not detectable or under the level of quantitation. However, there were occasional measurable impurities at a given month which fell again below LOQ at following time points. The reviewing chemist alerted the reviewer to these inconsistencies and it was decided that no attempt would be made to estimate a shelf life based on these data. The validity of the method will be discussed by the reviewing chemist and these attributes are not likely to become stability limiting.

2.7 Conclusions and Recommendations

The reviewer independently estimated expiries based on assay and on 60-minute dissolution data. Both attributes supported a shelf life extension beyond the observed 12-month data. Relying on the long shelf life (90 months) of the marketed 350 mg product, the sponsor requested a 24-month extension for the 250 mg tablet, which seems to go beyond ICH guidance. The actual granting of the shelf life is left to the expertise of the reviewing chemist.

The impurities data could not be analyzed as submitted but are not likely to be stability limiting. Any issues with respect to the validity of the method will be addressed by the reviewing chemist.

3. Appendix: Detailed Analysis Results

Table 2: Shelf Life Evaluation for Assay of Soma 250 mg Tablets in 100 ct Bottles

Source	SS	DF	MS	F-Statistic	P-Value
A	3.1859	4	0.7965	2.7718	0.0765
B	2.9233	2	1.4617	5.0868	0.0251
C	0.2626	2	0.1313	0.4569	0.6438
RESIDUAL	3.4481	12	0.2873		

Fitted Line	R-Square	Batch	Estimated Expiry Period
Y = 99.7693 - 0.0164 x Time	0.4478	270203	149
Y = 100.3360 - 0.0164 x Time	0.4478	270204	158
Y = 100.7526 - 0.0164 x Time	0.4478	270205	164
	.	~MIN~	149

Figure 1: Shelf Life for Assay of Batch 27-02-03s of Soma 250 mg Tablets in 100-ct Bottles

Table 3: Shelf Life Evaluation for Assay of Soma 250 mg Tablets in CR Pouch

Source	SS	DF	MS	F-Statistic	P-Value
A	7.0249	4	1.7562	5.9678	0.0070
B	6.7411	2	3.3706	11.4533	0.0017
C	0.2838	2	0.1419	0.4822	0.6289
RESIDUAL	3.5314	12	0.2943		

Fitted Line	R-Square	Batch	Estimated Expiry Period
Y = 100.1342 - 0.0573 x Time	0.6714	270203	95
Y = 101.5009 - 0.0573 x Time	0.6714	270204	108
Y = 101.3509 - 0.0573 x Time	0.6714	270205	106
	.	~MIN~	95

Figure 2: Shelf Life for Assay for Batch 27-02-03s of Soma 250 mg Tablets in CR Pouch

Table 4: Shelf Life Evaluation for Dissolution of Soma 250 mg Tablets in 100 ct Bottle

Source	SS	DF	MS	F-Statistic	P-Value
A	23.0222	4	5.7556	1.6931	0.1574
B	6.7222	2	3.3611	0.9887	0.3756
C	16.3000	2	8.1500	2.3974	0.0961
RESIDUAL	346.7497	102	3.3995		

Fitted Line	R-Square	Batch	Estimated Expiry Period
Y = 99.0333 - 0.0222 x Time	0.0049	27-02-03	170
Y = 99.4094 - 0.1520 x Time	0.0840	27-02-04	67
Y = 99.6012 - 0.2468 x Time	0.2446	27-02-05	54
	.	~MIN~	54

Figure 3: Shelf Life for Dissolution for Batch 27-02-05s of Soma 250 mg Tablets in 100-ct Bottle

Table 5: Shelf Life Evaluation for Dissolution of Soma 250 mg Tablets in CR Pouch

Source	SS	DF	MS	F-Statistic	P-Value
A	36.4168	4	9.1042	2.7234	0.0335
B	27.3519	2	13.6759	4.0910	0.0195
C	9.0649	2	4.5325	1.3558	0.2623
RESIDUAL	340.9778	102	3.3429		

Fitted Line	R-Square	Batch	Estimated Expiry Period
Y = 98.9953 - 0.1684 x Time	0.1896	27-02-03	81
Y = 98.2453 - 0.1684 x Time	0.1896	27-02-04	78
Y = 99.4675 - 0.1684 x Time	0.1896	27-02-05	83
	.	~MIN~	78

Figure 4: Shelf Life for Dissolution for Batch 27-02-04s of Soma 250 mg Tablets in CR Pouch

Table 6: Comparing Slopes of Packaging Based on Assay Data

Full Model

Source	DF	SS	MS	F value	Prob>F	R-Square
Model	11	13.5501	1.2318	4.2358	0.0015	0.660
Error	24	6.9796	0.2908	_	_	
Corrected Total	35	20.5297	_	_	_	

Item No.	Source	DF	SS	MS	F value	Prob>F
1	batch	2	4.0925	2.0462	7.0362	0.0039
2	PKG	1	1.7778	1.7778	6.1131	0.0209
3	batch*PKG	2	0.1376	0.0688	0.2366	0.7911
4	MONTH	1	0.8704	0.8704	2.9929	0.0965
5	MONTH*batch	2	0.0545	0.0273	0.0937	0.9108
6	MONTH*PKG	1	0.2686	0.2686	0.9237	0.3461
7	MONTH*batch*PKG	2	0.4919	0.2459	0.8457	0.4417

Final Model

Source	DF	SS	MS	F value	Prob>F	R-Square
Model	6	12.7351	2.1225	7.8969	0.0000	0.620
Error	29	7.7946	0.2688	_	_	
Corrected Total	35	20.5297	_	_	_	

Item No.	Source	DF	SS	MS	F value	Prob>F
1	batch	2	8.6489	4.3244	16.0892	0.0000
2	PKG	1	2.2003	2.2003	8.1862	0.0078
3	batch*PKG	2	1.0156	0.5078	1.8892	0.1693
4	MONTH	1	0.8704	0.8704	3.2383	0.0823

Table 7: Comparing Slopes of Packaging Based on Dissolution Data

Full and Final Model

Source	DF	SS	MS	F value	Prob>F	R-Square
Model	11	170.8651	15.5332	4.6076	0.0000	0.199
Error	204	687.7275	3.3712	_	_	
Corrected Total	215	858.5926	_	_	_	

Item No.	Source	DF	SS	MS	F value	Prob>F
1	batch	2	3.9461	1.9730	0.5853	0.5579
2	PKG	1	4.2020	4.2020	1.2464	0.2655
3	batch*PKG	2	0.4920	0.2460	0.0730	0.9297
4	MONTH	1	91.7053	91.7053	27.2025	0.0000
5	MONTH*batch	2	13.8588	6.9294	2.0555	0.1307
6	MONTH*PKG	1	0.7579	0.7579	0.2248	0.6359
7	MONTH*batch*PKG	2	11.5061	5.7531	1.7065	**0.1841***

***As** $p<0.25$ one cannot reduce this model.

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Roswitha Kelly
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	11-792/SE2-041
Submission Dates	11/10/12006; 2/8/2007; 4/12/2007; 6/14/2007; 7/10/2007
Brand Name	SOMA®
Generic Name	Carisoprodol
Reviewer	Lei Zhang, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology 2 (DCP2)
OND Division	Anesthesia, Analgesia, and Rheumatology Products (DAARP)
Applicant	MedPointe Pharmaceuticals
Type of Submission; Code	Efficacy Supplement; SE2
Relevant IND	IND 71,218
Formulation; Strength(s)	Tablet; 250 mg
Indication	For the relief of discomfort associated with acute, painful musculoskeletal conditions.
Proposed Dosing Regimen	The recommended dose of SOMA is 250 mg three times a day and at bedtime (b) (4)

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

1.1 Recommendations

From a Clinical Pharmacology perspective, the application is acceptable provided that the Sponsor and the Agency can come to a mutually satisfactory agreement regarding language in the package insert.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

This supplement NDA is an efficacy supplement for a new lower dose strength of SOMA® (250 mg tablets). SOMA® is currently marketed as 350 mg tablets. It was approved in May 1959 according to the requirements at that time. Safety and efficacy of the current 350 mg SOMA product were reviewed under DESI and deemed safe and effective with a Federal Register Notice (40 FR 29399) in August 1974. The approved dose regimen is 350 mg three times a day and at bedtime for adults. Usage in patients under age 12 is not recommended.

To support the approval for this sNDA for the SOMA 250 mg tablets, the Sponsor conducted 2 double-blinded, placebo-controlled clinical studies and two pharmacokinetic studies.

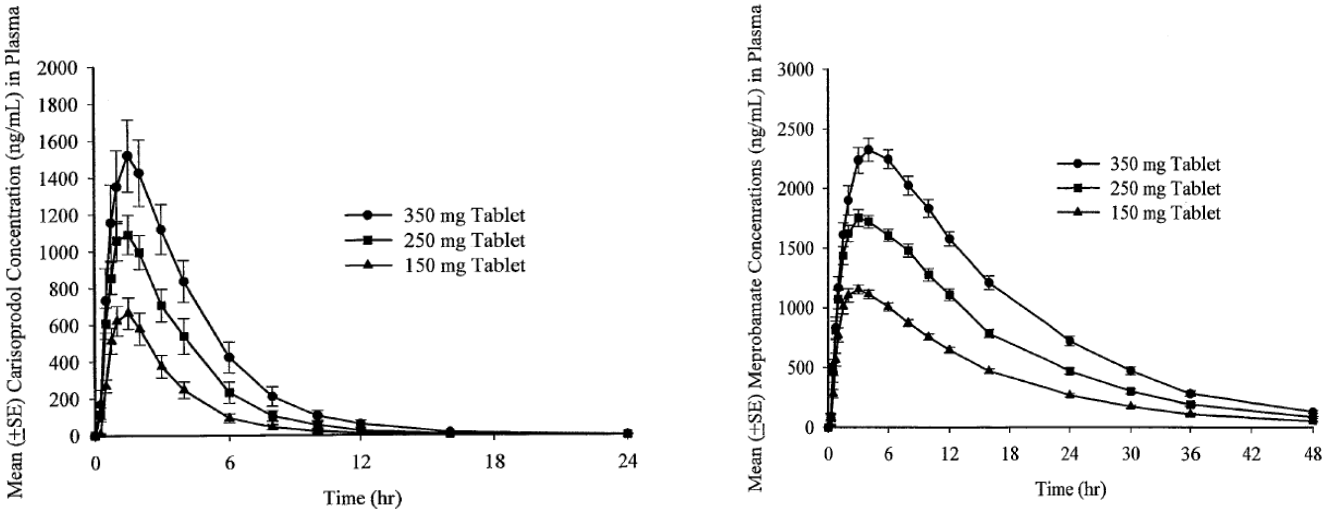
The two PK studies are: Study 501 (a relative bioavailability study) and Study 500 (food effect study). Both studies enrolled 12 male and 12 female subjects to allow a secondary analysis based on gender.

Study 501: Pharmacokinetics and Relative Bioavailability to 350 mg SOMA
Dose-normalized AUCt, AUCinf, and Cmax for carisoprodol and its active metabolite, meprobamate, were equivalent between 250 and 350 mg carisoprodol tablets (Table 1). Exposure of meprobamate was higher than carisoprodol (50% higher for Cmax and 6-fold higher for AUC). The half-life of meprobamate was also longer (10 hours vs. 2 hours for carisoprodol) (Table 1 and Figure 1).

Meprobamate is a Schedule IV controlled substance with known potential for abuse. Exposure of meprobamate in most patients is higher than that of carisoprodol after 2 hours post-dose. The sedative effect of carisoprodol may be partially due to meprobamate.

Table 1. Summary of the Pharmacokinetic Parameters (Mean ± SD) of Carisoprodol and Meprobamate and the 90% Confidence Intervals (Dose-Normalized) for the Comparison of the Pharmacokinetic Parameters (250 mg vs. 350 mg).

	250 mg (Test)	350 mg (Reference)	Ratios of Geometric Means (%)	90% CI Lower	90% CI Upper
Carisoprodol					
Cmax (µg/mL)	1.2 ± 0.5	1.8 ± 1.0	104.3	91.27	119.14
AUCt (µg*hr/mL)	4.5 ± 3.1	6.9 ± 5.0	91.89	85.47	98.79
AUCinf (µg*hr/mL)	4.5 ± 3.1	7.0 ± 5.0	92.02	85.67	98.84
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	105.33	102.55	108.17
AUCt (µg*hr/mL)	31 ± 5.6	44 ± 8.2	98.76	96.18	101.41
AUCinf (µg*hr/mL)	32 ± 6.2	46 ± 9.0	98.53	95.76	101.38
Tmax (hr)	3.6 ± 1.7	4.5 ± 1.9			
$T_{1/2}$ (hr)	9.7 ± 1.7	9.6 ± 1.5			

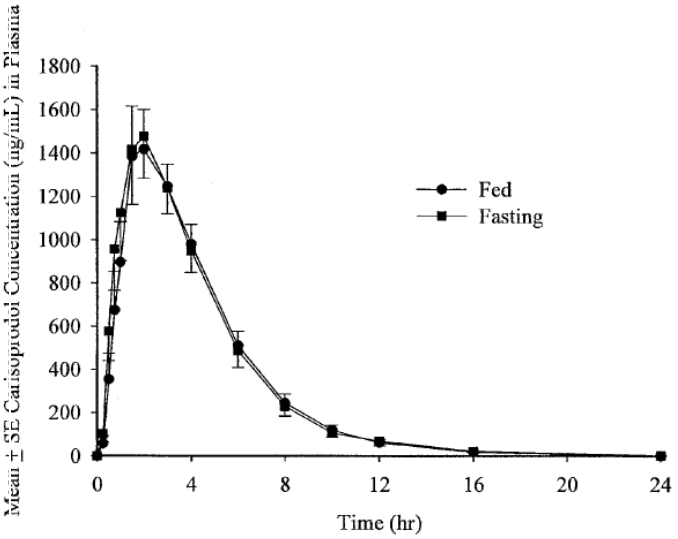


a. Carisoprodol b. Meprobamate

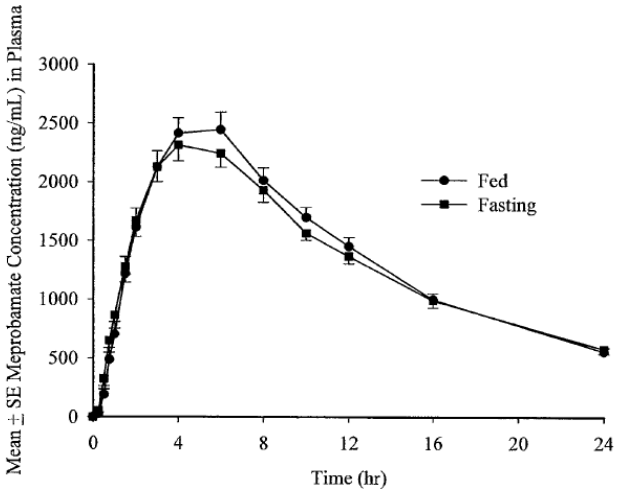
Figure 1. Mean ± SE Carisoprodol (a) and Meprobamate (b) Concentration (ng/mL) in Plasma After a Single Dose of a Carisoprodol Tablet Given to Healthy Subjects.

Study 500: Food Effect

A high fat meal does not affect C_{max} or AUC_{inf} following 350 mg SOMA dosing. Food also does not seem to change the absorption rate of carisoprodol.



a. Carisoprodol



b. Meprobamate

Figure 2. Mean ± SE Plasma Carisoprodol (a) and Meprobamate (b) Concentrations under Fasting (■) and Fed (●) Conditions.

Gender Effect (Study 501 and Study 500):

Both Studies 501 and 500 showed that exposure of carisoprodol and meprobamate were higher in female subjects than in male subjects. The gender difference was more profound for carisoprodol exposure indicating that body weight may not be the only factor contributing to higher exposure in female subjects and that overall metabolism of carisoprodol may be slower in female subjects (Table 2). The results were contrary to previous data cited in SOMA labeling that indicated females had higher clearance.

Table 2. Percent Difference of Means in Male and Female Subjects after Receiving 250 mg or 350 mg Carisoprodol Tablets (Studies 500 and 501).

*Difference of Means (%)	Carisoprodol		Meprobamate	
	Cmax	AUC(0-∞)	Cmax	AUC(0-∞)
Study 501-250 mg	23	72	18	8
Study 501-350 mg	61	79	29	15
Study 500-350 mg Fast	106	89	31	35
Study 500-350 mg Fed	74	83	36	29

*Percent difference of means = (Female-Male)/Male.

Box-and-Whisker plots for Cmax and AUC values of carisoprodol sorted by gender were shown in Figure 3 for all three doses in Study 501.

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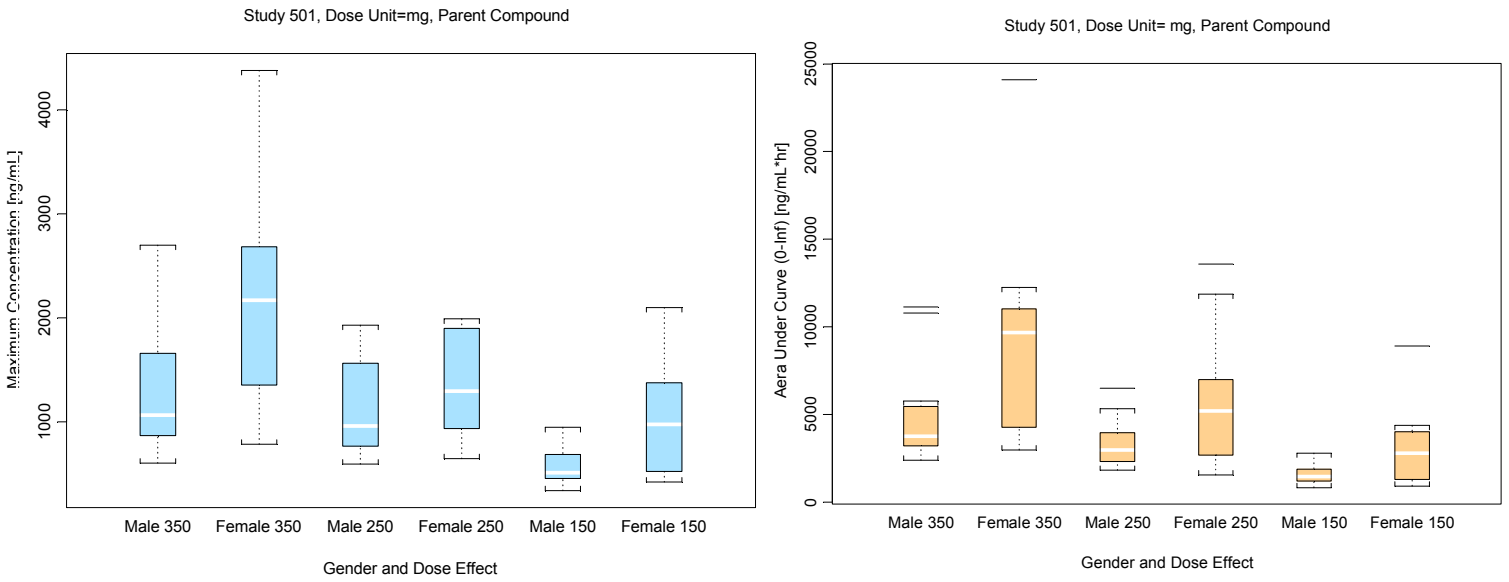


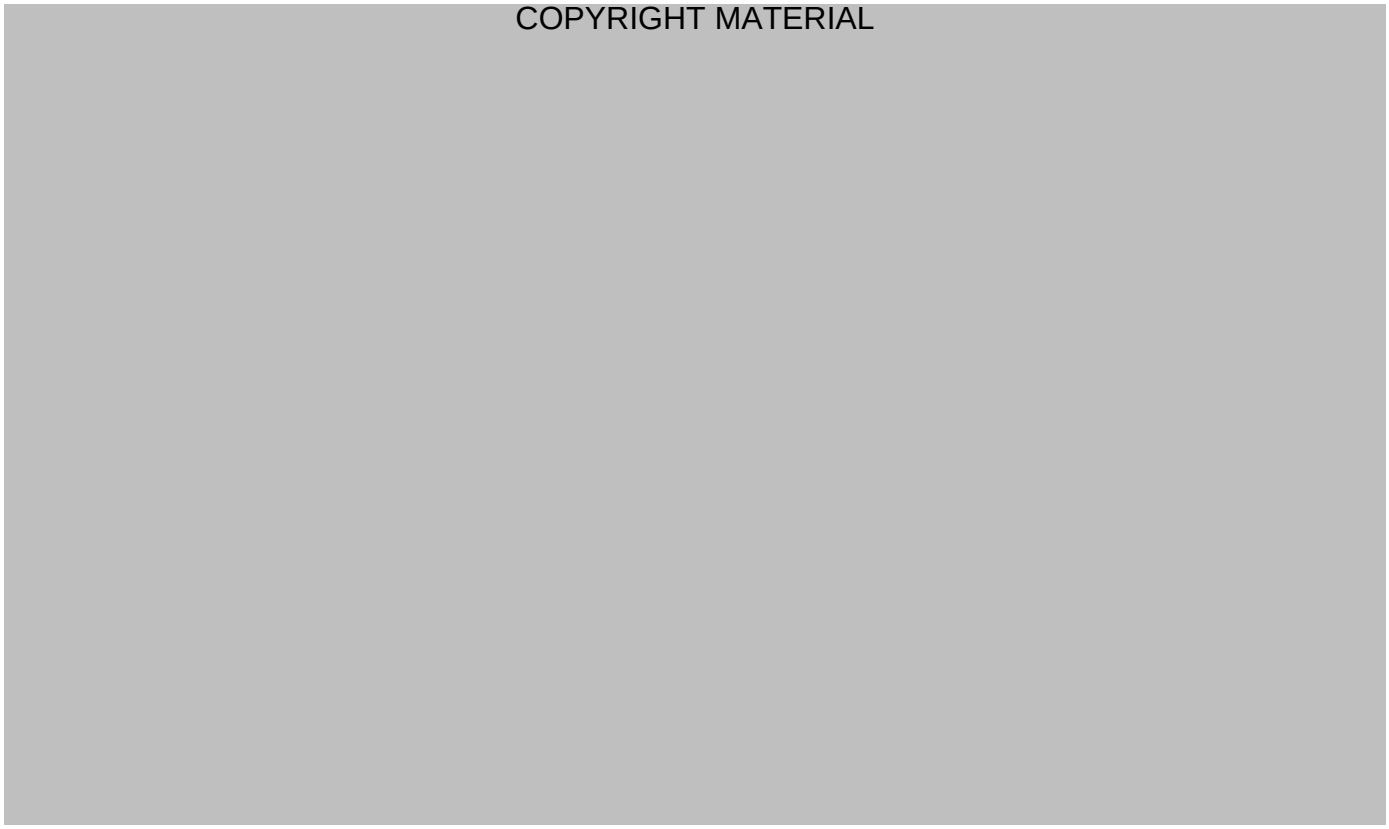
Cmax **AUCinf**

Figure 3. Box-and-Whisker Plots for Cmax and AUC Values of Carisoprodol Sorted by Gender (Study 501).

Effect of CYP2C19 Polymorphism (Literature):

Literature information is available on the effect of CYP2C19 polymorphism on the PK of carisoprodol.[1] Data from Reference 1 (Table 3 below) showed that in subjects with reduced function of CYP2C19 (CYP2C19 poor metabolizers, PMmeph), exposure of carisoprodol was four times that of extensive metabolizers (EM). In contrast, exposure of meprobamate was approximately half in poor metabolizers (PMmeph) compared to that in extensive metabolizers (EM). Half-life of carisoprodol was also longer in PM than EM (4 vs. 2 hours). It is not clear what other enzymes are involved in carisoprodol metabolism in poor metabolizers.

[1] Dalen, P., *et. al.,* Formation of meprobamate form carisoprodol is catalyzed by CYP2C19. *Pharmacogenetics* 6: 387-394, 1996.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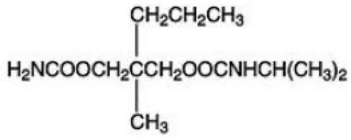
2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Table 2.1.1.1. Physical-Chemical Properties of Carisoprodol

Drug Name	Carisoprodol
Chemical Name	N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate
Structure and Molecular Formula	
	$C_{12}H_{24}N_2O_4$
Molecular Weight	260.33
Appearance	White, crystalline powder
Solubility	Very slightly soluble in water; freely soluble in alcohol, in chloroform, and in acetone; its solubility is practically independent of pH

SOMA (carisoprodol) 250 mg tablets are round, white tablets. The formulation of 250 mg SOMA tablets is the same as the current approved 350 mg SOMA tablets. Both active and inactive ingredients are proportional between the dose strengths. See Section 2.5.1 for composition information.

2.1.2 What is the proposed mechanism of drug action and therapeutic indication? What are the proposed dosage recommendations for the proposed indication?

Carisoprodol is a centrally acting skeletal muscle relaxant that does not directly relax tense skeletal muscles in man. The mode of action of carisoprodol in relieving acute muscle spasm of local origin has not been clearly identified, but may be related to its sedative properties.

The proposed indication for 250 mg SOMA tablets is slightly different from what is in the current SOMA 350 mg tablet labeling.

	Current SOMA Labeling (350 mg)	Proposed New Labeling (250 and 350 mg)
Indication	Carisoprodol is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions.	SOMA is indicated for the relief of discomfort associated with acute, painful musculoskeletal conditions. …. (b) (4)

		(b) (4)
Dosage and Administration	The usual adult dosage of `SOMA' (carisoprodol) Tablets, USP is one 350 mg tablet, three times daily and at bedtime. Usage in patients under age 12 is not recommended.	(b) (4) (b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the clinical pharmacology and clinical studies used to support dosing or claims?

Two PK studies (Study 500 and 501) were conducted to support human PK and biopharmaceutics requirements. These studies assessed bioequivalence of 250 mg SOMA tablets compared to 350 mg tablets after a single dose and food effect on 350 mg tablets (Table 2.2.1.1). In addition, gender effect was assessed.

With regard to the clinical component of the application, the Sponsor submitted 2 randomized, double-blinded, placebo-controlled, parallel-group, multi-center studies to support efficacy and safety (Study 502 and Study 505) (Table 2.2.1.1). They were conducted in the U.S. in adult patients 18-65 years of age with acute, idiopathic, mechanical low back pain. In Study MP502, patients were randomized 1:1:1 to one of the following three treatments (given three times a day and at bedtime) for seven days: 250 mg of carisoprodol tablets, 350 mg of carisoprodol tablets (the currently approved carisoprodol regimen), and placebo; and in Study MP505, patients were randomized 1:1 to the 250 mg carisoprodol dose regimen or placebo for seven days.

Table 2.2.1.1. PK and Clinical Studies.

Study	Design	Treatment Groups
MP500 (N=24)	R, open-label, single-dose, crossover PK study of food effects in healthy subjects	A Soma 350 mg fed B Soma 350 mg fast

MP501 (N=24)	R, open-label, single-dose, crossover, bioavailability study in healthy subjects	A Soma 150 mg B Soma 250 mg C Soma 350 mg
MP502 (N=826)	R, DB, PC, one-week trial in acute, painful lower back muscle spasm patients	Placebo QID (n=276) Soma 250 mg QID (n=271) Soma 350 mg QID (n=279)
MP505 (N=561)	R, DB, PC, one-week trial in acute, painful lower back muscle spasm patients	Placebo QID (n=284) Soma 250 mg QID (n=277)

2.2.2 What were the clinical endpoints used to assess efficacy in the pivotal clinical efficacy studies? What was the clinical outcome?

In both low back pain studies, the pre-specified, co-primary efficacy endpoints were the following patient-reported outcomes (PROs):

5-point PRO measures with Likert responses from 0 (worst outcome) to 4 (best outcome)

1) Relief from Starting Backache on Day #3
2) Global Impression of Change on Day #3

Of the seven, pre-specified, secondary efficacy endpoints in the two low back pain studies; the following two PRO endpoints were the most important:

24-point Roland-Morris Disability Questionnaire (RMDQ) (a PRO measure of function of low back pain patients)

1) RMDQ (Day #3 minus baseline)
2) RMDQ (Day #7 minus baseline)

Carisoprodol 250 mg demonstrated modest efficacy (compared to placebo) for the two primary efficacy endpoints in the acute low back pain studies (Table 2.2.2.1, obtained from Dr. Brodsky, reviewing Medical Officer). Results of the important secondary efficacy endpoints (e.g., RMDQ at Days #3 and #7) support the modest efficacy of carisoprodol 250 mg dose regimen.

In terms of safety, no new safety signals seen in the clinical trials, and no deaths and no treatment-related severe adverse events (SAEs). 250 mg of carisoprodol demonstrated a higher incidence of CNS discontinuation (DAEs) and CNS AEs compared to placebo (most frequent carisoprodol-associated AEs were CNS AEs).

Table 2.2.2.1. Results of the co-primary efficacy endpoints (i.e., GIC and RSB) in the low back pain studies.

Study	Parameter	Placebo	Carisoprodol 250 mg	Carisoprodol 350 mg
MP502	n	269	264	273
	GIC on Day #3, LS Mean (SE)	1.94 (0.06)	2.16 (0.06)	2.20 (0.06)
	Difference between carisoprodol and placebo (95% CI)	-	0.22 (0.07,0.37)	0.25 (0.10,0.40)
	p-value[1]	-	0.0046[2]	0.0011
	RSB on Day #3, LS Mean (SE)	1.40 (0.07)	1.75 (0.07)	1.82 (0.07)
	Difference between carisoprodol and placebo (95% CI)	-	0.35 (0.17,0.54)	0.42 (0.24,0.60)
	p-value[1]		0.0001[2]	<0.0001
MP505	n	278	269	-
	GIC on Day #3, LS Mean (SE)	1.70 (0.06)	2.24 (0.06)	-
	Difference between carisoprodol and placebo (95% CI)	-	0.53 (0.39,0.68)	-
	p-value[1]	-	<0.0001	-
	RSB on Day #3, LS Mean (SE)	1.12 (0.07)	1.83 (0.08)	-
	Difference between carisoprodol and placebo (95% CI)	-	0.71 (0.52,0.89)	-
	p-value[1]	-	<0.0001	-

1 p-values were calculated using an ANOVA model with treatment and pooled center as terms. The primary statistical population was the ITT population.
2 In Study MP502, the primary comparison was between the 250 mg carisoprodol and placebo groups and the other comparisons were exploratory.
SE is the standard error of the mean
Reference: Adapted from Volume 1, Table 3.6.2.1-1, Page 49

For final efficacy and safety assessment for this product please refer to Dr. Eric Brodsky (Medical Reviewer) and Dr. Ted Guo (Statistical Reviewer)'s reviews.

2.2.3 Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Carisoprodol and its major active metabolite, meprobamate, were measured in human plasma. Please refer to Section 2.6 Analysis for analytical details.

2.2.4 What is exposure-response relationship of carisoprodol in terms of efficacy and safety?

In one clinical trial (Study 502), 2 doses of carisoprodol was studied, 250 and 350 mg, allowing a dose-response analysis for efficacy and safety. Because exposure of carisoprodol is dose-proportional between 250 and 350 mg, dose-response is expected to reflect exposure-response.

For efficacy, although it was not a pre-specified analysis, carisoprodol 250 mg appeared equally efficacious as 350 mg.

For safety, overall there does not appear to be an appreciable across the board differences in safety between 250 mg and 350 mg doses of carisoprodol.

Females in general showed higher incidence of AEs than males (Table 2.2.4.1 from Dr. Eric Brodsky) indicating an exposure-dependence on AE.

Table 2.2.4.1. The most common AEs (≥ 1% in any treatment group) by gender[1] in the low back pain studies

Preferred Term[2]	Gender	Placebo n (%)[3]	Carisoprodol 250 mg n (%)[3]	Carisoprodol 350 mg n (%)[3]
Patients with ≥ 1 AE	Women	72 (22.2)	109 (39.6)	54 (35.1)
	Men	41 (17.4)	57 (20.9)	41 (32.8)
Somnolence or sedation	Women	17 (5.2)	52 (18.9)	25 (16.2)
	Men	14 (6.0)	21 (7.7)	22 (17.6)
Dizziness	Women	7 (2.2)	30 (10.9)	12 (7.8)
	Men	4 (1.7)	13 (4.8)	7 (5.6)
Headache	Women	8 (2.5)	19 (6.9)	6 (3.9)
	Men	3 (1.3)	7 (2.6)	3 (2.4)
Nausea	Women	7 (2.2)	2 (0.7)	6 (3.9)
	Men	8 (3.4)	4 (1.5)	6 (4.8)
Stomach discomfort, abdominal discomfort, or upper abdominal pain	Women	7 (2.2)	8 (2.9)	3 (2.4)
	Men	0 (0)	1 (0.4)	2 (1.6)
Fatigue, lethargy, or asthenia	Women	2 (0.6)	7 (2.5)	3 (1.9)
	Men	1 (0.4)	1 (0.4)	1 (0.8)
Diarrhea	Women	3 (0.9)	3 (1.1)	1 (0.6)
	Men	3 (1.3)	2 (0.7)	0 (0)
Disorientation	Women	0 (0)	1 (0.4)	2 (1.3)
	Men	0 (0)	0 (0)	0 (0)
Vomiting	Women	2 (0.6)	1 (0.4)	2 (1.3)
	Men	1 (0.4)	0 (0)	1 (0.8)
CPK increased	Women	2 (0.6)	0 (0)	0 (0)
	Men	1 (0.4)	2 (0.7)	2 (1.6)

1 There were 325, 275, and 154 females in the placebo, 250 mg, and 350 mg groups, respectively, and there were 235, 273, and 125 males in the placebo, 250 mg, and 350 mg groups, respectively in the safety population (patients who received at least one dose of study medication).
2 The preferred terms were coded using MedDRA Dictionary Version 8.0.
3 n (%) is the number (percentage) of patients who had at least one event. Patients were counted once within each preferred term and may have had more than one AE.
Reference: Adapted from Volume 16, Table 8.2.3-2, Pages 151-159.

2.2.5 What are the PK characteristics of 250 mg SOMA? Is PK dose proportional between 250 mg and 350 mg?

Single dose PK for carisoprodol and meprobamate were determined in Study 501 where subjects received a single dose of 150, 250 or 350 mg carisoprodol. Carisoprodol showed a Tmax of 2 hours and a half-life of 2 hours. The concentration related parameters, such as Cmax and AUCs, showed high intersubject variability. The variability could be due to polymorphism of

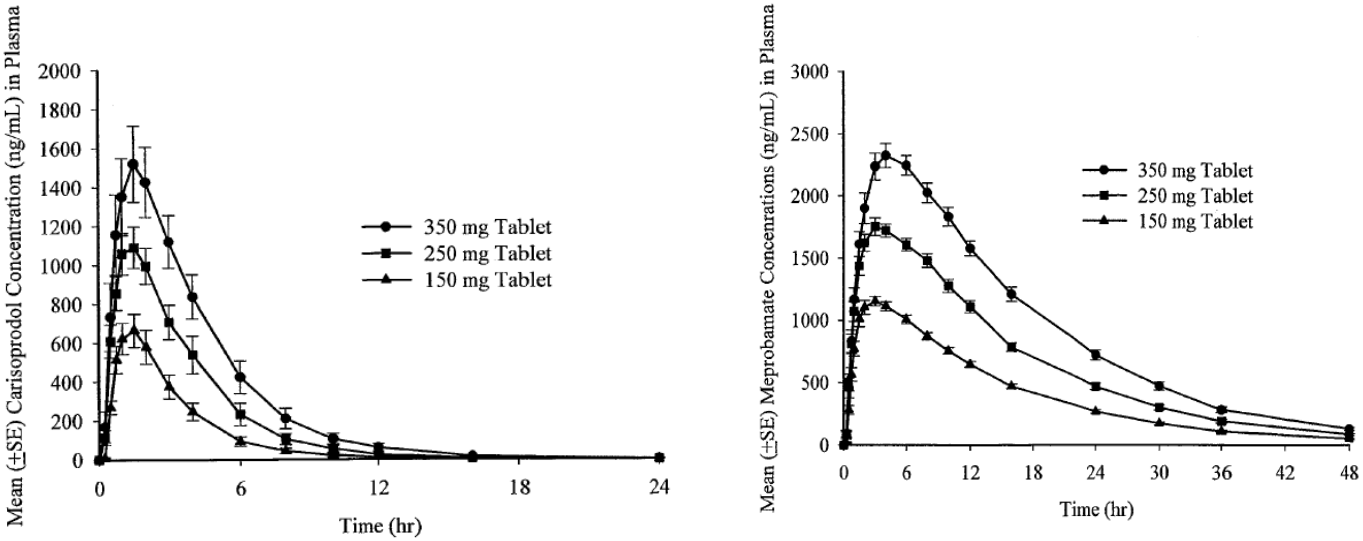
CYP2C19, the main enzyme that metabolizes carisoprodol to form meprobamate, and gender difference in carisoprodol PK (see Section 2.3.1)

Tmax for meprobamate is about 2-4 hours. The Cmax of meprobamate was 2.5 ± 0.5 µg/mL (mean ± SD, n=24) at the 350 mg dose, approximately 30% of those seen following a single 400 mg dose of meprobamate (Cmax of 8.0 µg/mL). Exposure of the metabolite meprobamate was higher than carisoprodol (50% higher for Cmax and 6-fold higher for AUC). The half-life of meprobamate was also longer (10 hours vs. 2 hours for carisoprodol) (Table 2.2.5.1 and Figure 2.2.5.1). Meprobamate is a Schedule IV controlled substance with known potential for abuse. Exposure of meprobamate in most patients is higher than that of carisoprodol after 2 hours post-dose. The sedative effect of carisoprodol may be partially due to meprobamate.

Dose-normalized AUCt, AUCi, and Cmax for carisoprodol and its metabolite, meprobamate, were equivalent between 250 and 350 mg carisoprodol tablets (Table 2.2.5.1) indicating that PK is dose-proportional between 250 and 350 mg.

Table 2.2.5.1. Summary of the Pharmacokinetic Parameters (Mean ± SD) of Carisoprodol and Meprobamate and the 90% Confidence Intervals (Dose-Normalized) for the Comparison of the Pharmacokinetic Parameters (250 mg vs. 350 mg).

	250 mg (Test)	350 mg (Reference)	Ratios of Geometric Means (%)	90% CI Lower	90% CI Upper
Carisoprodol					
Cmax (µg/mL)	1.2 ± 0.5	1.8 ± 1.0	104.3	91.27	119.14
AUCt (µg*hr/mL)	4.5 ± 3.1	6.9 ± 5.0	91.89	85.47	98.79
AUCinf (µg*hr/mL)	4.5 ± 3.1	7.0 ± 5.0	92.02	85.67	98.84
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	105.33	102.55	108.17
AUCt (µg*hr/mL)	31 ± 5.6	44 ± 8.2	98.76	96.18	101.41
AUCinf (µg*hr/mL)	32 ± 6.2	46 ± 9.0	98.53	95.76	101.38
Tmax (hr)	3.6 ± 1.7	4.5 ± 1.9			
$T_{1/2}$ (hr)	9.7 ± 1.7	9.6 ± 1.5			



a. Carisoprodol b. Meprobamate

Figure 2.2.5.1. Mean ± SE Carisoprodol (a) and Meprobamate (b) Concentration (ng/mL) in Plasma After a Single Dose of a Carisoprodol Tablet Given to Healthy Subjects.

Multiple dose PK for carisoprodol has not been determined. Based on single dose PK and assuming one-compartment model, accumulation of carisoprodol and meprobamate is predicted to be ~1.15 and 3 at steady-state with a dosing interval of 6 hours (QID).

2.2.6 What are the ADME (absorption, distribution, metabolism and elimination) characteristics of carisoprodol?

Absorption

Absolute bioavailability of carisoprodol has not been determined. The mean time to peak plasma concentrations (Tmax) of carisoprodol for the 250 mg and 350 mg doses was 1.5 ± 0.8 hours and 1.7 ± 0.8 hours, respectively.

Distribution

In spiked human sera, protein binding of carisoprodol was in the range of 41-67%, whereas meprobamate was bound to a lesser extent, 14-24%.[2]

Metabolism

Carisoprodol is metabolized by CYP2C19 to form its major active metabolite, meprobamate. CYP2C19 is a polymorphic enzyme. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. To a much lesser extent, carisoprodol is metabolized to hydroxyl-carisoprodol by a still unknown enzyme. Both hydroxyl-carisoprodol and meprobamate are

[2] Olsen H., *et.al.*, Carisoprodol elimination in humans. *The Drug Monit.*, 16(4):337-340, 1994.

subsequently metabolized to hydroxyl- meprobamate, conjugated and then excreted by urine (Figure 2.2.6.1).[1,3]

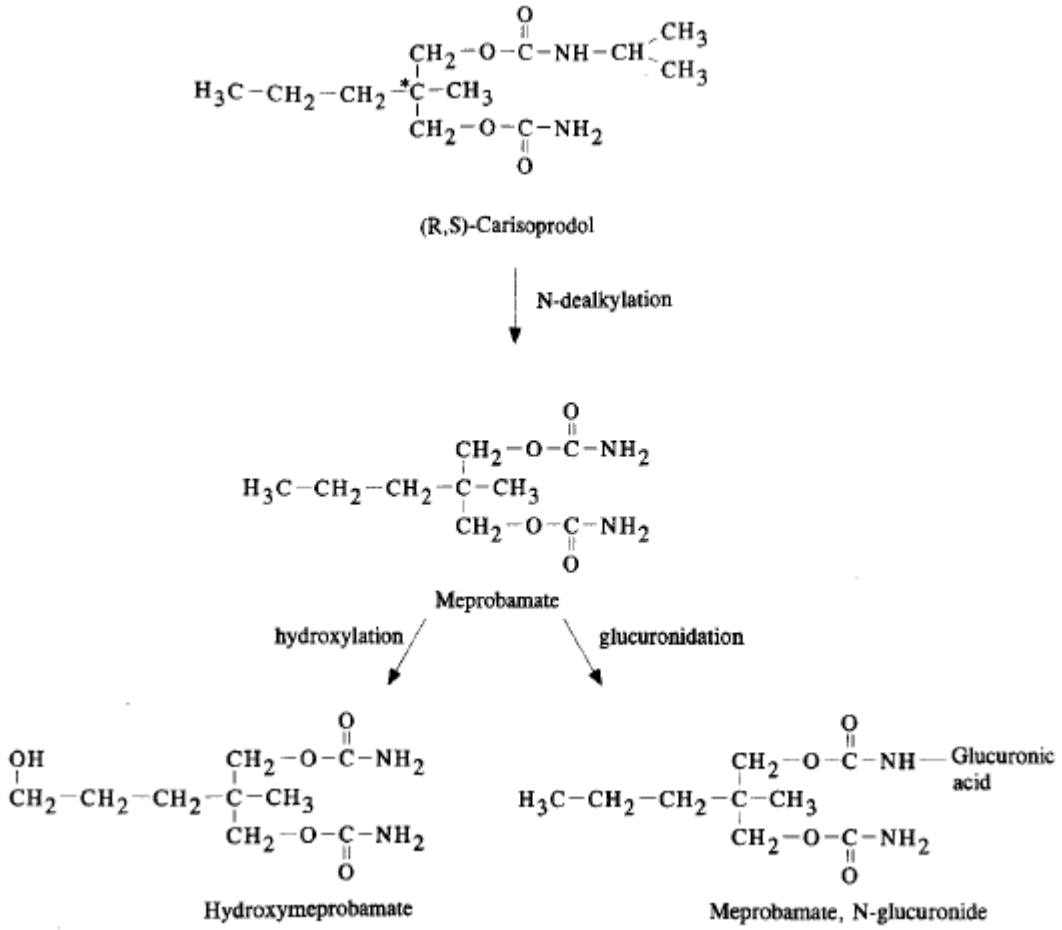


Figure 2.2.6.1. Metabolic pathways for carisoprodol and meprobamate.

Elimination

Carisoprodol is eliminated by both renal and non-renal routes. The mean terminal plasma elimination half-lives of carisoprodol and meprobamate are approximately 2 and 10 hours, respectively.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response?

From the current SOMA 350 mg tablet labeling, no PK data on pediatric and elderly patients were available. PK data on special population, e.g., patients with impaired renal or hepatic

[3] Bramness J.G., *et. al.*, Association between blood carisoprodol meprobamate concentration ratios and *CYP2C19* genotype in carisoprodol-drugged drivers:decreased metabolic capacity in heterozygous *CYP2C19*1/CYP2C19*2* subjects? *Pharmacogenetics* 13:383-388, 2003.

function were also not available. Because carisoprodol is eliminated by both liver metabolism and renal excretion, decreased clearance of carisoprodol is anticipated in these patients. Cautionary language is included.

Information on effect of gender and CYP2C19 activity on PK of carisoprodol are available from the studies conducted by the Sponsor and literature, respectively.

2.3.1.1 Gender

In the current SOMA 350 mg tablet labeling (see below), information on the effect of gender on PK is from a small PK study with 5 male and 5 female subjects. Data suggest that female subjects had a faster apparent oral clearance.

> The pharmacokinetics of carisoprodol was determined in a small in vivo biostudy of 5 men and 5 women. When the dose was normalized to 350 mg, the mean peak plasma concentration (Cmax) achieved was 2.29 ± 0.68 ug/mL. Women tended to reach peak plasma concentrations earlier than men (1.45 vs. 2.5 hours) and had a faster apparent oral clearance (0.772 vs. 0.38 L/hour/kg). The clinical significance of these findings is unknown and they may in part be due to the small number of subjects present in the trial.

In this submission, the Sponsor included equal numbers of male and female subjects (12 of each) in both PK studies which enables a secondary analysis to determine effect of gender on PK of carisoprodol.

Both Studies 501 and 500 showed that exposure of carisoprodol and meprobamate were higher in female subjects than in male subjects. The gender difference was more profound for carisoprodol exposure indicating that body weight may not be the only factor contributing to higher exposure in female subjects and that overall metabolism of carisoprodol may be slower in female subjects (Table 2.3.1.1.1). The results were contrary to previous data cited in SOMA labeling that indicated females had higher clearance.

Table 2.3.1.1.1. Percent Difference of Means in Male and Female Subjects after Receiving 250 mg or 350 mg Carisoprodol Tablets (Studies 500 and 501).

*Difference of Means (%)	Carisoprodol		Meprobamate	
	Cmax	AUC(0-∞)	Cmax	AUC(0-∞)
Study 501-250 mg	23	72	18	8
Study 501-350 mg	61	79	29	15
Study 500-350 mg Fast	106	89	31	35
Study 500-350 mg Fed	74	83	36	29

*Percent difference of means = (Female-Male)/Male.

Box-and-Whisker plots for Cmax and AUC values of carisoprodol stratified by gender were shown in Figure 2.3.1.1.1 for all three doses in Study 501.

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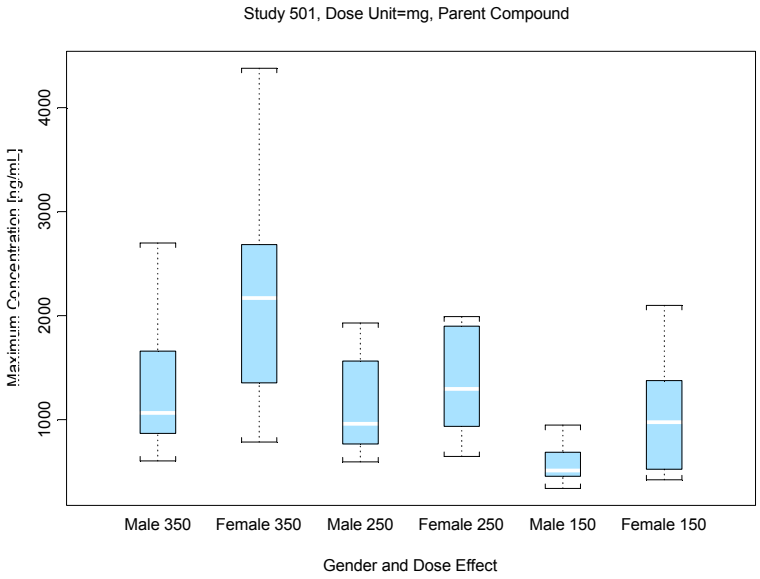
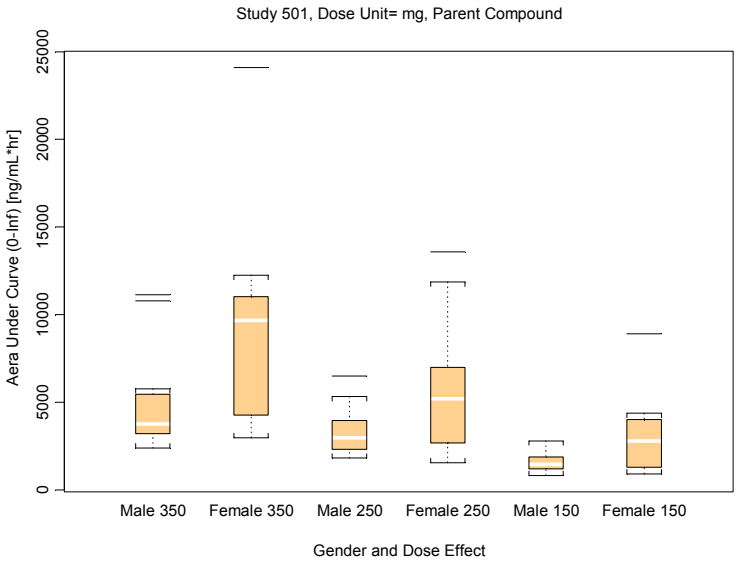
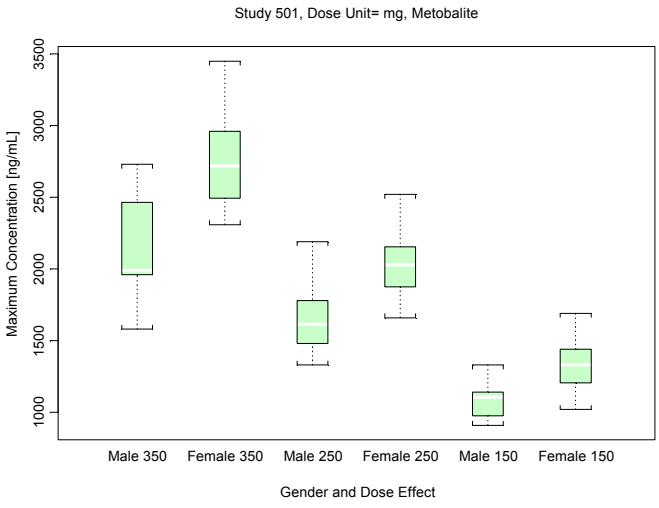


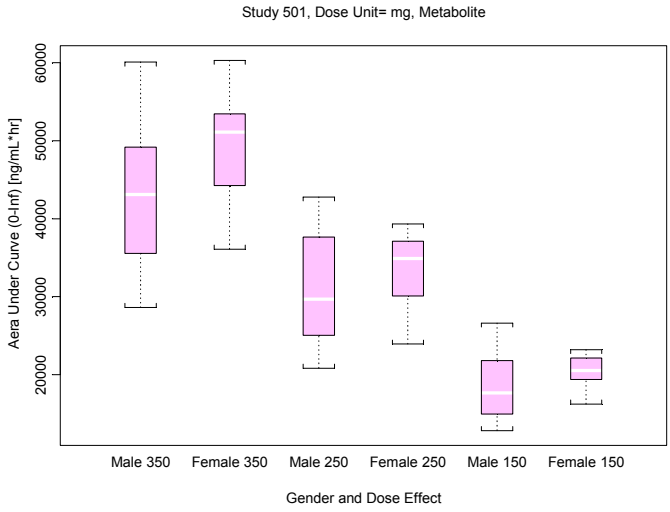


Cmax **AUCinf**

Figure 2.3.1.1.1. Box-and-Whisker Plots for Cmax and AUC Values of Carisoprodol Sorted by Gender (Study 501).

Box-and-Whisker plots for Cmax and AUC values of meprobamate stratified by gender were shown in Figure 2.3.1.1.2 for all 3 doses.





Cmax **AUCinf**

Figure 2.3.1.1.2. Box-and-Whisker Plots for Cmax and AUC Values of Carisoprodol Sorted by Gender (Study 501).

Results from Study 500 also showed females had higher exposure than males. Refer to Individual Study Review for gender analysis results (Section 4.2.2).

2.3.1.2 CYP2C19 Polymorphism

Literature information is available on the effect of CYP2C19 polymorphism on the PK of carisoprodol.[1] Data from Reference 1 (Table 2.3.1.2.1 below) showed that in subjects with reduced function of CYP2C19 (CYP2C19 poor metabolizers, PMmeph), exposure of carisoprodol was four times that of extensive metabolizers (EM). In contrast, exposure of meprobamate was approximately half in poor metabolizers (PMmeph) compared to that in extensive metabolizers (EM). Half-life of carisoprodol was also longer in PM than EM (4 vs. 2 hours). It is not clear what other enzymes are involved in carisoprodol metabolism in poor metabolizers. In this study poor metabolizers and extensive metabolizers were identified by phenotyping for CYP2C19 activity using the probe drug S-mephenytoin.

Plots were shown in Figures 2 and 3.[2]

2.3.2 What is the impact of any differences in exposure on efficacy or safety responses?

Based on limited dose-response data from Study 502 (Section 2.2.4), it seems that no improvement in efficacy from 250 mg to 350 mg but a slightly better safety for 250 mg. Increased exposure may result in higher incidence of CNS side effects.

Data showed that in certain patient populations, exposure of carisoprodol is increased. These patients include patients with reduced CYP2C19 activity (exposure is four times higher), females (exposure is 70-90% higher than males), and patients with impaired renal and/or hepatic function. These patients may benefit from a lower dose of SOMA to avoid exposure-dependent CNS side effects including somnolence and sedation. However, a lower dose strength SOMA tablet is not available. Caution should be exercised. In particular, for a female subject who is also a CYP2C19 poor metabolizer (PM), exposure could be substantially higher than a male subject who is an extensive metabolizer of CYP2C19.

2.4 Extrinsic Factors

Not Applicable. The Sponsor did not conduct new studies. Same information in the current SOMA 350 mg tablet will be used. Language on the potential effect of CYP2C19 inhibition and induction will be included in the Drug Interaction section of the label.

2.5 General Biopharmaceutics

2.5.1 What is the final-to-be marketed formulation (quantitative composition) of SOMA 250 mg tablets?

Quantitative composition for SOMA 250 and 350 tablets are listed in Table 2.5.1.1. The percent w/w composition and batch weight for the tablets containing 250 mg of carisoprodol are the same as the currently approved SOMA 350 mg tablet.

Table 2.5.1.1 Quantitative Composition of Carisoprodol 250 and 350 mg Tablets.

Ingredients	% w/w		mg/Tablet		Batch Formula (kg/Batch)	
	Proposed 250 mg Tablet	Currently Approved 350 mg Tablet	Proposed 250 mg Tablet	Currently Approved 350 mg Tablet	Proposed 250 mg Tablet	Currently Approved 350 mg Tablet
Carisoprodol, USP						(b) (4)
(b) (4) Starch, NF, (b) (4)						
(b) (4) Calcium Phosphate, NF						
Alginic Acid, NF						
Potassium Sorbate, NF (b) (4)						
Magnesium Stearate, NF						
(b) (						
Total	100%	100%				(b) (4)

2.5.2 Which batches were used in the pivotal clinical and bioavailability studies?

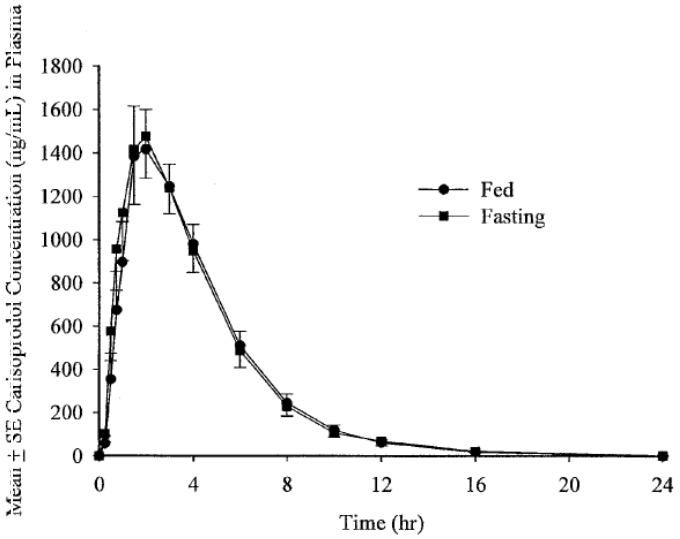
To-marketed-formulation of 250 and 350 mg SOMA were used in pivotal PK and clinical studies. The batch numbers are as follows:

250 mg: Lot Number 27-02-02c, manufactured by MedPointe Pharmaceuticals in batch sizes of over (b) (4) tablets.

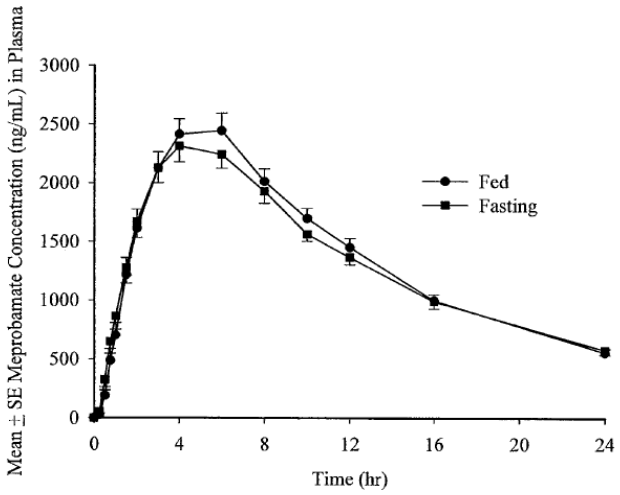
350 mg: Lot Number 2A10004A, manufactured in a batch size of over (b) (4) tablets.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form?

A high fat meal does not affect C_{max} or AUC_{inf} following 350 mg SOMA dosing (Table 2.5.3.1). Food also does not seem to change the absorption rate of carisoprodol.



a. Carisoprodol



b. Meprobamate

Figure 2.5.3.1. Mean Plasma Carisoprodol (a) and Meprobamate (b) Concentrations under Fasting (■) and Fed (●) Conditions.

Table 2.5.3.1. Summary of the 90% Confidence Intervals (Dose-Normalized) for the Comparison of the Pharmacokinetic Parameters of Carisoprodol and Meprobamate under Fasting (Reference) and Fed (Test) conditions.

	Ratios of Geometric Means (%)	90% CI Lower	90% CI Upper
	Carisoprodol		
Cmax (µg/mL)	97.4	84.26	112.66
AUCt (µg*hr/mL)	101.0	94.10	108.38
AUCinf (µg*hr/mL)	100.9	94.06	108.24
	Meprobamate		
Cmax (µg/mL)	108.75	103.21	114.59
AUCt (µg*hr/mL)	104.28	100.77	107.91
AUCinf (µg*hr/mL)	99.67	95.69	103.80

2.6 Analytical

2.6.1 Were the analytical methods used to determine carisoprodol and meprobamate in biological fluids adequately validated?

Yes, concentrations of carisoprodol and its metabolite, meprobamate, were adequately measured in human plasma by validated LC/MS/MS assays (b) (4) and summarized in Table 2.6.1.1. The method was used for sample analysis of both PK studies. In this method, carisoprodol and meprobamate were simultaneously assayed with (b) (4) the internal standard. The peak areas of the (b) (4) carisoprodol product ion and the (b) (4) meprobamate product ion were measured against the peak area of the (b) (4) (b) (4) internal standard product ion. Quantitation was performed using weighted (1/x2 for both analytes) linear least squares regression analyses generated from calibration standards prepared immediately prior to each run.

Recovery for carisoprodol is from 89-98% and for meprobamate is from 87-96%. The assays are selective for the analytes. No interference was observed.

Long-term stability of carisoprodol and meprobamate in frozen human plasma at -20°C was at least 99 days. The stability was long enough to cover the time span from sample collection to sample analysis.

Table 2.6.1.1. Analytical Methods Used for the Determinations of Carisoprodol and Meprobamate.

Analytes	Internal Standard	LOQ (ng/ml)	Linear Range (ng/ml)	Between Batch Precision (CV)	Between Batch Accuracy (Bias)	QC Samples (ng/mL)
Carisoprodol	(b) (4)	10	10-2500 (r^2> 0.998)	1.2%-4.8%	-3.0%-4.6%	30, 500, 2000
Meprobamate		8	8-2000 (r^2> 0.998)	0.8%-4.8%	-4.4%-3.5%	24, 400, 1600

3 LABELING RECOMMENDATIONS

The labeling recommendations that are mostly related to Clinical Pharmacology are shown below. Major changes are highlighted. Please refer to the approval letter for the full text of the final labeling.

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 be not used for more than seven days. [see *Dosage and Administration* (2)]

2 DOSAGE AND ADMINISTRATION

The recommended dose of SOMA is 250 mg to 350 mg four times a day. The recommended maximum duration of SOMA use is up to seven days because the effectiveness of SOMA use greater than seven days has not been established

Caution should be excised in administration to patients with impaired renal or hepatic function, female patients, or patients with reduced CYP2C19 activity. These patients will have higher systemic carisoprodol exposure.

5 WARNINGS AND PRECAUTIONS

5.4 Use in Patients with Hepatic or Renal Impairment

Carisoprodol is metabolized in the liver and excreted by the kidney; to avoid its excess accumulation, caution should be exercised in administration to patients with hepatic or renal impairment. *See Dosage and Administration (2); See Use in Specific Populations (8.6, 8.7); See Clinical Pharmacology (12.3).*

5,5 Use in Patients with Reduced CYP2C19 Activity

Carisoprold is metabolized to meprobamate by CYP2C19, encoded by polymorphic *CYP2C19* gene. Literature information showed that in patients with reduced function of CYP2C19 (CYP2C19 poor metabolizers), exposure of carisoprodol was four times that of extensive metabolizers. Caution should be exercised in administration of SOMA to patients with reduced CYP2C19 activity. *See Dosage and Administration (2); See Use in Specific Populations (8.8); See Clinical Pharmacology (12.3).*

5.6 Laboratory Testing

Genotype testing for *CYP2C19* gene is commercially available to identify patients with normal allele (*1) and the 2 most common allele variants that result in deficient CYP2C19 activity (*2 and *3).

7 DRUG INTERACTIONS

7.1 CNS Depressants

The sedative effects of SOMA and other CNS depressants (e.g., alcohol, benzodiazepenes, opioids, tricyclic antidepressants) may be additive. Therefore, appropriate caution should be exercised with patients who take more than one of these CNS depressants simultaneously. Concomitant use of SOMA and meprobamate (e.g., Miltown®, Equanil®), 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 CYP 2C19 to form meprobamate [*See Clinical Pharmacology (12.3)*]. Co-administration of CYP2C19 inhibitors, such as omeprazole and fluvoxamine, with SOMA could result in increased exposure of carisoprodol and decreased exposure of meprobamate. Co-administration of CYP2C19 inducers, such as rifampin and St. John;s Wort, with SOMA could result in decreased exposure of carisoprodol and increased exposure of meprobamate. Low dose aspirin also showed induction effect on CYP2C19. The full pharmacological impact of these alterations of exposures in terms of either efficacy or safety is unknown.

8 USE IN SPECIFIC POPULATION

8.4 Pediatric Use

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

8.5 Geriatric Use

The efficacy and safety of SOMA in patients over 65 years old has not been evaluated in clinical studies .

8.6 Renal Impairment

The safety of SOMA in patients with renal impairment has not been evaluated. Since SOMA is excreted by the kidney, caution should be exercised if SOMA is administered to patients with impaired renal function.

8.7 Hepatic Impairment

The safety of SOMA in patients with hepatic impairment has 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

Literature information showed that in patients with reduced function of CYP2C19 (CYP2C19 poor metabolizers), exposure of carisoprodol was four times that of extensive metabolizers. In contrast, exposure of meprobamate was approximately half in poor metabolizers compared to that in extensive metabolizers. The full pharmacological impact of these alterations of exposures in terms of either efficacy or safety is unknown. Caution should be exercised in administration of SOMA to patients with reduced CYP2C19 activity.

12 CLINCIAL PHARMACOLOGY

12.1 Mechanism of Action

Carisoprodol is a centrally acting skeletal muscle relaxant that does not directly relax these skeletal muscles in man. The mode of action of carisoprodol in relieving acute muscle spasm has not been clearly identified, but may be related to its sedative properties.

12.3 Pharmacodynamics

In animals, carisoprodol has been shown to produce muscle relaxation by blocking interneuronal activity and depressing transmission of polysynaptic neurons in the spinal cord and in the descending reticular formation of the brain. The onset of action is rapid and the effect lasts four to six hours. One of carisoprodol's metabolite, meprobamate is active as an anxiolytic. The degree to which it contributes to the efficacy of carisoprodol is unknown.

12.3 Pharmacokinetics

Pharmacokinetics of carisoprodol and its active metabolite meprobamate was studied in a crossover study of 24 healthy subjects (12 males and 12 females) who received a single dose of 250 mg or 350 mg carisoprodol (Table 2). The exposure of carisoprodol and meprobamate was dose proportional between 250 mg and 350 mg doses. Exposure of meprobamate in most patients is higher than that of carisoprodol after 2 hours post-dose. The Cmax of meprobamate was 2.5 ± 0.5 µg/mL (mean ± SD, n=24) at the 350 mg dose, approximately 30% of those seen following a single 400 mg dose of meprobamate (Cmax of 8.0 µg/mL).

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

Pharmacokinetic Parameters	**250 mg (Test)**	**350 mg (Reference)**
Carisoprodol		
Cmax (µg/mL)	1.2 ± 0.5	1.8 ± 1.0
AUCt (µg*hr/mL)	4.5 ± 3.1	6.9 ± 5.0
AUCinf (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
AUCt (µg*hr/mL)	31 ± 5.6	44 ± 8.2
AUCinf (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. SOMA may be administered with or without food.

Metabolism: Carisoprodol is metabolized in the liver via cytochrome enzyme, CYP 2C19, to form meprobamate. This enzyme exhibits genetic polymorphism. The prevalence of poor metabolizers in Caucasians and African American is approximately 3-5% and in Asian is approximately 15-20%. Literature information showed that in patients with reduced function of CYP2C19 (CYP2C19 poor metabolizers), exposure of carisoprodol was four times that of extensive metabolizers. In contrast, exposure of meprobamate was approximately half in poor metabolizers compared to that in extensive metabolizers.

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

Special Populations: The pharmacokinetic profile of carisoprodol in patients with renal impairment or hepatic impairment has not been evaluated. Because carisoprodol is metabolized by the liver and excreted by the kidneys, possible increased exposure of carisoprodol is expected if hepatic and/or renal function is impaired. SOMA should be used with caution in patients with impaired hepatic or renal function. Carisoprodol is dialyzable by peritoneal dialysis and hemodialysis.

Gender Exposure of both carisoprodol and meprobamate are higher in female than in male subjects. The difference is more profound for carisoprodol. Mean AUC values of carisoprodol and meprobamate in female subjects are 80-90% and 10-30% higher than those in male subjects, respectively.

Geriatric Patients: The pharmacokinetic profile of SOMA in geriatric patients has not been evaluated.

Pediatric Patients The pharmacokinetic profile of carisoprodol in pediatric patients (age <16 years) has not been evaluated.

Patients with Reduced CYP2C19 Activity Formation of meprobamate is mediated by CYP2C19. Literature information showed that in patients with reduced function of CYP2C19 (CYP2C19 poor metabolizers), exposure of carisoprodol was four times that of extensive metabolizers. In contrast, exposure of meprobamate was approximately half in poor metabolizers compared to that in extensive metabolizers. SOMA should be used with caution in patients with reduced CYP2C19 activity.

5 page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

4.2 Individual Study Review

4.2.1 Study MP501: Randomized, Open-Label, Crossover Trial on the Absorption of Carisoprodol from Carisoprodol Tablets 150 mg and 250 mg Relative to that from Carisoprodol Tablets 350 mg in Normal, Healthy Subjects

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Study Period:	February 28 to March 21, 2005
Principle Investigator:	Dennis Morrison, OD
Clinical Site:	BioKinetic Clinical Application, 1816 West Mount Vernon Street Springfield, MO 65802
Sample Analysis Period:	Between April 5, 2005 and April14, 2005
Analytical Site:	(b) (4)

Objective: To evaluate the bioavailability of carisoprodol from two investigational tablet formulations, one containing 150 mg carisoprodol and the other containing 250 mg carisoprodol relative to that from Soma 350 mg tablets, a marketed product. In addition, relative bioavailability assessments will be made for meprobamate, an active metabolite of carisoprodol.

(Reviewer's Note: The Sponsor will only seek marketing approval for 250 mg tablets. Review will be focused on 250 and 350 mg tablets.)

Study Design: This was a randomized, open-label, 3-period crossover study design, comparing the bioavailability of carisoprodol after dosing with a carisoprodol 150 mg tablet and a 250 mg tablet relative to that from a Soma 350 mg tablet.

Twenty-four healthy subjects (12 males and 12 females) who qualified for the study were enrolled to participate in the treatment phase. All subjects completed the three periods of study and were included in both the pharmacokinetic and safety populations.

The treatment sequences were to be randomized. Dosing was to be in the morning, and the dosing of the second and third periods of study was to be 7 days after the dosing of the previous period. The dose was one tablet of each strength taken with 240 mL water at room temperature. Blood samples were to be drawn at specified times over a 48-hour period.

The two treatment sequences had equal numbers of males and females, who were all under 40 years of age with an overall mean age of 22.8 years. Male subjects had an overall mean weight of 180.8 lbs; and the mean weight for females was 139.1 lbs. The majority of the subjects were Caucasian (92%).

Test Articles:
Test 1: 150 mg carisoprodol tablet (Lot Number 27-01-02c)
Test 2: 250 mg carisoprodol tablet (Lot Number 27-02-02c)
Both were manufactured by MedPointe Pharmaceuticals in batch sizes of over (b) (4) tablets.

Reference: Soma 350 mg Tablets (Lot Number 2A10004A), which was manufactured in a batch size of over (b) (4) tablets.

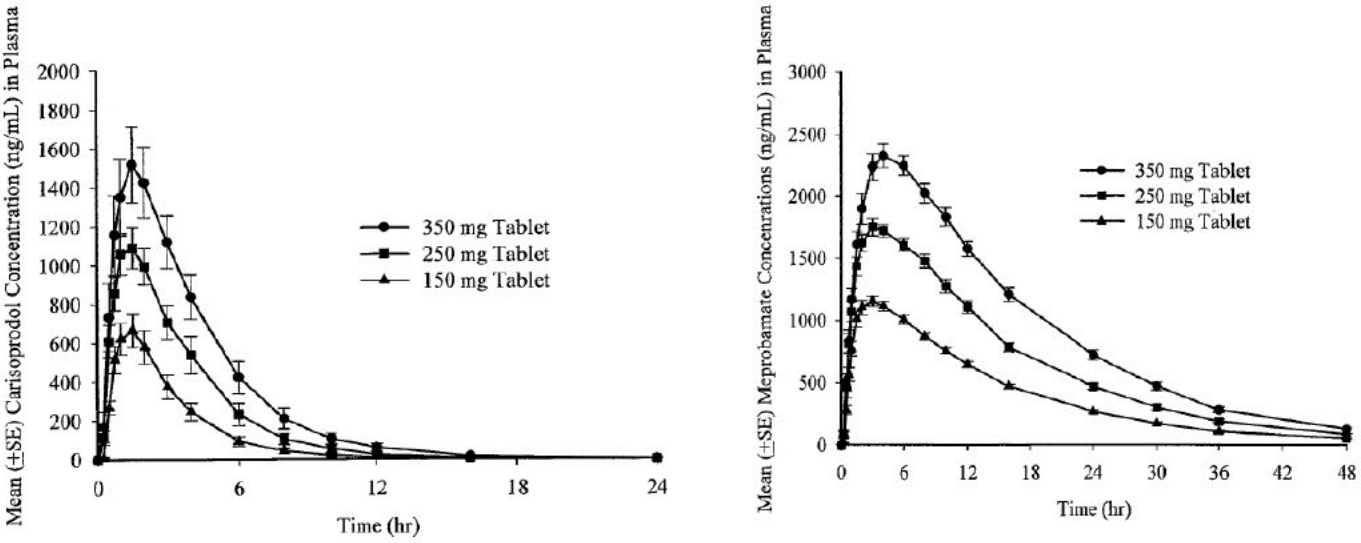
Sample Collection: pre-dose (0 hr), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, l2, 16, 24, 30, 36, and 48 hours post-dose (10 mL EDTA) in each period.

Sample Analysis: Plasma samples obtained during the clinical portion of this study were assayed to simultaneously measure carisoprodol and meprobamate by a validated and sensitive LC/MS/MS metho (b) (4) The range of the assay for carisoprodol was (b) (4) and for meprobamate (b) (4) The lower limit of quantification for carisoprodol and meprobamate was 10 ng/mL and 8 ng/mL, respectively. (b) (4) was used as an internal standard.

Pharmacokinetic Results:

PK Profiles

Concentration-time profiles for carisoprodol and metabolite, meprobamate, were shown in Figures 1a and 1b. PK parameters were summarized in Table 1 and Table 2.



a. Carisoprodol b. Meprobamate

Figure 1. Mean ± SE Cariosoprodol (a) and Meprobamate (b) Concentration (ng/mL) in Plasma After a Single Dose of a Carisoprodol Tablet Given to Healthy Subjects.

Table 1. Summary of the Pharmacokinetic Parameters Obtained for Carisoprodol After a Single Dose of a Carisoprodol Tablet Given to Healthy Subjects.

Parameter	150 mg Tablet n=24	250 mg Tablet n=24	350 mg Tablet n=24
Cmax (ng/mL)			
Mean ±SD	790 ± 457	1241 ± 491	1771 ± 970
(CV%)	(57.8)	(39.5)	(54.8)
Tmax (hr)			
Mean ±SD	1.5 ± 0.6	1.5 ± 0.8	1.7 ± 0.8
(CV%)	(42.4)	(50.1)	(49.8)
Median	1.5	1.5	1.5
(Range)	(0.75-3.0)	(0.75-4.0)	(0.75-4.0)
λz (1/hr)			
Mean ±SD	0.444 ± 0.103	0.429 ± 0.114	0.374 ± 0.088
(CV%)	(23.3)	(26.5)	(23.5)
t½λz (hr)			
Mean ±SD	1.66 ± 0.45	1.74 ± 0.52	1.96 ± 0.52
(CV%)	(26.8)	(29.9)	(26.6)
AUC(0-tlast) (hr*ng/mL)	2274 ± 1742	4461 ± 3055	6941 ± 4956
Mean ±SD	(76.6)	(68.5)	(71.4)
(CV%)			
AUC(0-∞) (hr*ng/mL)			
Mean ±SD	2317 ± 1764	4506 ± 3074	6997 ± 4971
(CV%)	(76.2)	(68.2)	(71.0)

Source reference: Table 14.1.12, Table 14.1.13, and Table 14.1.14

The maximum concentrations of carisoprodol, which increased with the increasing administered dose, were achieved about 1.5 hours after dosing for all treatments. The mean half-lives of the terminal disposition phase for carisoprodol were between 1 .7 hr and 2.0 hr for the tablet treatments. The concentration related parameters, such as Cmax and AUCs, showed high intersubject variability. The variability could be due to polymorphism of CYP2C19, the main enzyme that metabolizes carisoprodol, and gender difference in carisoprodol PK (see gender analysis at the later part of the review)

Carisoprodol is metabolized by CYP2C19 to form its major active metabolite, meprobamate. Meprobamate, is a Schedule IV controlled substance with known potential for abuse. PK of meprobamate was also monitored in the PK studies.

Tmax is about 2-4 hours for meprobamate. The mean Cmax values increased with the increasing dose of carisoprodol dose administered. The Cmax of meprobamate was 2.5 ± 0.5 µg/mL (mean ± SD, n=24) at the 350 mg dose, approximately 30% of those seen following a single 400 mg dose of meprobamate (Cmax of 8.0 µg/mL) (Table 2).

Compared to carisoprodol, meprobamate is about 50% higher than carisoprodol for Cmax, and about 6-fold higher than carisoprodol for AUC. The half-life is also longer (10 hours vs. 2 hours for carisoprodol). The half-lives for meprobamate were nearly the same and similar to half-life

values when meprobamate itself was orally administered. Hence, the half-life for meprobamate was actually representative of the elimination of meprobamate, rather than the formation from the parent drug.

Meprobamate is a Schedule IV controlled substance with known potential for abuse. Exposure of meprobamate in most patients is higher than that of carisoprodol after 2 hours post-dose. The sedative effect of carisoprodol may be partially due to meprobamate.

Table 2. Summary of the Pharmacokinetic Parameters Obtained for Meprobamate After a Single Dose of a Carisoprodol Tablet Given to Healthy Subjects.

Parameter	150 mg Tablet n=24	250 mg Tablet n=24	350 mg Tablet n=24
Cmax (ng/mL)			
Mean ±SD	1210 ± 203	1841 ± 307	2458 ± 467
(CV%)	(16.8)	(16.7)	(19.0)
Tmax (hr)			
Mean ±SD	2.5 ± 0.9	3.6 ± 1.7	4.5 ± 1.9
(CV%)	(37.1)	(47.9)	(42.3)
Median	2.0	3.0	4.0
(Range)	(1.5-4.0)	(2.0-10.0)	(2.0-10.0)
λz (1/hr)			
Mean ±SD	0.075 ± 0.013	0.074 ± 0.013	0.074 ± 0.012
(CV%)	(16.9)	(18.1)	(16.3)
t½λz (hr)			
Mean ±SD	9.55 ± 1.71	9.67 ± 1.73	9.63 ± 1.53
(CV%)	(17.9)	(17.9)	(15.9)
AUC(0-tlast) (hr*ng/mL)			
Mean ±SD	18837 ± 3188	31056 ± 5578	44081 ± 8181
(CV%)	(16.9)	(18.0)	(18.6)
AUC(0-∞) (hr*ng/mL)			
Mean ±SD	19572 ± 3540	32330 ± 6199	45980 ± 8984
(CV%)	(18.1)	(19.2)	(19.5)

Source reference: Table 14.1.16, Table 14.1.17, and Table 14.1.18

Relative Bioavailability

Based on the range of the lower and upper limits of the 90% confidence intervals for the dose adjusted AUC(0-∞) parameter for carisoprodol, the 250 mg carisoprodol tablet was bioequivalent to the marketed 350 mg Soma tablet (Table 3), but the 150 mg tablet was not (data not shown).

The rate of absorption of carisoprodol from the test tablets, assessed by comparison of Cmax values, was similar to that from the reference tablet. The 90% confidence limits for the Cmax parameter being within the 80-125% interval for the 150 mg and the 250 mg tablets was indicative of acceptable rates of carisoprodol absorption from the test tablets.

Table 3. Summary of the Dose-Normalized Means, Ratios, and the 90% Confidence Limits for the Comparison of the Carisoprodol Pharmacokinetic Parameters (250 mg vs. 350 mg).

250 mg tablet vs. 350 mg tablet

PK Variable	LS Mean Test	LS Mean Reference	LS Mean Difference	Lower 90% Confidence Limit	Upper 90% Confidence Limit	Geometric Mean Test	Geometric Mean Reference	Ratio Test:Ref. (%)	Lower Conf. Limit (%)	Upper Conf. Limit (%)
Ln[AUC(0-tlast)]	8.5615	8.6461	-0.0846	-0.1570	-0.0122	5226.4	5687.7	91.89	85.47	98.79
Ln[AUC(0-∞)]	8.5732	8.6564	-0.0832	-0.1547	-0.0117	5288.0	5746.6	92.02	85.67	98.84
Ln(Cmax)	7.3819	7.3400	0.0419	-0.0913	0.1752	1606.7	1540.7	104.3	91.27	119.14

Source: Statistical Methods in Appendix 16.4.1
NOTE: The geometric mean is EXP (Mean on log scale). The ratio Test/Reference=100*exp (Difference on log scale).

Data in Table 4 indicate that 250 mg carisoprodol tablets are bioequivalent to 350 mg carisoprodol tablets for meprobamate exposure as well.

Table 4. Summary of the Dose-Normalized Ratios, and the 90% Confidence Limits for the Comparison of the Meprobamate Pharmacokinetic Parameters (250 mg vs. 350 mg).

	Ratios	90% CI Lower	90% CI Upper
ln(Cmax)	105.33	102.55	108.17
ln(AUCt)	98.76	96.18	101.41
ln(AUCinf)	98.53	95.76	101.38

Analysis by Gender

PK profiles for carisoprodol and meprobamate stratified by gender were shown in Figure 2.

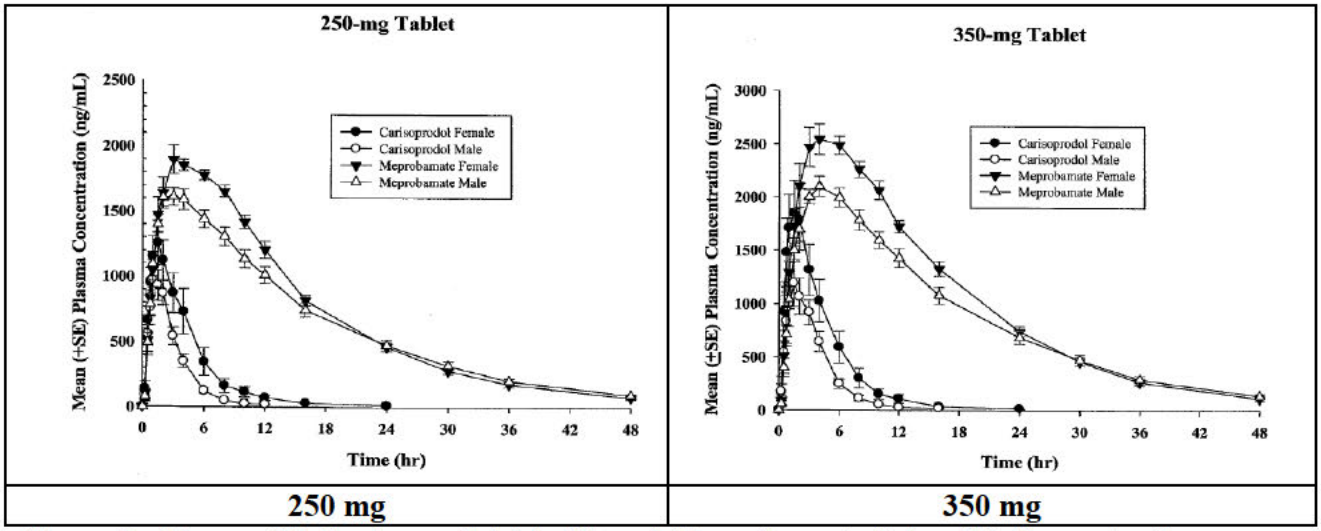


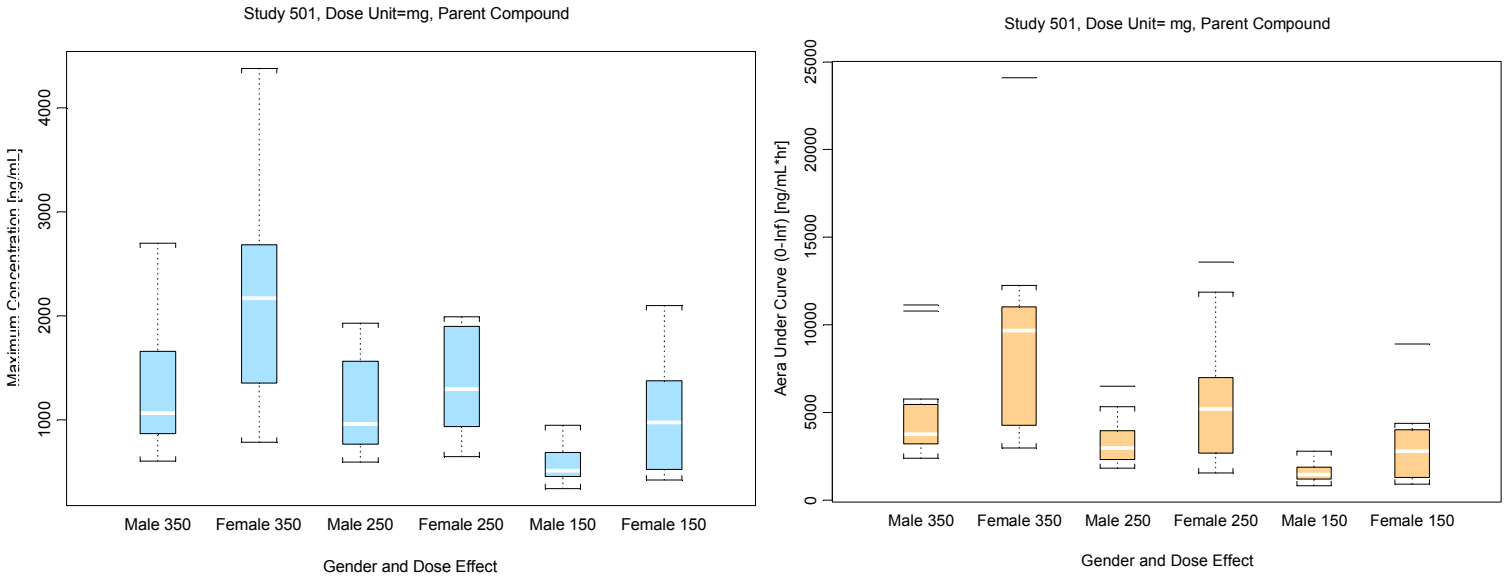
Figure 2. Mean ± SE Carisoprodol (circle) and Meprobamate (triangle) Concentration (ng/mL) in Plasma After a Single Dose of a Carisoprodol Tablet Given to Male (open symbols) and Female (closed symbols) Subjects.

Exposure (AUC and Cmax) of carisoprodol and meprobamate were higher in female subjects than in male subjects (Table 5). The difference was more profound for carisoprodol. Tmax and half-life values were similar between genders.

Table 5. PK Parameter (Mean ± SD) Comparison in Male and Female Subjects after Receiving 250 mg or 350 mg Carisoprodol Tablets.

	Carisoprodol			Meprobamate		
	Cmax (ng/mL)	AUC(0-∞) (ng/mL*hr)	Tmax (hr)	Cmax (ng/mL)	AUC (ng/mL*hr)	Tmax (hr)
250 mg						
Male	1113 ± 451	3321 ± 1423	1.4 ± 0.5	1654 ± 247	31003 ± 7369	2.9 ± 0.8
Female	1369 ± 514	5693 ± 3831	1.7 ± 1.0	2028 ± 244	33656 ± 4711	4.3 ± 2.1
Difference of Means (%)	**23.0**	**71.4**		**18.4**	**7.9**	
350 mg						
Male	1356 ± 706	5025 ± 2959	1.6 ± 0.9	2146 ± 331	42809 ± 9977	4.2 ± 1.3
Female	2186 ± 1046	8976 ± 5866	1.8 ± 0.8	2769 ± 368	49151 ± 6876	4.8 ± 2.4
Difference of Means (%)	**61.2**	**78.6**		**29.0**	**14.8**	

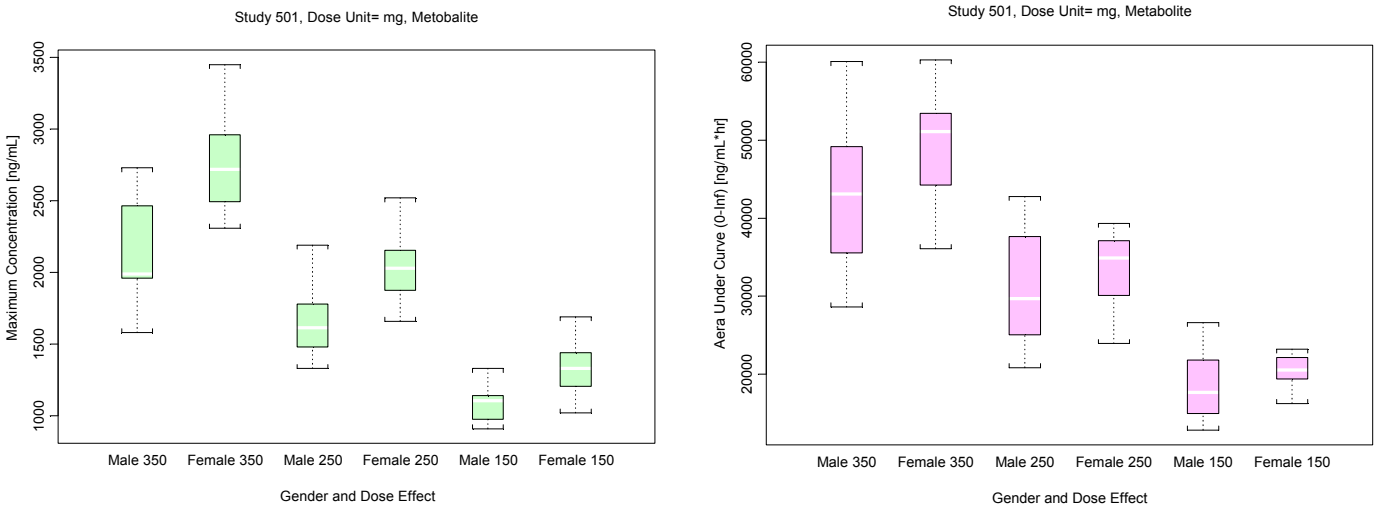
Box-and-Whisker plots for Cmax and AUC values of carisoprodol sorted by gender were shown in Figure 3 for all three doses. Exposures of carisoprodol in females appear to be more variable than males. Exposures of carisoprodol for females at 250 mg are similar to or higher than those in males at 350 mg.



Cmax **AUCinf**

Figure 3. Box-and-Whisker Plots for Cmax and AUC Values of Carisoprodol Sorted by Gender.

Box-and-Whisker plots for Cmax and AUC values of meprobamate sorted by gender were shown in Figure 4 for all 3 doses.



Cmax **AUCinf**

Figure 4. Box-and-Whisker Plots for Cmax and AUC Values of Carisoprodol Sorted by Gender.

Conclusions:

- Dose-normalized AUCt, AUCi, and Cmax for carisoprodol and its metabolite, meprobamate, were equivalent between 250 and 350 mg carisoprodol tablets.
- Exposure of meprobamate was higher than carisoprodol (50% higher for Cmax and 6-fold higher for AUC). The half-life of meprobamate was also longer (10 hours vs. 2 hours for carisoprodol).
- The Cmax of meprobamate was 2.5 ± 0.5 µg/mL (mean ± SD, n=24) at the 350 mg dose, approximately 30% of those seen following a single 400 mg dose of meprobamate (Cmax of 8.0 µg/mL).
- Contrary to previous data cited in the SOMA 350 mg tablet labeling that females had higher clearance, in this study, exposure of carisoprodol and meprobamate were higher in female subjects than in male subjects. The difference was more profound for carisoprodol exposure indicating that body weight may not be the only factor contributing to higher exposure in female subjects and that overall metabolism of carisoprodol may be slower in female subjects.
- Exposures of carisoprodol in females appear to be more variable than males. Exposures of carisoprodol for females at 250 mg are similar to or higher than those in males at 350 mg.

4.2.2 Study MP500: Randomized, Open-Label, Crossover Trial on the Effect of Food on the Absorption of Carisoprodol from Soma® (Carisoprodol) Tablets 350 mg in Normal, Healthy Subjects

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Study Period:	December 10 to December 20, 2004
Principle Investigator:	James Carlson, Pharm.D.
Clinical Site:	PRACS Institute, 4801 Amber Valley Parkway, Fargo, ND 58104
Sample Analysis Period:	Between January 6, 2005 and January 27, 2005
Analytical Site:	(b) (4)

Objective: To evaluate the effect of a high-fat meal on the rate and extent of absorption of carisoprodol from Soma 350 mg tablets.

Study Design: This was a randomized, open-label, crossover study design, comparing the pharmacokinetics of carisoprodol after dosing with a Soma 350 mg tablet 30 min after high-fat breakfast and in a fasting state with a one week washout between the two treatment periods.

Twenty-four healthy subjects (12 males and 12 females) were enrolled to participate in the treatment phase. All subjects completed the two periods of study and were included in both the pharmacokinetic and safety populations.

After meeting all entrance criteria, subjects were stratified by gender and randomized in a 1:1 ratio to one of two possible treatment sequences: Fasted → Fed and Fed → Fasting. The fed treatment group was dosed 30 minutes after the start of the meal. The fasting group received the dose after a l0-hour fast. Food was withheld from each treatment group for 4 hours after dosing. The dose was one Soma 350 mg tablet taken with 240 mL water at room temperature.

The breakfast meal consisted of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. This meal contained about 800-1000 calories, and about 50% of the total caloric content was derived from fat.

The two treatment sequences had equal numbers of males and females, who were all under 40 years of age with an overall mean age of 24 years. Male subjects in both sequences had an overall mean weight of 176.1 Lbs; and the mean weight for females was 159.3 Lbs. The majority of the subjects were Caucasian (92%).

Test Articles:
Soma 350 mg Tablets (Lot Number 2A10004A), which was manufactured in a batch size of over (b) (4) tablets.

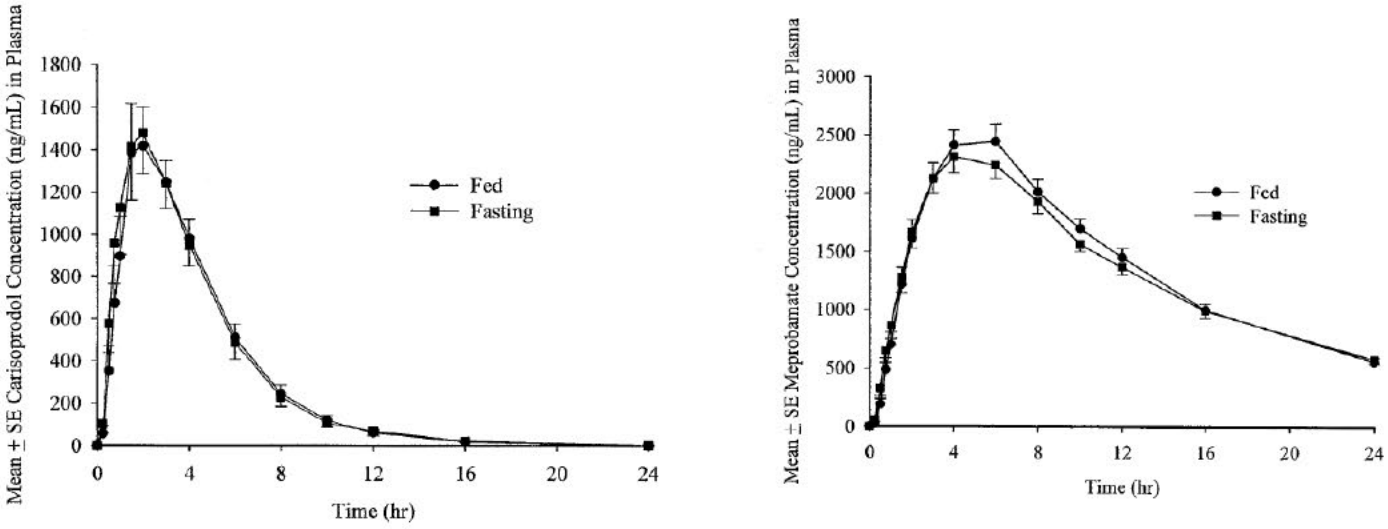
Sample Collection: pre-dose (0 hr), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, l2, 16, and 24 hours post-dose (10 mL EDTA) in each period.

Sample Analysis: Plasma samples obtained during the clinical portion of this study were assayed to simultaneously measure carisoprodol and meprobamate by a validated and sensitive LC/MS/MS metho (b) (4) The range of the assay for carisoprodol was (b) (4) and for meprobamate (b) (4) The lower limit of quantification for carisoprodol and meprobamate was 10 ng/mL and 8 ng/mL, respectively. (b) (4) was used as an internal standard.

Pharmacokinetic Results:

PK Profiles

The mean plasma concentration-time profiles of carisoprodol and metabolite, meprobamate, under fasting and fed conditions are shown in Figure 1 (a and b).



a. Carisoprodol

b. Meprobamate

Figure 1. Mean Plasma Carisoprodol (a) and Meprobamate (b) Concentrations under Fasting (■) and Fed (●) Conditions.

The mean pharmacokinetic parameters for carisoprodol and meprobamate from 24 subjects are summarized in Tables 1 and 2.

Table 1. Summary of the Pharmacokinetic Parameters Obtained for Carisoprodol after a Single Dose of One 350 mg Soma Tablet Given with a High-Fat Breakfast and in the Fasted State.

Parameter	Fed State n=24	Fasted State n=24
Cmax (ng/mL)		
Mean ±SD	1810 ± 978	1899 ± 1136
(CV%)	(54.0)	(59.8)
Tmax (hr)		
Mean ±SD	2.3 ± 1.0	1.9 ± 0.9
(CV%)	(42.5)	(47.9)
Median	2.0	1.75
(Range)	(1.0-4.0)	(0.75-4.0)
λz (1/hr)		
Mean ±SD	0.390 ± 0.078	0.372 ± 0.076
(CV%)	(19.9)	(20.3)
t½λz (hr)		
Mean ±SD	1.8 ± 0.4	1.9 ± 0.4
(CV%)	(20.7)	(22.0)
AUC(0-tlast) (hr*ng/mL)		
Mean ±SD	7048 ± 3690	7225 ± 4710
(CV%)	(52.4)	(65.2)
AUC(0-∞) (hr*ng/mL)		
Mean ±SD	7112 ± 3712	7295 ± 4744
(CV%)	(52.2)	(65.0)

Source reference: Table 14.1.10 and Table 14.1.11

Table 2. Summary of the Pharmacokinetic Parameters Obtained for Meprobamate after a Single Dose of One 350 mg Soma Tablet Given with a High-Fat Breakfast and in the Fasted State.

Parameter	Fed State n=24	Fasted State n=24
Cmax (ng/mL)		
Mean ±SD	2643 ± 690	2440 ± 693
(CV%)	(26.1)	(28.4)
Tmax (hr)		
Mean ±SD	4.7 ± 1.4	4.6 ± 1.5
(CV%)	(29.7)	(33.4)
Median	4.0	4.0
(Range)	(3.0-8.0)	(3.0-8.0)
λz (1/hr)		
Mean ±SD	0.081 ± 0.013	0.075 ± 0.017
(CV%)	(16.5)	(22.5)
t½λz (hr)		
Mean ±SD	8.8 ± 1.4	9.7 ± 2.5
(CV%)	(16.1)	(25.7)
AUC(0-tlast) (hr*ng/mL)		
Mean ±SD	32916 ± 7200	31634 ± 7255
(CV%)	(21.9)	(22.9)
AUC(0-∞) (hr*ng/mL)		
Mean ±SD	40136 ± 8837	40601 ± 10950
(CV%)	(22.0)	(26.9)

Source reference: Table 14.1.13 and Table 14.1.14

Relative Bioavailability (Fed vs. Fasting)

Table 3. Summary of the Means, Ratios, and the 90% Confidence Limits for the Comparison of the Carisoprodol Pharmacokinetic Parameters for the Fed and Fasted States.

PK Variable	LS Mean Fed	LS Mean Fasted	LS Mean Difference	Lower 90% Confidence Limit	Upper 90% Confidence Limit	Geometric Mean Fed	Geometric Mean Fasting	Ratio Fed:Fast (%)	Lower Conf. Limit (%)	Upper Conf. Limit (%)
Ln[AUC(0-tlast)]	8.7430	8.7332	0.0098	-0.0608	0.0804	6233.4	6205.3	101.0	94.10	108.38
Ln[AUC(0-∞)]	8.7525	8.7436	0.0089	-0.0613	0.0791	6326.5	6270.2	100.9	94.06	108.24
Ln(Cmax)	7.3818	7.4078	-0.0260	-0.1713	0.1192	1606.5	1648.8	97.4	84.26	112.66

Source: Statistical Methods in Appendix 16.4.1
NOTE: The geometric mean is EXP (Mean on log scale). The ratio Fed:Fasting=100*exp (Difference on log scale).

Table 4. Summary of the Dose-Normalized Ratios, and the 90% Confidence Limits for the Comparison of the Meprobamate Pharmacokinetic Parameters (Fed vs. Fast).

	Ratios	90% CI Lower	90% CI Upper
ln(Cmax)	108.75	103.21	114.59
ln(AUCt)	104.28	100.77	107.91
ln(AUCinf)	99.67	95.69	103.80

Additional Analysis by Gender

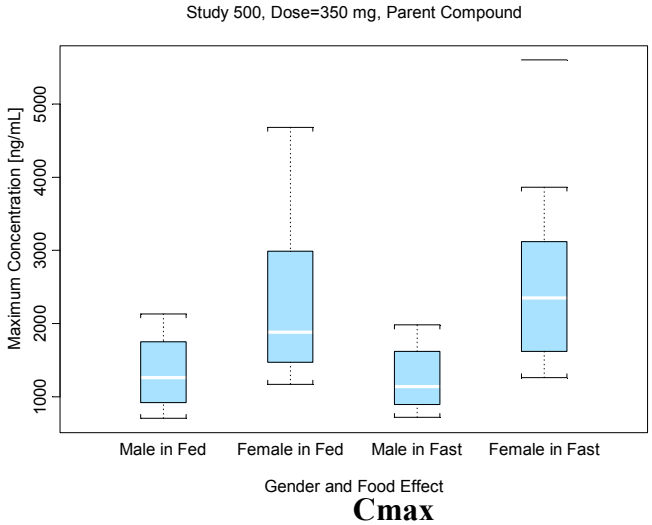
Consistent with the findings in Study 501, exposure of carisoprodol and meprobamate were higher in female subjects than in male subjects (Table 5). The difference was more profound for carisoprodol.

Table 5. PK Parameter (Mean ± SD) Comparison in Male and Female Subjects under Fasting and Fed conditions after Receiving 350 mg Carisoprodol Tablets.

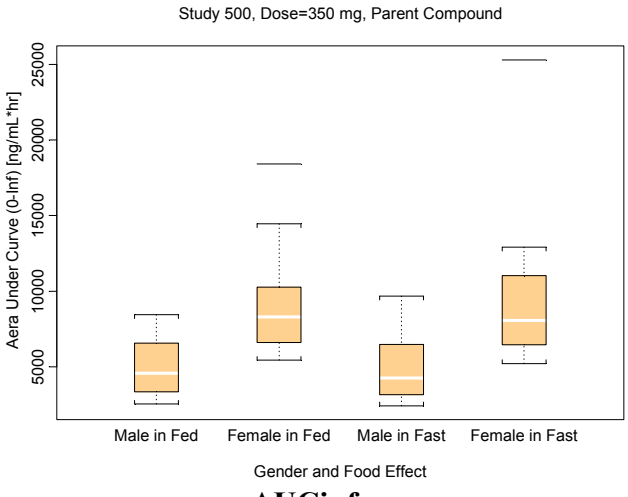
	Carisoprodol			Meprobamate		
	Cmax (ng/mL)	**AUC(0-∞) (ng/mL*hr)**	**Tmax (hr)**	**Cmax (ng/mL)**	**AUC(0-∞)* (ng/mL*hr)**	**Tmax (hr)**
Fasting						
Male	1243 ± 448	5142 ± 2361	2 ± 0.9	1986 ± 419	34291 ± 6788	4.4 ± 1.6
Female	2556 ± 1249	9693 ± 5448	1.9 ± 1.0	2857 ± 615	46326 ± 11306	4.7 ± 1.5
Difference of Means (%)	**105.6**	**88.5**		**30.5**	**35.1**	
Fed						
Male	1322 ± 499	5024 ± 2032	2.2 ± 0.9	2244 ± 514	35047 ± 6757	4.2 ± 1.2
Female	2301 ± 1107	9199 ± 3896	2.3 ± 1.1	3042 ± 621	45225 ± 7818	5.3 ± 1.4
Difference of Means (%)	**74.1**	**83.1**		**35.6**	**29.0**	

** %AUCextra values of Metobamate for some patients were >15% because PK were only sampled to 24 hours post-dose. For these patients AUC(0-∞) values may not be accurate.*

Box-and-Whisker plots for Cmax and AUC values of carisoprodol sorted by gender were shown in Figure 2 for both fed and fasting conditions.



Cmax

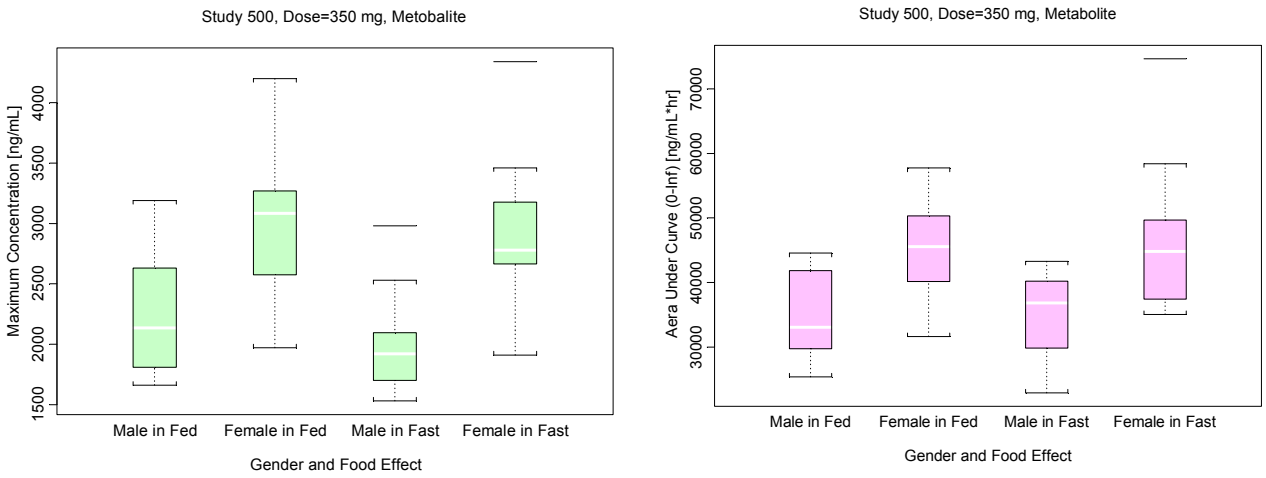


AUCinf

Figure 2. Box-and-Whisker Plots for Cmax and AUC Values of Carisoprodol Sorted by Gender.

<u>Reviewer's Note:</u> The outlier data in female dataset were from the same subject, Subject 18, who may be a slower metabolizer of CYP2C19. Meprobamate data for this subject were similar to other subjects.

Box-and-Whisker plots for Cmax and AUC values of meprobamate sorted by gender were shown in Figure 3 for both fed and fasting conditions.



Cmax **AUCinf**

Figure 3. Box-and-Whisker Plots for Cmax and AUC Values of Carisoprodol Sorted by Gender.

Conclusions:

- A high fat meal does not affect C_{max} or AUC_{inf} of carisoprodol or meprobamate following 350 mg SOMA dosing. Tmax was not affected either.
- Consistent with findings from Study 501, exposure of carisoprodol and meprobamate were higher in female subjects than in male subjects in this study. The difference was more profound for carisoprodol exposure. AUC of carisoprodol is ~80-90% higher in females. Cmax of carisoprodol is ~70-110% higher in females. AUC and Cmax of meprobamate is ~20-35% higher in females.

4.3 OCP Filing and Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	11-792 (SE2/S041)	Brand Name	SOMA
OCPB Division (I, II, III)	DCP2	Generic Name	Carisoprodol
Medical Division	DAARP	Drug Class	Skeletal muscle relaxant
OCPB Reviewer	Lei Zhang, Ph.D.	Indication(s)	For the relief of discomfort associated with acute, painful musculoskeletal conditions.
OCPB Team Leader	Suresh Doddapaneni, Ph.D	Dosage Form	Tablets, 250 mg
		Dosing Regimen	Three times a day and at bedtime
Date of Submission	11/10/2006	Route of Administration	Oral
Estimated Due Date of OCPB Review	7/19/2007	Sponsor	MedPointe
PDUFA Due Date	9/13/2007	Priority Classification	SE2
Division Due Date			IND 71,218

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
Human PK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X	(1)		1. Study MP501
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	(1)		2. Study MP501
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**1**	**1**	**1. Study MP501 (150, 250 mg vs. 350 mg tablets)**
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**	**1**	**1. Study MP500 (350 mg single dose)**
Dissolution:				**Will be reviewed by CMC reviewer.**
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**	**1**	**1**	**Effect of CYP2C19 polymorphism on PK**
Total Number of Studies		**3**	**3**	

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?	**X**	For Study MP501 • Provide analysis results based on gender • Provide 90% CI analysis results for the metabolite, meprobamate
QBR questions (key issues to be considered)	• **What is PK profile of 250 mg SOMA tablets? Is PK dose proportional?** • **Is there a food effect (done with the highest dose strength, 350 mg tablet)?** • **What is effect of gender on PK of carisoprodol?**	
Other comments or information not included above	**During review, it was found that CYP2C19 activity has significant impact on PK of carisoprodol.**	
Primary reviewer Signature and Date	**Lei Zhang**	
Secondary reviewer Signature and Date	**Suresh Doddapaneni**	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Lei K Zhang
7/27/2007 03:23:12 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
7/27/2007 03:39:57 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

OTHER REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: 8/29/07

TO: Sharon Turner-Rinehard, Regulatory Project Manager
Eric Brodsky, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products, HFD-170

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Carolanne Currier. CSO

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 11-792/SE2-041

APPLICANT: MedPointe Pharmaceuticals, Inc.

DRUG: Soma (carisoprodol)

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: (b) (4)

CONSULTATION REQUEST DATE: 1/18/07

DIVISION ACTION GOAL DATE: 10/11/07

PDUFA DATE: 10/13/07

I. BACKGROUND:

Soma (carisoprodol – NDA 11-792) has been marketed since 1959 as a muscle relaxant in tablet form. The currently approved dose for muscular pain is 350 mg 3 times a day (tid) and at bedtime (total 1400 mg dose). The study submitted in supplement SE2-041 for NDA 11-792 compared the efficacy of the original 350 mg tid + bedtime dosing regimen to a 250 mg tid + bedtime dosing regimen (total 1000 mg) and to placebo.

The clinical trials submitted in the supplement used protocol MP502: "Randomized, Double-Blind Trial of Carisoprodol 350-mg and 250-mg Tablets Compared to Placebo in Patients with Acute, Painful Musculoskeletal Spasm of the Lower Back." Primary efficacy endpoints were: 1) subject-rated relief from backache, and 2) subject-rated global impression of change. Since the safety profile of Soma is well known, the Division of Anesthesia, Analgesia and Rheumatology Products requested the inspection of a study at only one clinical site to evaluate efficacy of the lower dose. Dr. Ateeqahmed S. Patel's site was selected because he enrolled a relatively large number of study subjects compared to other study sites.

II. RESULTS (by protocol/site):

Name of CI/Site Number	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Ateeqahmed S. Patel, M.D./ Site #263	Atlanta, GA	MP502	3/19-21/07	4/20/07	NAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

Protocol # MP502

Ateeqahmed Patel, M.D., Atlanta, Georgia, Site #263:

a. What was inspected: At this site, 36 subjects were enrolled and 34 subjects completed the study. An audit of 35 subject records was conducted.

b. Limitations of inspection: none.

c. General observations/commentary: No significant deviations from regulations or deficiencies in the conduct of the study were noted.

d. Data acceptability/reliability: The study appears to have been conducted adequately and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

No problems were noted during the inspection of Dr. Patel's study with MP502. Data generated by this site appear acceptable in support of the respective indication.

{See appended electronic signature page}

Carolanne Currier, CSO

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Carolanne Currier
8/30/2007 11:41:37 AM
CSO

Draft is in your inbox for comparison if needed.

Constance Lewin
8/30/2007 12:11:26 PM
MEDICAL OFFICER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 27, 2007
To:	Eric Brodsky, M.D., Medical Officer
	Division of Anesthesia, Analgesia and Rheumatology Products
	Office of Drug Evaluation II
	Office of New Drugs
Thru:	Solomon Iyasu, M.D., M.P.H., Director
	Division of Surveillance, Research and Communication Support
	Office of Surveillance and Epidemiology
From:	Andrea Feight, D.M.D., M.P.H., Epidemiologist
	Division of Surveillance, Research and Communication Support
	Office of Surveillance and Epidemiology
Subject:	Duration of Use Analysis
Drug Name(s):	Soma® (carisoprodol)
Submission Number:	SE2
Application Type/Number:	NDA 11-792
Applicant/sponsor:	MedPointe Pharmaceuticals
OSE RCM #:	2007-95

CONTENTS

EXECUTIVE SUMMARY

The objective of this study was to characterize the duration of use for Soma® (carisoprodol). The study results indicate that the median duration of the longest period of use was 25 days. The mean duration was 69 days and was skewed by a minority of individuals with very lengthy utilization periods.

For the purpose of this study, an episode of therapy was defined as one or a series of consecutive prescription claims for an individual who received a prescription for Soma® with no more than a 15-day lag between the end of one prescription and the beginning of the next prescription. A successive prescription for the same patient that was dated more than 15 days after the ending date of the preceding prescription was not considered a part of that episode of treatment; rather, it was considered to be the onset of a new episode.

Key findings from the analysis:

- 63% of individuals had only 1 episode of use during the entire five-year period examined (2002-2006).
- The median duration of the longest episode of use was 25 days.
- 70% of individuals had their longest episode of use less than 31 days.
- Within the longest episode, 67% of individuals had only one prescription claim.

Other important findings:

- The mean age of individuals utilizing Soma® was 45.
- Females comprised the majority (60%) of users.
- The percentage of Soma® users who had only one prescription claim for the product over the entire five-year period of study was 53%.
- The mean number of prescriptions per individual was 5.1.
- The proportion of individuals who had more than 12 prescription claims for Soma® was 10%.
- 97% of prescriptions indicated a days supply of 30 days or less, and the mean days supply was 22.5.
- The payment mechanisms for the product as recorded on each prescription claim were as follows: third party (72%), cash (18%), and Medicaid reimbursement (10%).

1 BACKGROUND

In response to a request from the Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP), this review examines the duration of use for the analgesic Soma® (carisoprodol).

DAARP requested this review following the submission of an efficacy supplement by MedPointe Pharmaceuticals for a new lower dose (250 mg) Soma® tablet and a new dosing regimen (250 mg three times daily and at bedtime). Soma® was originally approved in 1959 and is currently marketed as a 350 mg tablet. The current labeling indicates under 'Drug Abuse and Dependence' that its use should be limited to the acute treatment setting and not for more than 2-3 weeks. The duration of the submitted clinical trials was one week, however the sponsor is proposing labeling for (b) (4) of use.

2 METHODS AND MATERIALS

2.1 STUDY DRUGS

All of the records in the analysis dataset are for the 350 mg tablet of Soma® or carisoprodol.

2.2 DATA SOURCE

Verispan, LLC: Vector One® Data Warehouse

The Vector One® database integrates outpatient retail prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims annually, representing over 160 million unique patients. Vector One® prescription records are obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores, however, mail order prescriptions are not included in the sample at this time.

The Verispan data draw from a sample of multiple payers, providers, and pharmacies and are not dependent upon prescription drug coverage through an insurer. The Verispan system gathers individual-specific information at the level of the pharmacy and thereby captures dispensed prescriptions for payers via third party insurance coverage, cash, a combination of third party coverage and cash, plus Medicaid. Because the data are not dependent upon insurance coverage, individuals do not need to be continuously enrolled in a system to be captured in the database. The Vector One® database contains a unique patient identifier that allows tracking of individual patients across suppliers and data sources so that patients can be followed over time and across services.

Verispan's Data Extraction Tool (DET) was utilized to download the data from the Vector One® Data Warehouse for this analysis. In contrast to data accessed through Verispan's online tools, such as Vector One®: National (VONA) and Total Patient Tracker (TPT), data downloaded through the **DET is not projected to the US population**. However, data accessed through the DET allows the user to perform custom data analyses that are not possible with the online tools, such as the duration of use per unique patient requested in this consult.

For this analysis, prescription claims in the Verispan, LLC Data Warehouse system were examined from January 1, 2002 –December 31, 2006.

2.3 DATA MANAGEMENT STRATEGY

A total of 10 datasets were downloaded on Feb 21-22, 2007 for each of the 2 USC drug classes (USC 59111 - single ingredient and USC 59112 - carisoprodol with aspirin or codeine) over the 5-year study period (calendar years 2002 – 2006). Preliminary analysis revealed that over 98% of the records were for the single ingredient carisoprodol or Soma®, and thus the analysis was limited to the 5 datasets for the single ingredient.

The variables available and utilized for downloading included the following: Patient Age, Patient Sex, Fill Date, Method of Payment, Drug Name, Strength, Dosage Form, MD Specialty, Unique Pt ID, Refill, Days Supply, and Quantity.

2.4 STUDY POPULATION

The study population includes individuals aged 1-85 years who were captured in the Verispan system as having one or more prescription claims for the drugs under study between January 1, 2002 and December 31, 2006. The original datasets were downloaded by USC class and year, and records for any drugs but those of interest were removed.

The five calendar-year datasets were merged to create a file containing (b) (4) total records, which were then examined for accuracy and reliability in data cleaning steps. Individuals and all of their associated claims were excluded from the dataset if one or more claims had an unknown or zero value for either the quantity of drug dispensed or the number of days for which the drug was prescribed (days supply).

A very small number of claims listed a days supply of over 360 days (e.g. 9,990 days) or a quantity over 720 days, and the associated individuals and all of their claims in the database were removed. Similarly, individuals and all of their associated claims were removed if they had multiple prescription claims and there was more than a 5-year difference in age between two consecutive prescriptions or if their age was missing in one or more claims.

Likewise, individuals and their associated claims were excluded if their gender was either unknown in any given claim or not consistent across all their claims. In addition, duplicate claims representing two different mechanisms of payment for a single dispensed prescription were reduced to a single claim.

Individuals and claims that were removed from the dataset during the all of the cleaning steps described above represented 0.53% and 0.04%, respectively, of the original, raw dataset. The counts of claims and individuals through the successive steps of the data cleaning process, utilizing the exclusion criteria described above, are illustrated in Table 1 of the Appendix. The final, cleaned dataset contained (b) (4) unduplicated records for (b) (4) unique individuals.

A sensitivity analysis was conducted by creating a second dataset cleaned in the same manner but excluding records for which the recorded days supply was more than 90 days (vs. 360 days in the primary dataset). Past analyses of Verispan DET data reveal that the most typical number of days supply indicated on prescription claims are 30, 60, or 90 days. The additional analysis was conducted to examine whether records with a days supply beyond the longest typical supply, 90 days, disproportionately influenced the analytical results.

2.5 MEASUREMENTS

The mean number of days supplied per prescription was calculated at the prescription claim level, based upon information provided by the dispensing pharmacy. At the level of the individual, simple mean values were determined for the number of dispensed prescriptions and age. The age of each study individual was calculated at the time of the first prescription, utilizing the recorded date of birth.

Claims data for the study population were used to determine an ‘episode’ of therapy for an individual. The episode of therapy was constructed upon an algorithm previously developed in the Division of Surveillance, Research and Communication Support. An episode of therapy was defined as one or a series of consecutive prescription claims for an individual who received a prescription with no more than a 15-day lag between the end of one prescription and the beginning of the next prescription. A successive prescription for the same patient that was dated more than 15 days after the ending date of the preceding prescription was not considered a part of that episode of treatment; rather, it was considered to be the onset of a new episode.

A start date and end date were derived for each episode in a manner that did not allow double counting of the treatment period in cases where prescriptions were refilled earlier than the days

supply would dictate. In addition, duplicate records for a combination of insurance reimbursement and cash co-pay were rectified to eliminate multiple counts for a single prescription.

The mean number of episodes per individual was derived by assigning count numbers to each episode for each individual. In addition, the longest episode of therapy for each individual was determined by sorting their episode lengths and outputing the longest episode. Additionally the duration of the longest episode of therapy was categorized into several ranges of number of days.

2.6 ANALYTIC METHODS

All analyses were performed using SAS statistical software version 9.1 (SAS Institute Inc, Cary, NC).

3 RESULTS

3.1 CHARACTERISTICS OF THE STUDY POPULATION

The mean age of individuals in the database at the time of first dispensing was 45.3. The mean age of individuals recorded at the time of each prescription fill was 47.2 (in part because the age of each individual increases over the study period). The group aged 17-64 accounted for 89% of the individuals in the dataset. Children under age 17 represented less than 1% of the study population, while those over 64 years of age accounted for only 10%.

Females accounted for 60.1% of the individuals in the study, while males accounted for 39.9%. Demographic characteristics of the individuals included in the study appear in Table 2 of the Appendix.

The Verispan DET data provide an indication of the method of payment for each dispensed prescription. In this study, the majority of claims were paid by Third Party (72%), followed by Cash (18%), and Medicaid (10%).

The top 5 specialties indicated for the prescribing physicians were as follows: Family Practice 34%, Internal Medicine 20%, Unspecified 6%, Surgery/Orthopedic 6%, and General Practice 4%.

3.2 DRUG UTILIZATION BY ELIGIBLE POPULATION

Over the entire five-year period covered in the analytical dataset, the mean number of prescriptions per individual for Soma® (carisoprodol) was 5.1 (median 1.0; range 1 to 816; SD 10.3). Table 3 of the Appendix displays the number and percent of prescription claims per person. 80% of individuals had no more than 5 prescriptions, while 12% had more than 10 prescriptions.

The mean number of ‘days supply’ specified in the prescription claims was 22.5 (median 30.0; range 1-360; SD 10.7). 97% of prescriptions indicated a days supply of 30 days or less. The number and percent of days supply indicated on each claim record is shown in Table 4 of the Appendix.

3.3 DURATION OF USE FOR SOMA® (CARISOPRODOL)

For the purpose of this study an episode of therapy was defined as the number of days supplied for a single prescription or a period of drug therapy during which no more than 15 days lapsed between subsequent prescriptions. The mean number of episodes per person over the study period was 2.1 (range 1-67; median 1.0; SD 2.5). Close to two-thirds of individuals (63%) had only 1 episode of therapy during the study period, while 85% of individuals had no more than three

episodes. The number and percent of episodes per person throughout the study appear in Table 5 of the Appendix.

The median duration of the longest episode was calculated to be 25 days (range 1-1912; mean 69, SD 151). Categorical data describing the longest episode of therapy is included in Table 6 of the Appendix. Based on the distribution of the data, the best measure to interpret duration of use is the median, since the data is skewed by a relatively small proportion of individuals with a very lengthy duration of use.

Considering only the longest episode of therapy for each individual, the mean number of prescriptions within that episode was 3.1 (range 1-816; median 1.0, SD 6.6). Within the longest episode, 67% of individuals had only 1 prescription and 12% had 2 prescriptions; 5% of individuals had more than 12 prescriptions.

The demographic characteristics of those individuals with the longest episode of therapy lasting more than 21 days was further examined (they represented 51.7% of the entire study population). These individuals were on average slightly older (46.9 vs 44.3). With regards to gender, females represented 61.7% (vs. 60.1% in the entire dataset). The mean days supply for this group was 27.3 days, versus 10.4 days in those individuals with the longest episode lasting less than 21 days.

4 DISCUSSION

While the mean age of individuals at the time of first prescription was 45.3, the mean age of individuals recorded at the time of each prescription fill was 47.2. Although this may reflect some differences in those who received multiple prescriptions versus a single prescription, the difference most likely reflects the fact that the age of each unique individual increases over the 5-year study period. The typical individual in this study receiving a dispensed prescription for Soma® was a female in her mid-forties.

Although two-thirds of individuals had two or fewer claims during the entire five-year study period, 12% had more than 10 claims. One individual had 816 claims during the 5 years, or 1826 days, of the study period. A qualitative examination of this individual's claims revealed a series of repeated claims for a days supply recorded as 1 to 7 days, with few or no lapses between prescriptions. There were an additional (b) (4) individuals with over 130 prescription claims, which would be equivalent to 26 prescriptions per year or one per 2 weeks for the entire 5-year period. It is possible that these individuals are participants in a pain treatment agreement. Some prescribers require such agreements, which outline the patient's responsibilities in obtaining the pain medication.

Although the majority of individuals had only one episode of therapy during the study period, the duration of the one episode could be quite lengthy, perhaps due to the use of a pain agreement, as described above. Thus it was important to identify and examine the longest episode for each individual. As such, the mean duration of the longest episode was calculated to be 69 days. However, based on the distribution of the data, the best measure to interpret duration of use is the median, since the data is skewed by a relatively small proportion of individuals with a very lengthy duration of use. The median duration of use was 25 days.

Based on this analysis, it appears that those with the longest durations of use have either a prescription of long duration or many prescriptions of short duration occurring in rapid succession. Of course, individuals with a lengthy duration of use consisting of consecutive prescriptions of long duration are also represented in the database.

As described in section 2.4, above, a sensitivity analysis was conducted to remove individuals and their associated claims if one or more of those claims indicated a days supply of more than 90 days. Despite the removal of (b) (4) records for (b) (4) individuals, there was no significant

change in the results from the primary analytical dataset, hence only the results of the primary analysis are included here.

Findings from this consult should be interpreted in the context of the known limitations of the database used. It is also important to emphasize that this study did not attempt to identify individuals who were new to therapy and also did not examine the drug utilization patterns of individuals who may have switched to or from any other medications. It is possible that individuals initiated use of Soma® prior to the study window and/or continued its use after the study window. Therefore, the estimates provided here may be underestimates of actual duration of use.

5 CONCLUSIONS

The main focus of this study was to characterize the duration of use for Soma®. The median duration of the longest episode was 25 days. Based on the distribution of the data, the best measure to interpret duration of use is the median, since the data is skewed by a relatively small proportion of individuals with a very lengthy duration of use. Although the current labeling recommends Soma® not be used for periods longer than 2-3 weeks, this study indicates the use is somewhat longer for most individuals and substantially longer for a minority of individuals.

APPENDIX 1

Table 1. Dataset Counts at the Record and Individual Level Across the Data Cleaning Steps, Based on Pre-determined Exclusionary Criteria, Verispan Vector One®, 2002-2006

Data cleaning steps	# records at beginning of step	# indivs at beginning of step	# claims with error	# indivs removed	# claims removed for those indivs	% raw records removed by cleaning
raw					(b) (4)	0.00%
quantity and days supply						0.14%
age (missing, age 0 or >5 yr diff)						0.05%
gender inconsistent						0.01%
extremes, dupes, invalid dates						0.33%

Source: Verispan Vector One®, DET, extracted February 2007

Table 2. Demographic Characteristics of the Study Population with One or More Prescription Claims, Verispan Vector One®, 2002-2006

Age in years	%
0 to 11	0.15
12 to 16	0.78
17 to 64	88.60
65 years or older	10.50
Gender	
Female	60.10
Male	39.90

Source: Verispan Vector One®, DET, extracted February 2007

Table 3. Number and Percent of Prescription Claims per Person, Verispan Vector One®, 2002-2006

	N	%
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
>12		
TOTAL		

Source: Verispan Vector One®, DET, extracted February 2007

Table 4. Number and Percent of Days Supply Indicated on Each Claim Record, Verispan Vector One®, 2002-2006

	N	%
1-7 days	(b) (4)	
8-14 days		
15-21 days		
22-30 days		
31-60		
61-90		
91-120		
121-150		
151-180		
181-210		
211-240		
241-270		
271-300		
301-330		
331-360		
TOTAL		

Source: Verispan Vector One®, DET, extracted February 2007

Table 5. Number and Percent of Episodes per Person, Verispan Vector One®, 2002-2006

	N	%
1	(b) (4)	
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
>12		
TOTAL		

Source: Verispan Vector One®, DET, extracted February 2007

Table 6. Duration of the Longest Episode of Therapy for Each Individual, Verispan Vector One®, 2002-2006

	N	%
1-7 days	(b) (4)	
8-14 days		
15-21 days		
22-30 days		
31-60		
61-90		
91-120		
121-150		
151-180		
181-210		
211-240		
241-270		
271-300		
301-330		
331-360		
>360		
TOTAL		

Source: Verispan Vector One®, DET, extracted February 2007

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/s/

Andrea Feight
6/28/2007 02:56:00 PM
DRUG SAFETY OFFICE REVIEWER

Solomon Iyasu
6/28/2007 05:02:21 PM
MEDICAL OFFICER

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO 22, STOP: 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**OSE REVIEW #:**
December 20, 2006	June 1, 2007	2006-1054
DATE OF DOCUMENT:	**PDUFA DATE**:	
November 10, 2006	September 13, 2007	

TO: Bob Rappaport, M.D.
Director, Division of Anesthesia, Analgesia and Rheumatology Products
HFD-510

THROUGH: Denise Toyer, PharmD., Deputy Director
Carol Holquist, RPh., Director
Division of Medication Errors and Technical Support, HFD-420

FROM: Tselaine Jones Smith, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: SOMA
(Carisoprodol Tablets, USP)
250 mg

NDA#: 11-792/ SE-2

NDA SPONSOR: MedPointe Pharmaceutical

RECOMMENDATIONS:

DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

DMETS would appreciate feedback of the final outcome of this consult. Please copy DMETS on any correspondence forwarded to the sponsor with information pertaining to this review. Additionally, we would be willing to meet with the Division for further discussion if needed. If you have further questions or need clarifications, please contact Nancy Clark, Project Manager, at 301-796-1187.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO 22, STOP: 4447
Center for Drug Evaluation and Research

LABEL AND LABELING REVIEW

DATE OF REVIEW: January 25, 2007

NDA#: 11-792/SE-2

NAME OF DRUG: SOMA
(Carisoprodol Tablets)
250 mg and 350 mg

NDA HOLDER: MedPointe Pharmaceutical

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthesia, Analgesia and Rheumatology Products (HFD-170), for an assessment of the labels and labeling for Soma 250 mg. This supplement provides for a new 250 mg strength of Soma. The sponsor (b) (4) of Soma. Soma is currently available as a 350 mg tablet.

PRODUCT INFORMATION

Soma 350 mg tablets, USP were approved on April 9, 1959 for the treatment of painful musculoskeletal conditions including muscle spasm. The usual recommended dose is 350 mg three times daily and at bedtime. The sponsor has proposed that the daily recommended dose of Soma be (b) (4)

II. ADVERSE EVENT REPORTING SYSTEM (AERS)

Soma 350 mg has been marketed since April 9, 1959; thus, DMETS searched the FDA Adverse Event Reporting System (AERS) for all post-marketing safety reports of medication errors associated with the proprietary name Soma. The MedDRA Preferred Higher Level Group Term (HLGT) "Medication Errors" and verbatim substance name "SOMA%" were used as search criteria. The search strategy revealed seven medication error cases. Three cases involved the wrong drug being given instead of Soma. Two cases involved the improper dose of Soma which resulted in overdosage. One case involved a dose omission and the final case concerned Soma being given at the wrong time. These cases are described below. See Attachment A for data source, type of error, narrative and reported outcomes for the cases mentioned above.

A. Wrong Drug (n=3)

- In the first case, a patient was given Carbamazepine 200 mg instead of Soma 350 mg. The patient experienced grand mal convulsions and had to be hospitalized.
- In the second case, it was reported that Soma Compound was given instead of Soma. Outcomes were not reported for this case.
- In the third case, Soma was ordered; however, the patient was given Tylenol #3. Outcomes were not reported for this case.

None of the cases ascertained causality of the medication errors.

B. Improper Dose (n=2)

- In the first case of improper dose, the patient was prescribed a higher dosing regimen of five to six times a day. The patient experienced shortness of breath and restlessness as a result of the higher dose.
- The second case of improper dose involved a patient taking twelve tablets of Soma per day for approximately six days instead of the prescribed four tablets per day. The patient experienced "seizure-like activity" and was hospitalized for observation.

None of the cases ascertained causality of the medication errors.

C. Dose Omission (n=1) and Dose Given at the Wrong Time (n=1)

- The final two cases involved dose omission (scheduled 2 pm dose not given) and the dose given at the wrong time (0600 instead of 2200). Outcomes were not reported for either case.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

DMETS assessed the above medication error cases to determine if the addition of the proposed 250 mg strength will increase the occurrence of these types of errors. Following the assessment, DMETS believes that the introduction of the new 250 mg strength will not increase these types of errors. However, there may be confusion upon the introduction of the new strength to the marketplace. This confusion is anticipated due to unfamiliarity and knowledge deficit of the new strength. In order to minimize this confusion, we recommend the following.

A. GENERAL COMMENTS

1. DMETS recommends that the sponsor implement an educational campaign that informs practitioners of the following:

   - The introduction of the new 250 mg strength of Soma on the market;
   - The new recommended dose starting of 250 mg three times a day and at bedtime; and
   - (b) (4)

2. Distinct labeling is also critical in order to minimize confusion between the two strengths. This new product will most likely be stored in close proximity in the pharmacy to Soma 350 mg, thereby increasing the likelihood for selection errors to occur in a busy clinic, pharmacy, or inpatient unit where the wrong product can be dispensed. Therefore, it is important to distinguish the Soma 250 mg labels and labeling from that of the Soma 350 mg labels and labeling. This may be accomplished with the use of boxing, contrasting color, or some other means.

3. DMETS recommends that the sponsor include a statement for a period not to exceed six months, indicating a 'new product strength'. This would remind practitioners of the new strength and help to minimize the chance of selection errors. For example: "New 250 mg strength". "New recommended daily dose of 250 mg three times daily and at bedtime".

B. CONTAINER LABELS (250 mg)

1. In accordance with 21 CFR 201.10(g)(2), ensure that the established name on the carton labels and container labeling is at least one-half the size of the proprietary name.

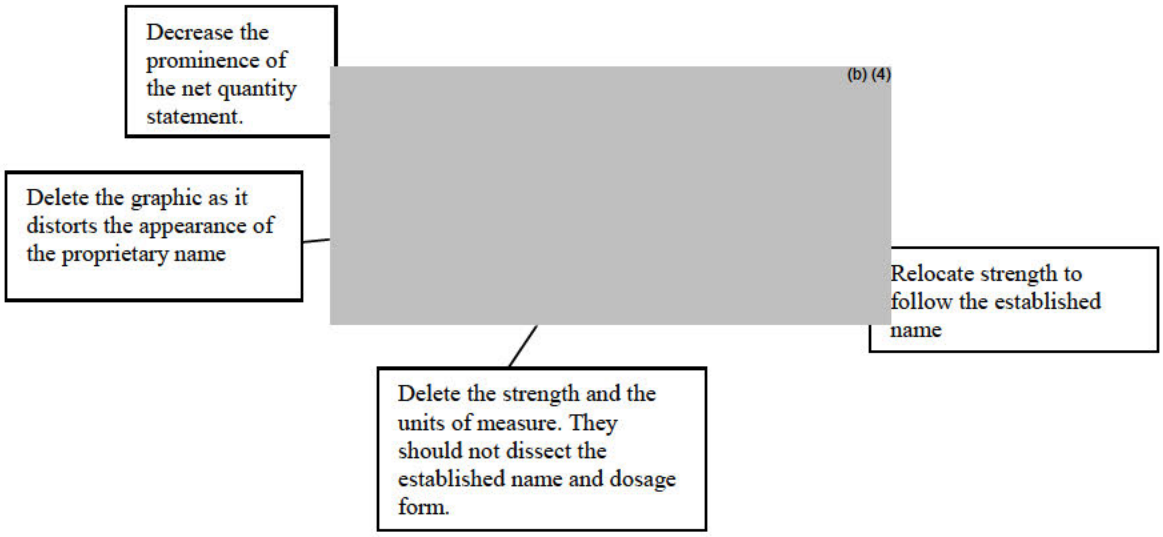
2. It appears that the product is the subject of a USP monograph. Please ensure that the appropriate USP designation appears in the established name (e.g., carisoprodol tablets, USP).

3. Decrease the prominence of the net quantity statement as this may be a visual distraction away from the strength.

4. Delete the graphic preceding the proprietary name, Soma, as it distorts the appearance of the proprietary name.

5. Revise the proprietary name, the established name and the strength to read as follows:

Soma
Carisoprodol Tablets, USP
250 mg



C. CARTON LABELING (4-Count Trade and 4- Count Professional Sample)

1. See Comments B1and B2.

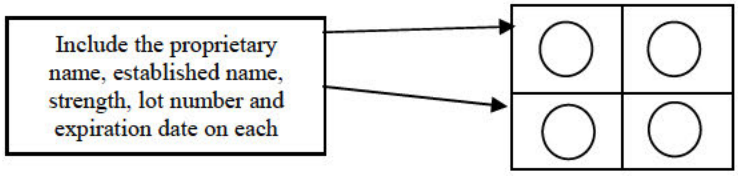
2. Revise the statement [redacted] (b) (4) to read as "Physician Sample- Not for Sale".

D. CARTON LABELING ([redacted] (b) (4)

1. See Comments B1, B2 and C2.

2. [redacted] (b) (4)

3. Once the tablets are punched out of the professional sample pack, you lose the important information printed on the reverse side. Furthermore, as patients pull back the foil in opening this configuration, more than one tablet may be accidentally exposed. DMETS recommends that each blister be designed such that removal of a tablet will not result in inadvertent exposure of remaining tablets. Additionally, DMETS recommends that each blister be labeled with the proprietary name, established name, strength, lot number and expiration date. For example:



4. Step 2 of the *Opening Instructions* (located on the back panel) s[redacted] (b) (4) and replace with "cut with scissors".

Attachment A

Source Case Number Date Received	Type of Error	Narrative	Outcome
AERS 3846587 10/03/2002	Improper Dose Resulting in Overdosage	Patient reported shortness of breath and restlessness after taking Carisoprodol tablets 350 mg. Suggested labeling dose is three times daily and once at bedtime. However, as per our telephone conversation with the pharmacist. We were informed that the patient was prescribed the dose for five to six times a day. This higher dose may have slightly contributed to the above mentioned side effects.	Shortness of breath and restlessness.
AERS 3951617 05/22/2003	Dose Omission	Order for Soma tid. Scheduled 10H 2P 10P. 2 pm dose not given as scheduled (omitted).	Not reported.
AERS 3955067 06/04/2003	Wrong Time	Medication (soma) given at 0600 instead of 2200.	Not reported.
AERS 6199876 12/12/2006	Wrong Drug	A refill prescription of carbamazepine 200 mg tablets was incorrectly filled with carisoprodol 350 mg tablets in a community retail pharmacy. Grand mal seizures and hospital emergency room intervention. Similar medication names and tablet appearance.	Grand mal convulsion ER intervention.
AERS 5721330 03/17/1995	Wrong Drug	There have been six incidents of Soma and Soma Compound being confused for each other. The incidents occurred at a small hospital with a drug room where nurses can obtain medications. RN's and LPN's were involved.	Not reported.
AERS 4128419 04/12/2004	Improper Dose Resulting in Overdosage	A pharmacist reported that on (b) (6) her spouse experienced "seizure like" activity while on Soma tablets, 350 mg. Her husband was hospitalized and observed for additional symptoms. He was discharged within one day with no observed events and the attending physicians indicated that the seizures "could not be attributed to Soma" Reporter indicated that her husband had been receiving Soma for the past 8 years without incident and prior to the seizure activity had taken 4 tabs daily, po. After a refill on March04, her husband "erroneously" began consuming 12 tabs daily, po. Post hospital discharge, the dose has been readjusted to 4 tabs daily, po and event has not reappeared. Patient continues therapy with Soma tablets, 350 mg. Event resolved. No additional information provided. Further information has been requested.	Seizures. Hospitalization.
AERS 3842969 05/05/2000	Wrong Drug	Tylenol #3 ordered, Soma given. These 2 drugs are side by side in narcotic cabinet. Soma was inadvertently pulled and given.	Not Reported.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tselaine Jones-Smith
6/12/2007 02:57:16 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
6/12/2007 04:08:44 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
6/12/2007 04:38:54 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Donald Klein, Ph.D., Reviewing Chemist
E-mail Address: Donald.klein@fda.hhs.gov
Phone: (301)-796-1689
Fax: (301)-796-9749

FROM: FDA
Division of Pharmaceutical Analysis, HFD-920
James Allgire
Room 1002
1114 Market Street
St. Louis, MO 63101

Through: B. J. Westenberger, Deputy Director, HFD-920
Phone: (314)-539-3869

SUBJECT: Methods Validation Report Summary

Application Number: NDA NDA 11-792/SE2-041

Name of Product: SOMA (Carisoprodol) Tablets, 250 mg

Applicant: MedPointe Pharmaceuticals, MedPointe Healthcare Inc.

Applicant's Contact Person: Michael I Bernhard, Ph.D.

Address: 265 Davidson Avenue
Suite 300
Somerset, NJ 08873-4120

Telephone: 732-564-2353 Fax: 732-564-2361

Date NDA Received by DPA: 5/09/2007

Date Samples Received by DPA: 5/22/2007

Date Analytical Completed by DPA: 6/12/2007

Laboratory Classification: **1.** Methods are acceptable for control and regulatory purposes. ☒
2. Methods are acceptable with modifications (as stated in accompanying report). ☐
3. Methods are unacceptable for regulatory purposes. ☐

Comments:

See page 2 for Cover Memorandum
See pages 3-7 for Summary of Results

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
1114 Market Street, Room 1002
St. Louis, Missouri 63101
Telephone (314) 539-3813
FAX (314) 539-2113

Date: June 8, 2007

To: Donald Klein, Review Chemist

From: Michael L. Trehy, Ph.D.

Subject: Evaluation of NDA 11-792/SE2-041
(b) (4) HPLC for the Analysis of Carisoprodol and Related Substances in the Drug Substance
(b) (4) HPLC for the Analysis of Carisoprodol and Related Substances in the 250 mg Tablets

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

- "(b) (4) High Performance Liquid Chromatographic Method for the Analysis of Carisoprodol and Related Substances in Carisoprodol Active Pharmaceutical Ingredient" (b) (4)
- (b) (4) High Performance Liquid Chromatographic Method for the Analysis of Carisoprodol and Related Substances in Carisoprodol and Related Substances in 250 mg Carisoprodol Tablets" (b) (4)

Noting your concern with the accuracy or precision of the HPLC test (Method (b) (4)) based on the results of the stability data submitted in the 3/2/07 Amendment, DPA cannot speculate on why the applicant's results appear to fluctuate. However, to evaluate the precision of the procedure, DPA analyzed the sample on two different days and obtained similar results on the (b) (4) impurity (b) (4) present. On the second day the initial solutions were reanalyzed and new samples were prepared. Although this was a very quick intermediate precision test, it leads us to conclude that the method is precise.

Drug Product

"[redacted] Performance Liquid Chromatographic Method for the Analysis of Carisoprodol and Related Substances in Carisoprodol and Related Substances in 250 mg Carisoprodol Tablets" [redacted]

Soma 250 mg tablets, lot 27-02-03s, were assayed for active ingredient, carisoprodol, and for impurities.

The product meets the applicant's specification of [redacted] of label claim. The sample was analyzed on two separate days and found to contain [redacted] of label claim. Of the known impurities [redacted] was detected. [redacted] was not detected in the first determination however a peak within the retention window for [redacted] was detected in the second determination corresponding to [redacted]. This amount is less than the reporting limit of [redacted]% and therefore would be reported only as "detected".

ASSAY DRUG PRODUCT		
(% label claim)		
	5/25/2007	5/29/2007
A1	[redacted]	
A2		
B1		
B2		

Actual % impurities found.

IMPURITIES DRUG PRODUCT
(%)

(b) (4)

Impurities reported per method instruction

(b) (4) (b) (4)

*Values (b) (4) % are reported as less than the level of quantitation

Drug Substance

"[redacted] High Performance Liquid Chromatographic Method for the Analysis of Carisoprodol and Related Substances in Carisoprodol Active Pharmaceutical Ingredient" [redacted]

Carisoprodol, lot 2E2406, was assayed for active ingredient, carisoprodol, and for impurities.

The product meets the applicant's specification of [redacted]. Sample was not dried prior to analysis. The sample was analyzed on two separate days and found to contain [redacted] carisoprodol. Of the known impurities [redacted] in the first analysis and at [redacted] in the second analysis. These amounts are close to the reporting limit of [redacted] Amounts less than [redacted] would be reported as "detected" per the method instructions.

	ASSAY API (%w/w)	
	5/24/2007	5/31/2007
A1	[redacted]	
A2		
A3		
A4		

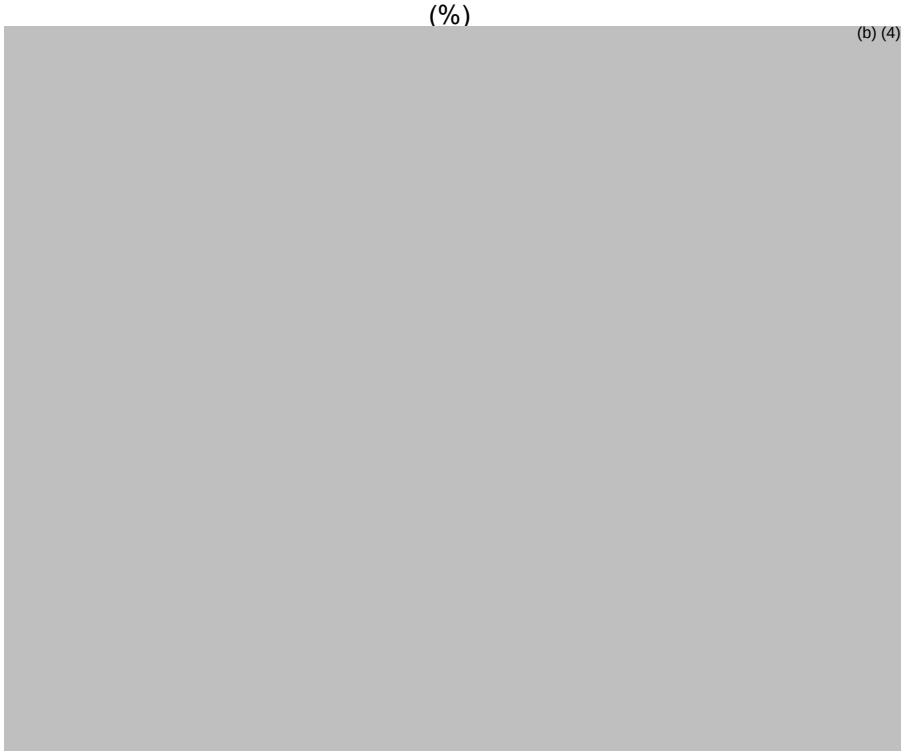
Actual % impurities found.

IMPURITIES, API
(%)

Impurities reported per method instructions.

IMPURITIES, API

(%)



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/s/

James F Allgire
6/12/2007 01:46:31 PM

Benjamin Westenberger
6/12/2007 03:05:47 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REQUEST

TO: **FDA**
Division of Pharmaceutical Analysis, HFD-920
Attn: Nick Westenberger
Room 1002
1114 Market Street
St. Louis, MO 63101

FROM: Donald Klein, Reviewing Chemist
E-mail Address: donald.klein@fda.hhs.gov
Phone: (301)-796-1689
Fax.: (301)-796-9749

Through: James Vidra, Branch Chief, Branch VII
Phone: (301)-796-1767
and
Michael Folkendt, ONDC Methods Validation Coordinator, ONDQA
Phone: 301-796-1670

SUBJECT: Methods Validation Request

Application Number: NDA 11-792/SE2-041

Name of Product: 250 mg and 350 mg

Applicant: MedPointe Pharmaceuticals, MedPointe Healthcare Inc.

Applicant's Contact Person: Michael I Bernhard, Ph.D.

Address: 265 Davidson Avenue
Suite 300
Somerset, NJ 08873-4120

Telephone: 732-564-2353 Fax: 732-564-2361

Date NDA Received by CDER: **11/13/2006**

Chemical/Therapeutic Type: Painful musculoskeletal conditions

Date of Amendment(s) containing the MVP: **11/13/07 and 3/5/07**

Special Handling Required: No

DATE of Request: **May 4, 2007**

DEA Class: N/A

Requested Completion Date: **8/1/2007**

Format of Methods Validation Package

PDUFA User Fee Goal Date: **9/13/2007**

☒ Paper ☐ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request Form*. Upon receipt of the samples, perform the tests indicated in item 3 of the attached *Methods Validation Request Form* as descr bed in the MV package. We request your report to be submitted in DFS promptly upon completion, but not later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. If the requested completion date cannot be met, please promptly notify the reviewing chemist and the ONDC Methods Validation Coordinator.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying Methods Validation Report Summary). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DFS. Send the complete report, with the DFS signed *Methods Validation Report*

Summary, by overnight courier to the above reviewing chemist. All information relative to this application is to be held confidential as required by 21 CFR 314.430.

ATTACHMENT(S): *Methods Validation Request Form*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	METHODS VALIDATION REQUEST	NDA # 11-792, SE2-041

← SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
Carisoprodol (drug substance)	(b) (4) mg	USP Reference Standard
250 mg Tablets	20 tablets	Lot 27-02-03s
(b) (4)	(b) (4) mg	(b) (4)
	(b) (4) mg	(b) (4)
	(b) (4) mg	USP Reference Standard

↑ Contents of Attached Methods Validation Package:	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	Vol. 3, p. 10
Specifications/Methods for New Drug Substance(s)	Vol. 2, pp. 41 - 52
Specifications/Methods for Finished Dosage Form(s)	Vol. 3, pp. 31 - 43
Supporting Data for Accuracy, Specificity, etc.	Validation Volume; (b) (4)
Applicant's Test Results on NDS and Dosage Forms	3/2/07 Amendment
Other: Copies of all the needed information will be provided with these MV Forms. Updated stability data in the 3/2/07 Amendment	n/a 3/2/07 Amendment

→ **REQUESTED DETERMINATIONS** (Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.)

Method ID	Method Title	Volume/Page	MV Request Category (see attached page)	Comments
(b) (4)	(b) (4) HPLC for the Analysis of Carisoprodol and Related Substances in the Drug Substance	Validation Volume, pp. 274 - 353	**6**	This is a new test method for the drug substance
(b) (4)	(b) (4) HPLC for the Analysis of Carisoprodol and Related Substances in the 250 mg Tablets	Validation Volume, pp. 174 - 289	**6**	This is a new test method for the drug product

Additional Comments: **See attached page; In brief, the drug product stability data (3/2/07 Amendment) shows the test method not to be precise. For example, the stability data for Lot 27-02-03S at 25C/60%RH shows the following:**

(b) (4) (known) at (b) (4) Months is (b) (4) % but at (b) (4) months it is Not Detected.

(b) (4) (known) at (b) (4) Months is (b) (4) % and (b) (4) % but at (b) (4) months is (b) (4).

Each Lots showing this type of variation is listed on the pages attached to the copies provided with these forms.

Methods Validation Request Criteria

MVP Request Category	Description
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a "for cause" reason.

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/s/

Michael Folkendt

5/4/2007 02:22:52 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 11-792 Supplement # 41 Efficacy Supplement Type SE- 2

Proprietary Name: SOMA
Established Name: Carisoprodol Tablets, USP
Strengths: 250 mg

Applicant: MedPointe Pharmaceuticals
Agent for Applicant (if applicable):

Date of Application: November 10, 2006
Date of Receipt: November 13, 2006
Date clock started after UN:
Date of Filing Meeting: December 19, 2006
Filing Date: January 12, 2007
Action Goal Date (optional): User Fee Goal Date: September 13, 2007

Indication(s) requested: Relief of discomfort associated with acute, painful musculoskeletal conditions

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☒ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☒

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☒

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☐
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? Yes If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: IND (b) (4)

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) February 7, 2006 – included with current NDA submission NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) N/A NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☒ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: December 19, 2006

NDA #: 11-792

DRUG NAMES: SOMA

APPLICANT: MedPointe Pharmaceuticals

BACKGROUND: An NDA was approved for the 350 mg tablets for SOMA for the relief of discomfort associated with acute, painful musculoskeletal conditions. The Sponsor is submitting this application to seek approval for the 250 mg tables for the same indication.

ATTENDEES: Rigoberto Roca, Jeffrey Siegel, Sarah Okada, Eric Brodsky, Lawrence Leshin, Joan Buenconsejo, Lei Zhang, Donald Klein, Sharon Turner-Rinehardt

ASSIGNED REVIEWERS (including those not present at filing meeting):

Discipline/Organization	**Reviewer**
Medical:	Eric Brodsky
Secondary Medical:	Sarah Okada
Statistical:	Joan Buenconsejo
Pharmacology:	Lawrence Leshin
Statistical Pharmacology:	
Chemistry:	Donald Klein
Environmental Assessment (if needed):	
Biopharmaceutical:	Lei Zhang
Microbiology, sterility	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Sharon Turner-Rinehardt
Other Consults:	OSE, ORP, DMETS, DSI

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO ☐

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☐ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Sharon Turner-Rinehardt
Regulatory Project Manager
Version 6/14/2006

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

*If "**No**," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)
YES ☐ NO ☐

*If "**Yes**," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?
YES ☐ NO ☐

*If "**Yes** "contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?
   YES ☐ NO ☐

   (***Pharmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

*If "**No**," to (a) skip to question 6. Otherwise, answer part (b and (c)).*

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "**No**," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No**," to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes**," to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No**," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES ☐ NO ☐

*If "**No**," skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES ☐ NO ☐

*If "**Yes**," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*
Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Turner-Rinehardt
1/19/2007 06:20:26 PM
CSO

Parinda Jani
1/20/2007 08:10:14 PM
CSO

DSI CONSULT: Request for Clinical Inspections

Date: January 18, 2006

To: Constance Lewin, M.D., M.P.H., Branch Chief, GCP1, HFD-46
Leslie Ball, M.D., Branch Chief, GCP2, HFD-47

From: Sharon Turner-Rinehardt, Regulatory Project Manager, HFD-170
Division of Division of Anesthesia, Analgesia, and Rhuematology Products

Subject: **Request for Clinical Site Inspections**
NDA 11-792/s041
MedPointe Pharmaceuticals, MedPointe Healthcare, Inc.
SOMA 250 mg Tablets

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. Please inspect **one** of the sites listed in the following table.

This NDA provides data for the following: A new lower dose at 250 mg and a new dosing regimen of 250 mg three times a day and at bedtime.

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site #241 **Principal Investigator:** Stephen C. Cohen, MD **Address:** Sun Research Institute 730 North Main Avenue, Suite 424 San Antonio, TX 78205	MP502	27	Relief of discomfort associated with acute, painful musculoskeletal conditions

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site #263 **Principal Investigator:** Ateeqahmed S. Patel, MD **Address:** 1745 Old Spring House Lane, Suite 420, Atlanta, GA 30338	MP502	34	Relief of discomfort associated with acute, painful musculoskeletal conditions
Site #283 **Principal Investigator:** Simon Babazadeh, MD **Address:** Crest Clinical Trials, Inc. 3340 West Ball Road, Suite I Anaheim, CA 92804	MP502	31	Relief of discomfort associated with acute, painful musculoskeletal conditions
Site #566 **Principal Investigator:** Vladimir Samonte, MD **Address:** Quality of Life Medical Center, LLC 21520 South Pioneer Blvd., Suite 203, Hawaiian Gardens, CA 90716,	MP505	40	Relief of discomfort associated with acute, painful musculoskeletal conditions

Domestic Inspections:

We have requested inspections because (please check all that apply):

__X__ Enrollment of large numbers of study subjects

__X__ High treatment responders (specify:)

____ Significant primary efficacy results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.

____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) July 31, 2007. We intend to issue an action letter on this application by (division action goal date) September 11, 2007. The PDUFA due date for this application is September 13, 2007.

Should you require any additional information, please contact Sharon Turner-Rinehardt.

Concurrence: (if necessary)

Sarah Okada, MD; Acting Clinical Team Leader, Medical Team Leader
Eric Brodsky, MD; Medical Reviewer, Medical Reviewer

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Turner-Rinehardt

1/19/2007 06:03:04 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

11–792/S041

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 11-792 SUPPL # 041 HFD # 170

Trade Name SOMA

Generic Name Carisoprodol

Applicant Name Medpointe Pharmaceuticals

Approval Date, If Known September 13, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

This supplement is to propose a 250 mg tablet which is a lower dose than the currently approved 350 mg tablet.

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 11-792 and others (see attached list) Carisoprodol

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

The clinical studies that are essential for approval are MP502 and MP505.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

MP502 and MP505

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # 71,218 YES ☒ ! NO ☐
! Explain:

Investigation #2

IND # 71,218 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Sharon Turner-Rinehardt
Title: Regulatory Project Manager
Date: August 30, 2007

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Active Ingredient Search Results from "OB_Rx" table for query on "carisoprodol."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
040252	AB	No	ASPIRIN; CARISOPRODOL	TABLET; ORAL	325MG;200MG	CARISOPRODOL AND ASPIRIN	ACTAVIS TOTOWA
012365	AB	Yes	ASPIRIN; CARISOPRODOL	TABLET; ORAL	325MG;200MG	SOMA COMPOUND	MEDPOINTE PHARM HLC
089594	AB	No	ASPIRIN; CARISOPRODOL	TABLET; ORAL	325MG;200MG	CARISOPRODOL AND ASPIRIN	PAR PHARM
040116	AB	No	ASPIRIN; CARISOPRODOL	TABLET; ORAL	325MG;200MG	CARISOPRODOL AND ASPIRIN	SANDOZ
040283	AB	No	ASPIRIN; CARISOPRODOL; CODEINE PHOSPHATE	TABLET; ORAL	325MG;200MG;16MG	CARISOPRODOL, ASPIRIN AND CODEINE PHOSPHATE	ACTAVIS TOTOWA
012366	AB	Yes	ASPIRIN; CARISOPRODOL; CODEINE PHOSPHATE	TABLET; ORAL	325MG;200MG;16MG	SOMA COMPOUND W/ CODEINE	MEDPOINTE PHARM HLC
040118	AB	No	ASPIRIN; CARISOPRODOL; CODEINE PHOSPHATE	TABLET; ORAL	325MG;200MG;16MG	CARISOPRODOL, ASPIRIN AND CODEINE PHOSPHATE	SANDOZ
040188	AA	No	CARISOPRODOL	TABLET; ORAL	350MG	CARISOPRODOL	ACTAVIS TOTOWA
040397	AA	No	CARISOPRODOL	TABLET; ORAL	350MG	CARISOPRODOL	COREPHARMA
011792	AA	Yes	CARISOPRODOL	TABLET; ORAL	350MG	SOMA	MEDPOINTE PHARM HLC
089346	AA	No	CARISOPRODOL	TABLET; ORAL	350MG	CARISOPRODOL	MUTUAL PHARM
040576	AA	No	CARISOPRODOL	TABLET; ORAL	350MG	CARISOPRODOL	NEIL
081025	AA	No	CARISOPRODOL	TABLET; ORAL	350MG	CARISOPRODOL	SANDOZ
040755	AA	No	CARISOPRODOL	TABLET;	350MG	CARISOPRODOL	SUN PHARM

				ORAL		INDS LTD
040245	**AA**	No	CARISOPRODOL	TABLET; 350MG ORAL	CARISOPRODOL	VINTAGE PHARMS
087499	**AA**	No	CARISOPRODOL	TABLET; 350MG ORAL	CARISOPRODOL	WATSON LABS
040152	**AA**	No	CARISOPRODOL	TABLET; 350MG ORAL	CARISOPRODOL	WATSON LABS
086179	**AA**	No	CARISOPRODOL	TABLET; 350MG ORAL	CARISOPRODOL	WATSON LABS
040124	**AA**	No	CARISOPRODOL	TABLET; 350MG ORAL	CARISOPRODOL	WEST WARD

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through July, 2007
Patent and Generic Drug Product Data Last Updated: August 30, 2007

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rigoberto Roca

9/13/2007 05:57:29 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 11-792 Supplement Type (e.g. SE5): SE2 Supplement Number: 041

Stamp Date: November 13, 2006 PDUFA Goal Date: September 13, 2007

HFD 170 Trade and generic names/dosage form: SOMA (carisoprodol)/ 250 mg Tablets

Applicant: MedPointe Pharmaceuticals Therapeutic Class: Analgesic

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

X Yes. Please proceed to the next question.

❑ No. PREA does not apply. Skip to signature block.

**** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.***

Indication(s) *previously approved* (please complete this section for supplements only): Relief of discomfort associated with acute, painful musculoskeletal conditions using 350 mg Soma tablets.

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 1

Indication #1: Relief of discomfort associated with acute, painful musculoskeletal conditions

Is this an orphan indication?

❑ Yes. PREA does not apply. Skip to signature block.

X No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

❑ Yes: Please proceed to Section A.

X No: Please check all that apply: X Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- **❑ Products in this class for this indication have been studied/labeled for pediatric population**
- **❑ Disease/condition does not exist in children**
- **❑ Too few children with disease to study**
- **❑ There are safety concerns**
- **❑ Other:**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr.__0__ Tanner Stage_____
Max_____ kg_____ mo._____ yr.__12__ Tanner Stage_____
Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

X Other: Fails to provide meaningful therapeutic benefit over existing therapies for this pediatric population and are unlikely to be used in a substantial number of pediatric patients.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Sharon Turner-Rinehardt
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- ❑ **Yes. PREA does not apply. Skip to signature block.**
- ❑ **No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**
- ❑ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Sharon Turner-Rinehardt

5/30/2007 03:58:03 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Maternal Health Team/Richardae Araojo

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Sharon Turner-Rinehardt, RPM/Steve Leshin, Pharm/Tox Reviewer

Division of Anesthesia, Analgesia and Rheumatology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
08-06-07		11-792	Label	November 13, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
SOMA	P		08-31-07

NAME OF FIRM: MedPointe Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The current label for Soma has inadequate information in the pregnancy section of the labeling. There was no reference to a pregnancy category. We would propose Pregnancy Category C (see attached for brief summary of labeling). Are there other human data that provide information on the issue of the pregnancy category? Does a category C seem reasonable based on the available information? I will forward the WORD version of the working copy of the label separately. If you have any questions, contact Sharon Turner-Rinehardt at (301) 796-2254.

SIGNATURE OF REQUESTOR
Sharon Turner-Rinehardt

METHOD OF DELIVERY (Check one)
☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

PLR format Label provided by Sponsor contained the following:

(b) (4)

Proposed Division's revised PLR format Label:

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Turner-Rinehardt

8/6/2007 11:58:45 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS

FROM: Sharon Turner-Rinehardt, RPM (Eric Brodsky, MO)
Division of Anesthesia, Analgesia and Rheumatology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
7-16-07		11-792	Efficacy Supplement (SE2)	11-10-06

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE
SOMA	S	Analgesic	Tentative

NAME OF FIRM: MedPointe Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- X PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- X REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- X SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Do you agree with [redacted (b) (4)] seizure PRECAUTION in the Soma label (while [redacted (b) (4)] seizures in the pos[redacted] SE REACTIONS and the OVERDOSAGE sectio[redacted]

[redacted (b) (4)]

1) Contradictory cases (some seizures are associated with carisoprodol exposure and some seizures are associated with carisoprodol withdrawal);
2) No cases of seizure in all Soma controlled trials (submitted in this efficacy supplement or in the literature);
3) Many cases have multiple confounders (patients were exposed to known products that reduce the seizure threshold including tricyclic antidepressants, antipsychotic, wellbutrin);
4) The other five muscle relaxants (Flexeril, Robaxin, Parafon Forte, Norflex, and Skelaxin) approved for the same indication do not have seizure WARNINGS or PRECAUTIONS and are not known to have evidence of a causal association with seizures.

Seizure risk should be in the OVERDOSAGE section because many post-marketing cases seen in overdose of carisoprodol with other drugs (prescription and illegal) known to cause seizures.

Enclosed are the cases of seizure from:

1) The sponsor (submitted in 2005); and
2) Joann Lee's narratives of AERS reports in adult patients she obtained in March of 2007.

If you have any questions, please contact Sharon Turner-Rinehardt at (301) 796-2254.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Sharon Turner-Rinehardt	X MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

Seizures associated with carisoprodol exposure or withdrawal

	Number (Date of report)	History	Comments
1)	83-32 (6/83)	57 year old male with a history of seizure disorder (1 one year prior to admission) drug and alcohol abuse (taking soma 4 pills 4-5 times per day, lopressor, dyazide) was hospitalized with tonic-clonic seizures. Stopped soma four days prior to admission. CT scan of brain was abnormal. Drug screen was negative.	Possible seizure due to soma withdrawal but overdosing on Soma (hx of seizures, and possible electrolyte abnormality, drug and alcohol abuse)
2)	88-05 (2/88)	45 year old male (taking tolectin, malathion) had an ER visit for tonic clonic seizures one to two hours after taking 2 soma pills. ER physician and neurologist stated that the seizures were "purely psychogenic". Neurologic work-up was negative including EEG	No seizure
3)	88-04 (1/88)	30 year old with prior history of head trauma (s/p MVA 8 years prior to event) on soma for several months had catatonic seizures. EEG was negative	**Possible clean case of seizure due to soma exposure**
4)	90050001 (4/90)	40 year old female (remote history of cocaine use) taking 6 soma pills daily and acetaminophen/codeine (300/60 mg) had seizures. EEG and CT brain were negative.	Possible seizure due to soma exposure but overdose
5)	90100012 (11/90)	33 year old male (taking clomipramine HCl, thioridazine, lovastatin, soma for several years states 30 pills per day), 1.5 days after he stopped taking Soma had had a generalized seizure and was hospitalized.	Possible seizure due to soma withdrawal but overdosing on Soma, on tricyclic antidepressant and mellaril known to cause seizures
6)	91110009 (10/91)	37 year old female (taking codeine, alprazolam, soma) with back pain had an ER visit for a seizure (one week after soma discontinuation)	Possible seizure due to soma withdrawal but may have discontinued alprazolam or may be due to cocaine
7)	920230006 (2/92)	24 year old male with history of back pain from a MVA overdosed on soma had a seizure. Drug screen was positive for benzodiazepenes (but benzos were given in the ambulance) but no other drugs or alcohol. In ICU had a grand mal seizure. Given dilantin and phenobarbital. Went to psychiatric ward after ICU.	Possible seizure due to soma overdose
8)	93080016 (8/93)	45 year old male pharmacist with a remote history of seizures (last one 27 years ago) reported that he had a seizure (using ½ pill of soma BID, flurbiprofen, hydrocodone/acetaminophen). Using soma for back pain after MVA.	**Possible clean case of seizure due to soma exposure (hx of seizures)**
9)	95020009 (2/95)	42 year old male with a history of seizures, HTN was found unconscious at home and was suspected of a soma overdose. He had a seizure about 1-2 hours after overdose. Treated with diazepam. Soma/meprobamate level was 62 micrograms/mL.	Possible seizure due to soma overdose (hx of seizures)
10)	1999070023 (7/99)	36 year old male (drinks alcohol and taking flurbiprofen) taking one pill of soma per day for one month had a seizure (about 48 hours after stopping soma). Hospitalized and had continued to have seizures.	**Possible seizure due to soma withdrawal, but maybe due to alcohol withdrawal**
11)	2000090019	30 year old male was on soma for low back pain and two to three	Seizure probably not

	(10/00)	weeks later he had a seizure. Treated with tegretol. Then had at least one more seizure off soma (about 2 months after initial seizure)	due to soma
12)	2001090021 (0/01)	45 year old female (taking 3 pills of soma daily for about 2 years for back pain, and taking kadian, prozac, zonegran, iron). She stopped soma for 2 days and had seizure movements and nausea. No mention of hospitalization or ER visit.	May not of had a seizure
13)	2002020015 (2/02)	17 year old male with a history of ADHD, depression intentionally overdosed to get high on soma, 10 pills of wellbutrin, and gabapentin and had a seizure (also taking venlafaxine)	Seizure probably due to wellbutrin and overdose
14)	2004030020 (3/04)	30 year old (taking soma for 8 years QID) had a seizure like activity and was hospitalized (prior to event erroneously taking 12 pills per day). Discharged on soma QID.	Seizure possibly due to soma overdose
15)	3928506 (Case#5) (5/02)	25 year old male (s/p MVA) on hydrocodone/acetaminophen/soma for about one month prior to event for headache and muscle strain. He had another MVA due to a seizure	**Possible clean seizure case due to Soma exposure**
16)	200600747 (Case #23) (3/06)	51 year old male herniated discs had several seizures after reducing his soma dose (one the next day, one 1.5 days later, one a few days, one observed seizure in ER)	**Possible clean seizure due to Soma withdrawal**

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/s/

Sharon Turner-Rinehardt

7/16/2007 05:20:41 PM

From:	Turner-Rinehardt, Sharon
To:	"Bernhard Michael";
CC:	
Subject:	N11-792, S041 Soma: CMC Information Requests
Date:	Wednesday, July 11, 2007 5:03:11 PM
Attachments:	

Dear Michael,

We have validated the test methods and have found them acceptable. However, based on the drug product Batch Analyses and the updated stability data submitted in the amendment dated March 2, 2007, we have the following CMC requests.

Refer to the drug product COAs on pages 84 - 89 (Volume 1.3), the proposed drug product Specifications (Release and Stability) on pages 104 - 105 (Volume 1.3), and the updated drug product stability data in Attachment B in the amendment dated March 2, 2007:

a. Individual Specified Unknown Impurities/Degradants and Individual Unknown Impurities/Degradants are both proposed in the drug product Specifications (Release and Stability), but you are inconsistent in monitoring and/or reporting the respective values. Specifically, in the COAs and in the stability data only the Single Unknown Degradation Products/Single Unknown Impurity is listed. Revise your proposed drug product Specifications accordingly to be consistent with the respective data you reported.

b. Each of the following proposed drug product Specification (Release and Stability) Acceptance Criteria can be lowered/tightened:

(b) (4)

(b) (4)

We ask that you provide the requested information by 3 pm (EST) Friday, July 13, 2007. If you have any questions, please contact me.

Regards,
Sharon

Sharon Turner-Rinehardt
Regulatory Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22 Room 3191
Silver Spring, MD 20993-0002
Phone: (301) 796-2254
Fax: (301) 796-9722/9723
Email: sharon.turner-rinehardt@fda.hhs.gov

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/s/

Sharon Turner-Rinehardt

7/11/2007 06:04:17 PM

CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 11-792/s-041

DISCIPLINE REVIEW LETTER

MedPointe Pharmaceutical
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Attention: Michael Bernhard, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Bernhard:

Please refer to your supplemental new drug application (sNDA) dated November 10, 2006 received November 13, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SOMA (carisoprodol), 250 mg.

The Division of Medication Errors and Technical Support (DMETS), of the Office of Surveillance and Epidemiology, has completed its review of your proposed labeling and has identified the following deficiencies:

1. CONTAINER LABELS (250 mg)

   a. In accordance with 21 CFR 201.10(g)(2), ensure that the established name on the carton labels and container labeling is at least one-half the size of the proprietary name.

   b. Distinguish the Soma 250 mg labels (100 count) from that of the Soma 350 mg labels (100 (b) (4) count); for example, by using different boxing, contrasting color, or some other means. Distinct labeling is critical in order to minimize confusion between the two strengths.

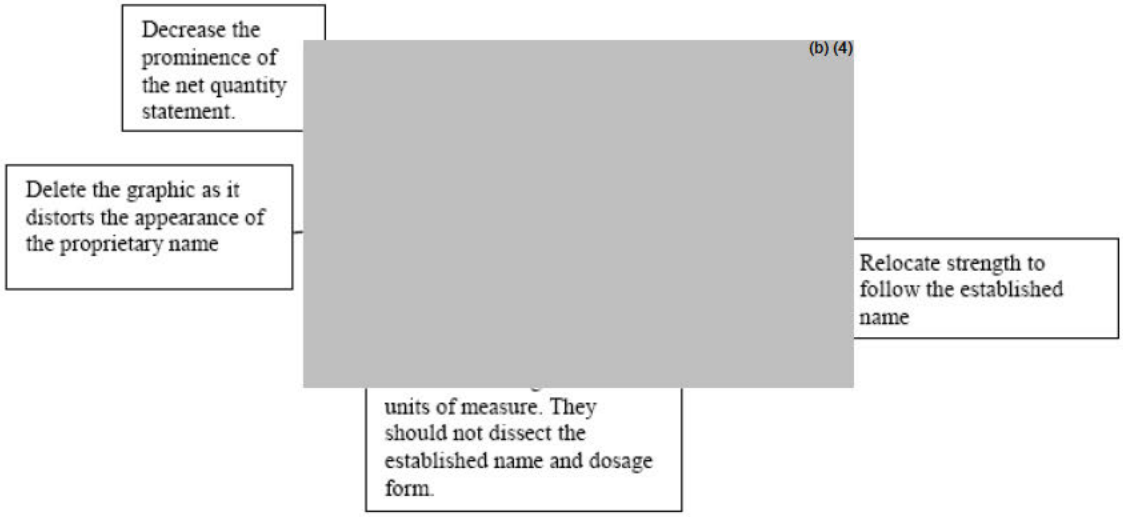
   c. Ensure that the appropriate USP designation appears in the established name (e.g., carisoprodol tablets, USP) as it appears that the product is the subject of a USP monograph.

   d. Decrease the prominence of the net quantity statement as this may be a visual distraction away from the strength.

   e. Delete the graphic preceding the proprietary name, Soma, as it distorts the appearance of the proprietary name.

f. Revise the proprietary name, the established name, and the strength to read as follows:

Soma
Carisoprodol Tablets, USP
250 mg



2. CARTON LABELING (4-Count Trade and 4- Count Professional Sample)

a. See Comments 1a and 1b.

b. Revise the statement (b) (4) to read as "Physician Sample- Not for Sale."

3. CARTON LABELING (b) (4)

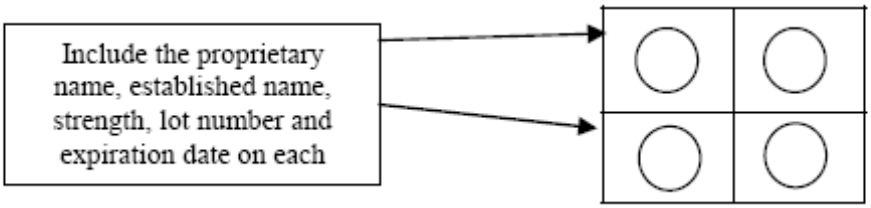
a. See Comments 1a, 1b, and 2b.

b. (b) (4)

c. Design each blister such that removal of a tablet will not result in inadvertent exposure of remaining tablets. As patients pull back the foil in opening this configuration, more than one tablet may be accidentally exposed.

d. Label each blister with the proprietary name, established name, strength, lot number, and expiration date to ensure that once the tablets are punched out of the professional

sample pack this important information printed on the reverse side is maintained. For example:



e. Step 2 of the *Opening Instructions* (located on the back panel) (b) (4) replace with "cut with scissors."

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Sharon Turner-Rinehardt, Regulatory Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
6/26/2007 03:17:47 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

METHODS VALIDATION MATERIALS RECEIVED

NDA 11-792/S-041

Michael I Bernhard, Ph.D.
MedPointe Pharmaceuticals, MedPointe Healthcare Inc.
265 Davidson Avenue
Suite 300
Somerset, NJ 08873-4120

Dear Dr. Bernhard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SOMA (Carisoprolol) Tablets, 250 mg and to our May 14, 2007 letter requesting sample materials for methods validation testing.

We acknowledge receipt on May 22, 2007 of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have any questions, you may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (james.allgire@ fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

James F Allgire

5/22/2007 12:22:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

REQUEST FOR METHODS VALIDATION MATERIALS

NDA 11-792/SE2-041

Michael I Bernhard, Ph.D.
MedPointe Pharmaceuticals, MedPointe Healthcare Inc.
265 Davidson Avenue
Suite 300
Somerset, NJ 08873-4120

Dear Dr. Bernhard:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SOMA (Carisoprolol) Tablets, 250 mg and 350 mg.

We will be performing methods validation studies on Carisoprodol API and SOMA (Carisoprolol) Tablets, 250mg, as described in NDA 11-792, SE2-041.

In order to perform the necessary testing, we request the following sample materials and equipments:

Drug Substance
- Carisoprolol – 5 gms

Drug Product
- SOMA tablets – 60 tablets

Reference Standards
- Carisoprodol – 600 mg
- (b) (4) – 50 mg
- (b) (4) – 50 mg
- (b) (4) – 75 mg

HPLC Column
- (b) (4)

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: James Allgire
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. Contact me for a copy of the DEA documents or if you have questions. You may contact me by telephone (314-539-3813), FAX (314-539-2113), or email (james.allgire@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

James Allgire
Team Leader
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

James F Allgire

5/14/2007 10:05:13 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 11-792

INFORMATION REQUEST LETTER

MedPointe Pharmaceutical
Attention: Michael Berhard, Ph.D.
Senior Director, Regulatory Affairs
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Dear Dr. Bernhard:

Please refer to your November 10, 2006 supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SOMA® (carisoprodol) Tablets, 250 mg.

We are reviewing the Chemistry, manufacturing and controls section of your submission and have the following comment and information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. [redacted (b) (4)] DMF [redacted (b) (4)] has been sent a letter dated May 7, 2007 stating that DMF [redacted (b) (4)].

If you have any questions, call Sharon Turner-Rinehardt, Regulatory Project Manager, at (301) 796-2254.

Sincerely,

James D. Vidra, Ph.D.
Branch Chief
Branch 7, Division of Post-Marketing Evaluation
ONDQA, CDER

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/s/

Jim Vidra

5/7/2007 10:07:04 AM

From:	Turner-Rinehardt, Sharon
To:	"Bernhard Michael";
CC:	
Subject:	CMC Information Request for N11-792, SE2-041
Date:	Thursday, May 03, 2007 1:42:15 PM
Attachments:	

Hello Michael,

I have another CMC request. Please provide the information below as soon as possible.

Refer to page 91 in Section 4.4.6 in Volume 3 and Attachments 1 and 2 in the amendment dated March 2, 2007. Provide a brief comparison of the proposed packaging for the 250 mg tablet vs. the current packaging of the 350 mg tablet. If the container closure system (bottle, closure, etc) is identical, then please state as such. In the case where different DMFs are referenced for the 350 mg tablet, provide the DMF number. The letter of authorization is not needed for the current 350 mg tablet packaging.

If you have any questions, please let me know.

Regards,
Sharon Turner-Rinehardt, RPM

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/s/

Sharon Turner-Rinehardt

7/11/2007 06:12:26 PM

CSO

From:	Turner-Rinehardt, Sharon
To:	"Bernhard Michael";
CC:	
Subject:	Information Request for NDA 11,792 s041: Stability Data
Date:	Wednesday, May 02, 2007 4:53:43 PM
Attachments:	Stab_Format.doc

Dear Michael,

Please provide the 12 months of stability data for the 250 mg tablet in SAS format. I have attached a Word document with the preferred format. Please provide this information as soon as possible and if you have any questions, let me know.

Regards,
Sharon

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/s/

Sharon Turner-Rinehardt
5/3/2007 01:47:26 PM
CSO

From:	Turner-Rinehardt, Sharon
To:	"Bernhard Michael";
CC:	
Subject:	Information Request for NDA 11,792 s041
Date:	Wednesday, April 18, 2007 4:17:52 PM
Attachments:	

Dear Michael,

Please provide the following information to facilitate the review of your submission for NDA 11-792 Soma:

1. Refer to page 123 in Volume 4 of the original submission. Provide a copy of the COA for the [redacted] (b) (4) impurity.

2. Refer to the amendment dated March 2, 2007 and the test method section pertaining to the drug product impurities/degradants of the same amendment. The drug product test method (pp. 136 - 148, Volume 3; and validation data: [redacted] (b) (4) in the Validation Volume) will be recommended for validation because of the variation of the impurity levels reported in the drug product stability data. Please provide the following information that is needed for the test method validation forms:

a. The amount of each impurity needed.

b. The amount of drug product needed.

c. The Lot #s of each impurity that will be provided.

d. The Lot # of the drug product to be provided.

e. Special Handling needed for the impurity or drug product.

3. Refer to the amendment dated March 2, 2007, pages 3, 8 - 11 and the cover letter. Are you proposing [redacted] (b) (4) Expiration Dating Period for the 250 mg tablet or a 36 Month Expiration Dating Period?

4. Provide the timeframe for when the 18 month long term stability data will be available.

If you have any questions, please let me know.

Regards,

Sharon Turner-Rinehardt
Regulatory Project Manager
Phone: (301) 796-2254
Fax: (301) 796-9722/9723
Email: sharon.turner-rinehardt@fda.hhs.gov

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/s/

Sharon Turner-Rinehardt

4/20/2007 01:18:34 PM

CSO

From:	Turner-Rinehardt, Sharon
To:	"Bernhard Michael";
CC:	
Subject:	Information Request #2 NDA 11,792
Date:	Tuesday, March 27, 2007 2:14:07 PM
Attachments:	

Dear Michael,

I have another information request regarding NDA 11,792. Please respond to the following request as soon as possible.

1. Please refer to all the drug substance COAs and/or batch analysis as well as DMF (b) (4) Also, refer to the proposed particle size specification and supportive discussion (Volume 2) for the (b) (4) drug substance. Based on the drug substance batch analyses and/or COAs (registration batches and clinical batches), you accepted drug substance lots that were not (b) (4) i.e., meeting the DMF (b) (4) particle size specification (which is discussed later in the DMF). Based on our evaluation of DMF (b) (4) and the proposed particle size specifications in this supplement along with the CMC meeting minutes dated February 7, 2005 in your submission (Volume 2), the drug substance manufacturing is not clear. We cannot discuss the specifics of DMF (b) (4) therefore, you may need to contact the DMF (b) (4) holder in order to answer this question.

2. Provide a description of the packaging (p. 45 in Section 4.3.3.2, Vol. 2) used for the protection of the (b) (4) drug substance for storage while waiting to be used for manufacturing of the drug product.

Regards,
Sharon Turner-Rinehardt
Regulatory Project Manager

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/s/

Sharon Turner-Rinehardt
3/27/2007 02:49:51 PM
CSO

From:	Turner-Rinehardt, Sharon
To:	"Bernhard Michael";
CC:	
Subject:	Information Request for NDA 11,792 s041
Date:	Monday, March 26, 2007 6:28:00 PM
Attachments:	

Dear Michael,

Provide the pharmacokinetic datasets for studies MP500 and MP501 in SAS format. Please provide this information with the other requested information. If you have any questions, please let me know.

Regards,
Sharon Turner-Rinehardt
Regulatory Project Manager

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/s/

Sharon Turner-Rinehardt

4/20/2007 01:14:58 PM

CSO

From: Turner-Rinehardt, Sharon
Sent: Monday, March 26, 2007 6:28 PM
To: 'Bernhard Michael'
Subject: Information Request for NDA 11,792 s041

Importance: High

Dear Michael,

Provide the pharmacokinetic datasets for studies MP500 and MP501 in SAS format. Please provide this information with the other requested information. If you have any questions, please let me know.

Regards,
Sharon Turner-Rinehardt
Regulatory Project Manager

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/s/

Sharon Turner-Rinehardt
3/26/2007 06:40:13 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 11-792

INFORMATION REQUEST LETTER

MedPointe Pharmaceutical
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Attention: Michael Bernhard, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Bernhard:

Please refer to your November 10, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Soma (Carisoprodol), 250 mg Tablets.

We also refer to your submission dated February 1, 2007.

We are reviewing the Clinical section of your submission and have the following information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. According to 21 CFR 314.50(f)(2), the efficacy supplement application "is required to contain copies of individual case report forms for each patient ... who did not complete the study because of an adverse event." Submit case report forms (CRFs) for the following patients in Study MP502: 245/0005, 253/0010, 211/0013, 283/0033, 253/0004, 257/0005, 259/0027, 264/0004, 283/0032, and 241/0008. In addition, submit CRFs for the following patients in Study MP505: 504/0002, 556/0008, 545/0007, 557/0004, 524/0003, and 540/0017.

2. Submit a MedDRA "coding dictionary" ─ a list of all investigator verbatim terms and the preferred terms to which they were mapped ─ that includes bidirectional coding (i.e., from verbatim term to preferred term and from preferred term to verbatim term).

3. You submitted adverse event (AE) and adverse event causing discontinuation (DAE) tables according to MedDRA preferred terms (PTs) and system organ class (SOC) terminology. Submit AE and DAE tables for all levels of the MedDRA hierarchy (including the lowest level term, high level term, and high level group term) for the pooled low back pain studies (i.e., Studies MP502 and MP505).

4. In your February 1, 2007 response to Question 1 of our January 6, 2006 information request, you stated that you request "a partial waiver for conducting pediatric studies in pediatric patients ages birth to less than 12 years of age." (b) (4) ccording to 21 CFR 201.57(c)(9)(iv)(D)(1), when "a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the `Pediatric Use' subsection of the labeling must" describe "the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population." Therefore, provide safety/efficacy studies, literature reports, pharmacokinetic data, or other data to support the use of carisoprodol in pediatric patients (b) (4)

5. In your February 1, 2007 response to Question 1 of our January 6, 2006 information request, you stated that since 1959, (b) (4)

6. The "Geriatric Use" subsection of the "USE IN SPECIFIC POPULATIONS" section of your proposed SOMA label states that the (b) (4) If available, provide "other clinical experience" of the safety and/or efficacy of the use of carisoprodol in geriatric patients, compared to younger patients [see 21 CFR 201.57(c)(9)(v)(B)(1)].

7. The mean (SD) baseline CPK value for the pooled placebo group in Studies MP502 and MP505 was 182.5 (604.9) units/liter; whereas, the mean (SD) baseline CPK values for the pooled 250 mg and 350 mg carisoprodol groups were 138.5 (154.7) and 136.3 (152.6) units/liter, respectively (see Volume 16, Table 8.2.4-1, Pages 210-211). Considering that Studies MP502 and MP505 were randomized, explain why the placebo group had a significantly greater mean baseline CPK value, compared to the mean baseline CPK values of the carisoprodol groups.

If you have any questions, call Sharon Turner-Rinehardt, Regulatory Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Parinda Jani
Chief, Project Management Staff
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Parinda Jani
3/13/2007 04:56:24 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Dr. Stella Machado, Director of Biometrics Division VI	FROM *(Name, Office/Division, and Phone Number of Requestor)*: Donald N. Klein, Ph.D., Branch VII (CMC Reviewer); Sharon Turner-Rinehart, PM (Division of Anesthesia , Analgesia and Rheumatology Products)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
4/16/2007	n/a	11-792, SE2-041	Efficacy supplement and 3/2/07 Amendment	3/2/07

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Soma Tablets	10 Month Review Clock	Painful musculoskeletal Conditions	7/1/07

NAME OF FIRM: MedPointe Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☒ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: The 3/2/07 amendment has the following: Data Analysis, Unit-Dose (b) (4) Pouch (Attachment C); Data Analysis, 100-Count HDPE Bottle Package (Attachment D); Unit-Dose (b) (4) Pouch and 100-Count HDPE Bottle Package (Attachment E); Report (b) (4) (Attchment F); and Report MISC 2005-039 (Attachment G). Please evaluate.

Please let Sharon Turner-Rinehardt(x62254) know who the assigned reviewer will be and she will provide them with the information.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Sharon Turner-Rinehardt	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Sharon Turner-Rinehardt
4/17/2007 11:11:00 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 11-792/s041

MedPointe Pharmaceutical
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Attention: Michael Bernhard, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Bernhard:

Please refer to your November 10, 2006, supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SOMA (carisoprodol), 250 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 12, 2007, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified potential review issues and request that you submit the following information. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

1. A request for a full waiver for conducting pediatric studies in pediatric patients ages birth to less than 12 years of age was submitted in this supplement. According to the Pediatric Research Equity Act (PREA) of 2003, you are required to address all pediatric subpopulations. Therefore, you should either propose and support a full waiver request that includes all pediatric patients from birth to 16 years of age or request a partial waiver in pediatric patients from birth to 12 years of age and provide safety and efficacy data for the use of the 250 and 350 mg SOMA dosage regimens in pediatric patients 12 to 16 years of age.

   Both the currently approved SOMA label and your proposed SOMA label do not include information on the safety and effectiveness of the 250 and 350 mg dosing regimes in pediatric patients 12 to 16 years of age. We recommend you submit this data for this efficacy supplement, if available.

2. Provide the English translations for the following 5 publications submitted in support of your sNDA submission.

Study	Volume/Page
Baïsset, A.; Roux, G.; Montastruc, P.; Dumas, J.C.; Traves, J.; Auriac, A. 1975. Therapie 30(2):247-257.	5/80
Baïsset, A.; Cotonat, J.; Montastruc, P. 1976. Therapie 31(5):667-679.	5/92
Hoffmeister, F. 1964. Arch Int Pharmacodyn Ther 148:382-396.	5/343
Kato, R. 1967. Pathol Biol 15(3):158-163.	6/37
Lanza, M.; Goude, F. 1967. C R Seances Soc Biol Fil 16l(3):640-642.	6/92

3. For study MP501, provide results of analysis based on gender and the 90% confidence interval results for the metabolite, meprobamate.

4. Provide the Certificate of Analysis (CoA), date and site of manufacture, the intended use, the drug substance used to manufacture the drug product and the drug substance CoA for each of the following drug product lots.

   a. Lot 27-02-02C
   b. Lot 27-01-02C
   c. Lot 2A1004A
   d. Lot 7K1056N
   e. Lot 8A1005N
   f. Lot 9B1007N
   g. Lot 0C1018N
   h. Lot 1C151NN
   i. Lot 7A1001A
   j. Lot 7B1014A
   k. Lot 8C1023A
   l. Lot 7J1051A
   m. Lot 7G135NA
   n. Lot 2454
   o. Lot 2565
   p. Lot 2566

5. Provide calculations to support the request for categorical exclusion for environmental assessment.

In addition, we have the following comments regarding the labeling submitted in the WORD format with your supplemental NDA and the discrepancies identified between the WORD format and the SPL format of the label which was submitted on January 9, 2007. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances, and FDA recommendations to provide for labeling quality and consistency.

General Label Comments:

1. HIGHLIGHTS OF PRESCRIBING INFORMATION must be limited to one-half page, in 8 point type, two-column format [see 21 CFR 201.57(d)(8)]. We also recommend the same for the FULL PRESCRIBING INFORMATION (FPI): CONTENTS. In addition, all labeling information, headings, and subheadings must be a minimum of 8 points [see 21 CFR 201.57 (d)(6)].

2. The format (i.e., indentation) regarding the paragraphs under the sections and subsections should be consistent throughout the entire label.

HIGHLIGHTS OF PRESCRIBING INFORMATION

3. Under RECENT MAJOR CHANGES, the reference number (b) (4) should be deleted because this section does not apply to the 5 sections that should be referenced under this section [see 21 CFR 201.57 (a)(5)]. Also, the date will be the month/year that the supplement is approved, not (b) (4) Please delete dates and leave as "mm/yy."

4. A (b) (4) cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting; therefore, delete (b) (4) [see 21 CFR 201.57 (a)(11)].

5. The revision date is the month/year that the supplement is approved, not (b) (4) (b) (4) Please delete. Also, the word "revised" must be spelled completely and the entire text should be right justified.

FULL PRESCRIBING INFORMATION (FPI): CONTENTS

6. Delete all periods after the numbers for the section headings in the Contents [see 21 CFR 201.56 (d)(1)].

7. The heading must be "INDICATIONS AND USAGE" not (b) (4) Please correct.

8. The heading must be "PATIENT COUNSELING INFORMATION" not (b) (4) Please correct.

9. The footnote *Section or subsections omitted from the full prescribing information should be right justified. Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.

10. A horizontal line must separate the Contents and FPI [see 21 CFR 201.57(d)(2)].

FULL PRESCRIBING INFORMATION (FPI):

11. Consistently indent all paragraphs, headings, subheadings throughout the FPI. For overall formatting, refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for examples of labeling in the new format.

12. Any new or modified text under DOSAGE AND ADMINISTRATION in the FULL PRESCRIBING INFORMATION (FPI) must be marked with a vertical line ("margin mark") on the left edge [see 21 CFR 201.57(d)(9) and Implementation Guidance]. Please add vertical line.

13. For the DOSAGE FORMS AND STRENGTHS, provide a description of the identifying characteristics of the dosage form [see 21 CFR 201.57(c)(4)(ii)].

14. The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by numerical identifier. For example, *see Drug Abuse and Dependence (9)* or *Use in Specific Populations (8.6, 8.7)*. The cross-reference should be italicized to achieve emphasis because the cross-reference is embedded in the text in the FPI. Do not use bold print or all capital letters. Fix all cross-references throughout the label [see "Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" at http://www.fda.gov/cder/guidance/6005dft.htm].

15. Regarding Postmarketing Experience, delete the (b) (4) It should read **Postmarketing Experience**, no (b) (4) Remove the (b) (4) from "Because these reactions re 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 experience." Also, use a colon instead of (b) (4) after Cardiovascular, Central Nervous System, Gastrointestinal and Hematologic to be consistent with format.

16. Delete the phrase (b) (4) under the Pharmacokinetics subsection as it appears out of place. Also, provide a consistent header for the first paragraph under Pharmacokinetics as in the Absorption, Metabolism, Elimination headers.

17. Remove the [redacted] (b) (4) and [redacted] (b) (4) at the end of the FPI. The revision date at the end of Highlights replaces the revision information.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission. If you have any questions, call Sharon Turner-Rinehardt, Regulatory Project Manager, at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Bob Rappaport, M.D.
Director
Division of Anesthesia, Analgesia and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Bob Rappaport

1/26/2007 10:54:32 AM

From: Turner-Rinehardt, Sharon
Sent: Friday, January 12, 2007 2:34 PM
To: Bernhard Michael
Subject: NDA 11-792: Request

Importance: High
Dear Michael,

Can you provide me with the following as soon as possible:

1. 3 pouch packages for the 250 and 350 mg Soma tablets
2. The labels (carton/container, etc) for the 350 mg Soma tablets

If you have any questions, please let me know.

Regards,
Sharon Turner-Rinehardt
Regulatory Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Turner-Rinehardt
1/22/2007 12:30:18 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: ODS**			FROM: Sharon Turner-Rinehardt, RPM (Eric Brodsky, MO) Division of Anesthesia, Analgesia and Rheumatology Products	
DATE 1-11-07	IND NO.	NDA NO. 11-792	TYPE OF DOCUMENT Efficacy Supplement (SE2)	DATE OF DOCUMENT 11-10-06
NAME OF DRUG: SOMA	PRIORITY CONSIDERATION: S		CLASSIFICATION OF DRUG: Analgesic	DESIRED COMPLETION DATE 4-11-07

NAME OF FIRM: MedPointe Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- X PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- X DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- X REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- X SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: MedPointe Pharmaceuticals submitted an efficacy supplement for a new lower dose (250 mg) SOMA (carisoprodol) tablet and a new SOMA dosing regimen (250 mg three times a day and at bedtime). SOMA was originally approved in 1959 and is currently marketed as 350 mg tablets. The currently approved SOMA label does not include information on the safety and effectiveness of SOMA in pediatric patients 12 to 16 years old, although it states that the "efficacy and safety of carisoprodol in patients under 12 years of age has not been determined." Another issue that we will be evaluating is the duration of the submitted clinical trials which was one week, but the sponsor is proposing labeling for (b) (4) of use, in accordance with the currently approved SOMA label. Therefore, we are requesting your assistance with the following information:

1. Please conduct a search of recent post-marketing serious adverse events of SOMA in the following three populations: adults, pediatric patients 12 to 16 years, and pediatric patients less than 12 years
2. Please provide actual use data for these three populations over the last several years
3. Please provide the mean or median numbers of days, adult patients are prescribed SOMA (e.g. using the IMS National Disease and Therapeutic Index).

If you have any questions, please contact Sharon Turner-Rinehardt at (301) 796-2254.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Sharon Turner-Rinehardt	X MAIL ☐ HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Sharon Turner-Rinehardt
1/11/2007 11:24:11 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Janice Weiner
Office of Regulatory Policy

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Sharon Turner-Rinehardt, RPM (Eric Brodsky, MO)
Division of Anesthesia, Analgesia and Rheumatology Products,HFD-170

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1-11-07		11-792/s41	Efficacy Supplement (SE2)	11-10-06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
SOMA	S	Analgesic	4-5-07

NAME OF FIRM: MedPointe Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☒ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: MedPointe Pharmaceuticals submitted an efficacy supplement for a new lower dose (250 mg) SOMA (carisoprodol) tablet and a new SOMA dosing regimen (250 mg three times a day and at bedtime). MedPointe requests an exclusivity period of three years under 21 CFR 314.108(b)(5) for conducting two new safety/efficacy studies of 250 mg SOMA tablets. Please advise us on the appropriateness of MedPointe's exclusivity request given SOMA's regulatory history (see below).

In a Pre-IND meeting in 2004 between MedPointe and the FDA (DAARP and ORP), MedPointe asked the FDA regarding the possibility of three years of exclusivity for the new SOMA dosing regimen. In this meeting, ORP stated that "Based on the current DESI findings, the possibility for granting exclusivity based on clinical trials of the 250 mg dose is uncertain".

Regulatory History: SOMA 250 mg capsules were originally approved on November 18, 1959 (the 350 mg SOMA tablet was approved on May 8, 1959). A FR Notice (35 FR 13854) published on September 1, 1970 stated that 250

mg SOMA capsules and the 350 mg tablets were "possibly effective". A FR Notice (40 FR 29399) published on August 15, 1974 reclassified 250 mg SOMA capsules as lacking substantial evidence of effectiveness and the 350 mg tablets as effective. In August 1974, Wallace Pharmaceuticals (the predecessor of MedPointe) withdrew the 250 mg SOMA capsules (the 350 mg SOMA tablets remained on the market).

The minutes from the P-IND meeting referenced above will be emailed to Janice Weiner. If you have any questions, please contact Sharon Turner-Rinehardt at (301) 796-2254.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Sharon Turner-Rinehardt	☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Sharon Turner-Rinehardt
1/11/2007 12:44:17 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 11-792/S-041 **PRIOR APPROVAL SUPPLEMENT**

MedPointe Pharmaceutical
265 Davidson Avenue, Suite 300
Somerset, NJ 08873-4120

Attention: Michael Bernhard, Ph.D.
Senior Director, Regulatory Affairs

Dear Dr. Bernhard:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	SOMA®
NDA Number:	11-792
Supplement number:	041
Review Priority Classification:	Standard (S)
Date of supplement:	November 10, 2006
Date of receipt:	November 13, 2006

This supplemental application proposes to provide a 250 mg Soma® (carisoprodol) tablet for the relief of discomfort associated with acute, painful musculoskeletal conditions.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 12, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be September 13, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any question, call me at (301) 796-2254.

Sincerely,

{See appended electronic signature page}

Sharon Turner-Rinehardt
Regulatory Project Manager
Division of Anesthesia, Analgesia and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Sharon Turner-Rinehardt

11/28/2006 10:44:04 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Dr. Hussong, HFD-805

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Donald N. Klein, Ph.D., Branch VII

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12/15/2006	n/a	11-792, SE2-041	Efficacy supplement	11/10/06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Soma Tablets	10 Month Review Clock	Painful musculoskeletal Conditions	6/1/07

NAME OF FIRM: MedPointe Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Microbiology Consult; Please evaluate the new microbiological Release and Stability Specifications for the new 250 mg tablet.

SIGNATURE OF REQUESTOR
Donald N. Klein

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Teshara Bouie

12/15/2006 03:25:05 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS

FROM: Sharon Turner-Rinehardt, RPM (Eric Brodsky, MO)
Division of Anesthesia, Analgesia and Rheumatology Products
HFD-170

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12-11-06		11792	Efficacy Supplement (SE2)	11-10-06

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
SOMA	S	Analgesic	June 1, 2007

NAME OF FIRM: MedPointe Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- X PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the label and carton/container for NDA 11,792 SOMA from MedPointe Pharmaceuticals. The PDUFA date is September 13, 2007. The link for the label and medication guide is provided below and the carton/container will be hand delivered to Jenna Lyndly. If you have any questions, please contact me at (301) 796-2254. \\CDSESUB1\N11792\S_041\2006-11-10

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Sharon Turner-Rinehardt	X MAIL X HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sharon Turner-Rinehardt
12/11/2006 05:39:43 PM