Line of Business: Medi-Cal
Effective Date: June 1, 2016
Renewal Date: August 16, 2017

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee.

Drugs: Amrix (cyclobenzaprine ER), Baclofen, Carisoprodol, Chlorzoxazone, Cyclobenzaprine, Dantrolene sodium, Metaxalone, Methocarbamol, Orphenadrine, Tizanidine

Policy/Criteria:

1. Dantrolene
   a. Dantrolene will be approved for the treatment and prevention of malignant hyperthermia
   b. Dantrolene will be approved for the control of clinical spasticity resulting from motor neuron disorders (e.g. spinal cord injury, stroke, cerebral palsy or multiple sclerosis) when the following criteria are met:
      i. Failure or clinically significant adverse effects to ONE of the formulary alternatives: baclofen or tizanidine

2. Chlorzoxazone, Orphenadrine, Orphenadrine ER, Metaxalone
   a. Treatment of acute, painful musculoskeletal condition (e.g. neck pain, low back pain)
   b. Failure or clinically significant adverse effects to TWO of the formulary alternatives: cyclobenzaprine IR, methocarbamol or tizanidine.

3. Carisoprodol
   a. Treatment of acute, painful musculoskeletal condition (e.g. neck pain, low back pain)
b. Failure or clinically significant adverse effects to TWO of the formulary alternatives: cyclobenzaprine IR, methocarbamol or tizanidine

c. Must not take concurrently with an opioid (e.g. hydrocodone/APAP, oxycodone) AND a benzodiazepine (e.g. alprazolam). (i.e. Three drug combination)

d. Limit to short-term use only (i.e. no more than 1 month)
   i. Request for extended use will be reviewed as case-by-case by MCAL Pharmacist

4. Amrix (cyclobenzaprine ER)
   a. Treatment of acute, painful musculoskeletal condition (e.g. neck pain, low back pain)
   b. Inadequate response to formulary cyclobenzaprine
   c. Failure or clinically significant adverse effects to the following formulary alternatives: methocarbamol and tizanidine

Clinical Justification:

Comparison of FDA Approved Indications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Limitation</th>
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<tbody>
<tr>
<td><strong>Anti-spasticity Agents</strong></td>
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<tr>
<td>baclofen (Lioresal)</td>
<td>For the alleviation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms, concomitant pain, clonus and muscular rigidity</td>
<td></td>
</tr>
<tr>
<td>dantrolene sodium</td>
<td>For the control of clinical spasticity resulting from upper motor neuron disorders such as spinal cord injury, stroke, cerebral palsy or multiple sclerosis</td>
<td>Not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders.</td>
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<tr>
<td>tizanidine (Zanaflex)</td>
<td>For the acute and intermittent management of increased muscle tone associated with spasticity</td>
<td>Short duration of therapeutic effect. Should be reserved for those daily activities and times when relief of spasticity is most important.</td>
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</tbody>
</table>

**Anti-spasmodic Agents**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>Limitation</th>
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</thead>
<tbody>
<tr>
<td>carisoprodol (Soma)</td>
<td>Should only be used for acute treatment periods up to 2-3</td>
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<tr>
<td>cyclobenzaprine</td>
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As an adjunct to rest, physical therapy, and other measures for the relief of discomfort associated with acute, painful musculoskeletal conditions

The modes of action of these drugs have not been clearly identified, but likely due to their sedative properties. Do not directly relax tense skeletal muscles.

### Dosage and Precautions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult Dosage</th>
<th>Precaution and Comments</th>
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| baclofen (Lioresal)           | Starting: 5mg po tid for 3 days Titration: increase by 5mg tid every 3 days Max: 20mg po qid | • Withdrawal syndrome (e.g. hallucination, psychosis, seizure)  
• Dose cautiously in renal impairment or seizure disorders |
| dantrolene sodium (Dantrium)  | Spasticity titration:  
Week 1: 25mg po daily x 1 week  
Week 2: 25mg po tid  
Week 3: 50mg po tid  
Week 4 and thereafter: 100mg po tid Max: 100mg po qid | • Black box warning: Dose-dependent fatal hepatotoxicity (most common between 3 and 12 months of therapy)  
• Contraindicated in hepatic disease  
• Periodic LFT recommended |
| tizanidine (Zanaflex)         | Initial: 4mg po every 6-8 hours Titration: increase dose by 2-4mg as tolerated Max dose: 36mg | • Dose-related hypotension (20% decrease in blood pressure)  
• Hepatotoxicity  
• Withdrawal: hypertension, tachycardia, hypertonia  
• Hallucination, delusions (3%)  
• Periodic LFT is recommended  
• Avoid in hepatic disease  
• Dose cautiously if CrCl< 25mL/min |
| **Anti-spasmodic Agents**     |                                                                             |                                                                                        |
| carisoprodol (Soma)           | 250mg to 350mg po four times daily up to 2-3 weeks | • Schedule IV: abuse potential  
• Abused to enhance opiate effects, or |
<table>
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<tr>
<th><strong>Drug</strong></th>
<th><strong>Dosage</strong></th>
<th><strong>Side Effects</strong></th>
<th><strong>Additional Information</strong></th>
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</thead>
</table>
| cyclobenzaprine (Flexeril, Fexmid), cyclobenzaprine ER (Amrix) | IR: 5mg po tid, increased to 7.5mg or 10mg tid for 2-3 weeks  
ER: 15mg or 30mg po daily for 2-3 weeks | • Adverse effects (e.g. anticholinergic effects) similar to tricyclic antidepressants  
• Compared to carisoprodol, dry mouth is more frequent, but dizziness is less frequent  
• Avoid in moderate or severe hepatic impairment | |
| chlorzoxazone (Parafon, Forte DSC) | Starting: 250mg to 500mg po tid to qid  
Max: 750mg po tid to qid | • Dizziness, drowsiness  
• GI irritation and rare GI bleeding  
• Urine discoloration (orange, red or purple)  
• Rare hepatotoxicity | |
| metaxalone (Skelaxin) | 800mg po tid to qid | • Contraindicated in serious liver or renal impairment  
• Periodic LFT recommended in patients with liver impairment  
• Less sedating  
• Paradoxical muscle cramps  
• Mild withdrawal syndrome | |
| methocarbamol (Robaxin) | 1500mg to 2000mg po qid | • Urine discoloration (brown, brown-black, green)  
• Less drowsiness than cyclobenzaprine | |
| orphenadrine, orphenadrine ER (Norflex) | 100mg po bid | • Anticholinergic side effects (e.g. dry mouth, urinary retention)  
• Rare aplastic anemia | |
American College of Physicians and the American Pain Society 2007: A Joint Clinical Practice Guideline, Diagnosis and Treatment of Low Back Pain

- Clinicians should provide patients with evidence-based information on low back pain with regard to their expected course, advise patients to remain active, and provide information about effective self-care options (Strong recommendation, moderate-quality evidence).
- For patients with low back pain, clinicians should consider the use of medications with proven benefits in conjunction with back care information and self-care. Clinicians should assess severity of baseline pain and functional deficits, potential benefits, risks and relative lack of long-term efficacy and safety data before initiating therapy (Strong recommendation, moderate-quality evidence).
- For most patients, first-line medication options are acetaminophen or nonsteroidal anti-inflammatory drugs.
- There is little evidence for the efficacy of baclofen or dantrolene, also known as anti-spasticity drugs, for low back pain. However, tizanidine has been well studied for low back pain. Other skeletal muscle relaxants are an option for short-term relief of acute low back pain, but all are associated with central nervous system adverse effects (primarily sedation).
- There is no compelling evidence that skeletal muscle relaxants differ in efficacy or safety.
- For patients who do not improve with self care options, clinicians should consider the addition of nonpharmacologic therapy with proven benefits—for acute low back pain, spinal manipulation; for chronic or subacute low back pain, intensive interdisciplinary rehabilitation, exercise therapy, acupuncture, massage therapy, spinal manipulation, yoga, cognitive-behavioral therapy, or progressive relaxation (weak recommendation, moderate-quality evidence).

Comparative Efficacy and Safety of Skeletal Muscle Relaxants for Spasticity and Musculoskeletal Conditions: A Systematic Review 2004

- Included 101 randomized trials at poor to fair quality
- Patient population: adults and pediatric patients with spasticity or a musculoskeletal syndrome
- Skeletal muscle relaxants included: baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, tizanidine
- Anti-spasticity agents: Baclofen, tizanidine and dantrolene are effective compared to placebo in patients with spasticity (primarily multiple sclerosis).
  - Baclofen and tizanidine have comparable efficacy and adverse effects
  - Tizanidine is associated with more dry mouth, and baclofen more weakness
- Anti-spasmodic agents: Cyclobenzaprine, carisoprodol and orphenadrine are effective compared to placebo in patients with musculoskeletal conditions (primarily acute back or neck pain).
  - Tizanidine also demonstrated efficacy in comparison to placebo in treating musculoskeletal pain conditions.
  - Cyclobenzaprine has been evaluated in the most clinical trials and has consistently been found to be effective.

**The Department of Justice: Prescription Drug Diversion, Combating the Scourge 2012**

The abuse of prescription drugs is not isolated to just one drug. Abusers and addicts routinely abuse prescription drugs in combination with one another to enhance the effects. The activity significantly increases the risk of potential harm to the individual. This combination is often referred to as the “trinity” or “holy trinity,” and is typically hydrocodone or oxycodone used in combination with alprazolam and carisoprodol.

To address this problem, DEA published a Final Rule in the Federal Register on December 12, 2011 that designated carisoprodol as a schedule IV controlled substance, effective January 11, 2012. Furthermore, on August 22, 2014, the DEA published a ruling to transfer hydrocodone combination products from schedule III to schedule II of the Controlled Substances Act.

**Carisoprodol Pharmacology & Drug Overdose Statistics**

- Carisoprodol is metabolized extensively by the liver through CYP450 enzyme. Its active metabolite, meprobamate has a half-life of about 10 hours with benzodiazepine-like, anti-anxiolytic properties.
- Carisoprodol, alone or in combination, accounted for more than 30,000 emergency department visits in 2009.
- According to the U.S. Centers for Disease Control and Prevention, 13% of opioid related mortality was associated with concomitant benzodiazepines consumption in 1999. By 2011, the percentage had increased to 31%.
- Benzodiazepines accounted for 373,000 emergency department visits in 2009.

**References:**


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<tbody>
<tr>
<td>08/16/2017</td>
<td>• Renewed with no updates/changes</td>
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