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<td>SUPPLIER:</td>
<td>Chesapeake</td>
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<tr>
<td>TELEPHONE:</td>
<td>973-808-8000</td>
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### APPROVAL

- [ ] APPROVED AS IS
- [X] NOT APPROVED - REPROOF IS REQUIRED

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Chesapeake®
CARISOPRODOL Tablets for Oral use

CARISOPRODOL 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)

DOSE AND ADMINISTRATION

Recommended dose is 250 mg to 350 mg three times a day and at bedtime. (2)

TABLETS AND STRIPS

Tablets: 250 mg (3)

CARISOPRODOL TABLETS, USP

250 mg/350 mg TABLETS, USP

CARISOPRODOL Tablets for Oral use

DOSAGE AND ADMINISTRATION

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

DOSAGE FORM AND STRENGTH

350 mg Tablets: White to off-white, round convex tablets, debossed with ‘CL’ above ‘022’

CONTRAINdications

CARISOPRODOL is contraindicated in patients with a history of acute intermittent porphyria or a hypersensitivity reaction 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).

Report SUSPECTED ADVERSE REACTIONS to Rising Pharmaceuticals at 1-201-961-9000 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)

Hypersensitivity reactions to a carbamate such as meprobamate (4).

Drug Interactions

Dosage and Administration (2)

--- CARISOPRODOL is contraindicated in patients who have a history of or who use CARISOPRODOL in combination with other drugs with abuse potential. However, there have been post-marketing adverse event reports of CARISOPRODOL-associated abuse when used without other drugs with abuse potential. Withdrawal symptoms have been reported following abrupt cessation after prolonged use. To reduce the chance of CARISOPRODOL dependence, withdrawal, or abuse, CARISOPRODOL should be used with caution in addiction prone patients and in patients who abuse drugs. Withdrawal of CARISOPRODOL should not be used more than two to three weeks for the relief of acute musculoskeletal discomfort.

CARISOPRODOL, and one of its metabolites, meprobamate (a controlled substance), may have abuse potential. Withdrawal symptoms have been reported following abrupt cessation after prolonged use. To reduce the chance of CARISOPRODOL dependence, withdrawal, or abuse, CARISOPRODOL should be used with caution in addiction prone patients and in patients who abuse drugs. Withdrawal of CARISOPRODOL should not be used more than two to three weeks for the relief of acute musculoskeletal discomfort.

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CARISOPRODOL Tablets are available as 250 mg, 350 mg, and 500 mg tablets. CARISOPRODOL Tablets are white to off white, Round and flat, convex tablets, debossed with ‘CL’ above ‘022’ by Mirror Pharmaceuticals, LLC, for oral administration.

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.

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 dose of 250 mg CARISOPRODOL and 350 mg CARISOPRODOL (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 CARISOPRODOL, which is approximately 30% of the Cmax of meprobamate (approximately 8 μg/mL) after administration of a single 400 mg dose of meprobamate.

The half-life of meprobamate is approximately 10 hours.

**Gender:** Exposure of CARISOPRODOL is higher in female than in male subjects (approximately 30 to 50% a weight adjusted basis). Overall, the half-life of CARISOPRODOL is comparable between female and male subjects.

**Patients with Reduced CYP2C9 Activity:** CARISOPRODOL should be used with caution in patients with reduced CYP2C9 activity. Published studies indicate that patients who are poor CYP2C9 metabolizers have a 4-fold increase in exposure to CARISOPRODOL, and compared to normal CYP2C9 metabolizers, to meprobamate compared to normal CYP2C9 metabolizers. The prevalence of poor metabolizer was lower in Caucasians and African Americans is approximately 3 to 5% and in Asians is approximately 15 to 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.

CARISOPRODOL 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.

CARISOPRODOL 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 toxicity 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 body surface area comparison. The significance of these findings for human fertility is not known.

**14 CLINICAL STUDIES**

The safety and efficacy of CARISOPRODOL 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 pulposus, spondylolisthesis or spinal stenosis); with inflammatory back pain, or with evidence of a neuromuscular 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., CARISOPRODOL 250 mg, CARISOPRODOL 350 mg, or placebo) and in Study 2 patients were randomized to two treatment groups (i.e., CARISOPRODOL 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 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 CARISOPRODOL 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**

<table>
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<tr>
<th>Study</th>
<th>Parameter</th>
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<th>350 mg CARISOPRODOL</th>
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<td>Number of Patients</td>
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<td>364</td>
<td>364</td>
</tr>
<tr>
<td></td>
<td>Difference between CARISOPRODOL and Placebo, Mean (SE)</td>
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<td>1.8 (0.1)</td>
<td>1.8 (0.1)</td>
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<tr>
<td></td>
<td>Global Impression of Change, Mean (SE)</td>
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<td></td>
<td>Number of Patients</td>
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<td>276</td>
<td>276</td>
</tr>
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<td></td>
<td>Difference between CARISOPRODOL and Placebo, Mean (SE)</td>
<td>0.4 (0.1)</td>
<td>0.4 (0.1)</td>
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</tr>
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</table>

**17.1 Sedation**

Patients should be advised that CARISOPRODOL may cause drowsiness and/or dizziness, and has been associated with motor vehicle accidents. Patients should be advised to avoid taking CARISOPRODOL 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 CARISOPRODOL 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 CARISOPRODOL Should Only Be Used for Short-Term Treatment**

Patients should be advised that treatment with CARISOPRODOL should be limited to acute use (up to two or three weeks) for the relief of acute, musculoskeletal discomfort. In the post-marketing experience with CARISOPRODOL, cases of dependence, withdrawal, and abuse have been reported with prolonged use. If the musculoskeletal symptoms still persist, patients should contact their healthcare provider for further evaluation.

To report SUSPECTED ADVERSE REACTIONS, contact Rising Pharmaceuticals at 1-201-941-1000 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.