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# Drug Class Literature Scan: Muscle Relaxants, Oral

**Date of Review:** September 2019

**Date of Last Review:** March 2017
**Literature Search:** 01/01/17 – 07/25/19

**Current Status of PDL Class:**
See **Appendix 1**.

**Conclusions:**
- There was no new clinical efficacy or safety evidence that would change current policy.
- There is no evidence to support using baclofen for alcohol use disorder (AUD) based on a good-quality systematic review and meta-analysis.[1]

**Recommendations:**
- No changes to the preferred drug list (PDL) are recommended based on a review of the clinical evidence.
- After evaluation of costs in executive session, make methocarbamol tablets preferred.

**Summary of Prior Reviews and Current Policy**
- Review of the muscle relaxant class in 2017 resulted in no changes to the PDL. Previous reviews have demonstrated no differences in the clinical efficacy between skeletal muscle relaxants for musculoskeletal conditions.
- Evidence is insufficient to draw firm conclusions regarding the comparative effectiveness between baclofen, tizanidine or dantrolene for spasticity.
- The skeletal muscle relaxants, tizanidine, cyclobenzaprine, and baclofen are more efficacious than placebo for short-term (5 to 7 days) pain relief of acute low back pain (LBP).
- Dantrolene and chlorzoxazone are associated with rare serious dose-related hepatotoxicity.
- Prior authorization (PA) criteria limits the use of muscle relaxant therapy to 3 months due to insufficient evidence of efficacy beyond 5-7 days. The use of carisoprodol is limited to an equivalent of a two weeks supply (56 tablets), which is consistent with prescribing information, every 90 days. Prior authorization criteria is also in place to prevent the use of carisoprodol with opioids due to safety concerns. There were no claims for carisoprodol last quarter.
- Preferred therapies in the class are: baclofen, cyclobenzaprine and tizanidine.

**Methods:**
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the

Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

**New Systematic Reviews:**

*Cochrane – Baclofen for Alcohol Use Disorder*
A 2018 Cochrane review identified 12 randomized controlled trials evaluating the use of baclofen (10 mg to 150 mg daily) for AUD.[1] The mean patient age was 48 years old and 68% were male. The trials were small, 100 patients or less, and all patients had a diagnosis of alcohol dependence and were currently using alcohol. Eleven of the trials compared baclofen to placebo and there was one active treatment comparison of baclofen to acamprosate. All of the included trials were found to be at low risk of bias for all domains.[1]

For the primary outcome of relapse-return to any drinking, the efficacy for baclofen was similar to placebo (RR 0.88; 95% CI, 0.74 to 1.04; p=0.002) based on moderate quality evidence from 5 trials; however, heterogeneity was high ($I^2$=77%).[1] There was moderate quality evidence that for the outcome of percent of heavy drinking days at the end of treatment the results for baclofen and placebo were similar with a MD of 0.25 (95% CI, -1.25 to 1.76) based on 3 trials.[1] There was high quality evidence that there was no difference between baclofen and placebo for the outcomes of at least one adverse event, dropout rate at the end of treatment and dropouts due to adverse events. There was low evidence for the outcomes of frequency of use by the percentage of days abstinent. Overall, there was no differences between baclofen and placebo for outcomes related to alcohol use disorder.

After review, eleven systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

**New Guidelines:**

*NICE – Cerebral Palsy*
NICE released guideline recommendations for the management and treatment of cerebral palsy in adults in 2019.[2] Pharmacotherapy recommendations were provided for spasticity and dystonia. Treatments for spasticity included: enteral baclofen and enteral diazepam. The recommendation for enteral baclofen was based on limited evidence in children and young adults. NICE recommends against the use of enteral diazepam due to no evidence of efficacy and side effects such as drowsiness, vomiting and abdominal pain; however, acute, short-term use for pain and anxiety may be appropriate.[2] Intrathecal baclofen was determined to be appropriate for spasticity or dystonia in adults if managed by a specialty service. Overall, there was limited evidence for drug treatment for spasticity and dystonia in patients with cerebral palsy.[2]

**New Formulations:**
None identified.

**New FDA Safety Alerts:**

**Table 1. Description of New FDA Safety Alerts**

| Generic Name | Brand Name | Month / Year of Change | Location of Change (Boxed Warning, Warnings, CI) | Addition or Change and Mitigation Principles (if applicable) |
|---|---|---|---|---|
| Metaxalone[3] | Skelaxin® | 3/2018 | Adverse reactions | CNS: cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of serotonergic drugs with metaxalone used within the recommended dosage range and with metaxalone as a single agent taken at doses higher than the recommended dose. |

**References:**


1. Minozzi S, Saulle R, Rosner S. Baclofen for alcohol use disorder. *Cochrane Database of Systematic Reviews*. 2018;1:CD012557. doi:10.1002/14651858.CD012557.pub2
2. National Institute for Health and Care Excellence. Cerebral palsy in adults. January 15, 2019. Available at: Nice.org.uk/guidance/ng119. Accessed July 5, 2019.
3. Skelaxin Prescribing Information. Corepharma LLC, Middlesex, NJ. 2018.

**Appendix 1:** Current Preferred Drug List

| Generic | Brand | Form | PDL |
|---|---|---|---|
| baclofen | BACLOFEN | TABLET | Y |
| cyclobenzaprine HCl | CYCLOBENZAPRINE HCL | TABLET | Y |
| tizanidine HCl | TIZANIDINE HCL | TABLET | Y |
| tizanidine HCl | ZANAFLEX | TABLET | Y |
| carisoprodol | CARISOPRODOL | TABLET | N |
| carisoprodol | SOMA | TABLET | N |
| carisoprodol/aspirin/codeine | CARISOPRODOL-ASPIRIN-CODEINE | TABLET | N |
| chlorzoxazone | CHLORZOXAZONE | TABLET | N |
| chlorzoxazone | LORZONE | TABLET | N |
| cyclobenzaprine HCl | AMRIX | CAP ER 24H | N |
| cyclobenzaprine HCl | CYCLOBENZAPRINE HCL ER | CAP ER 24H | N |
| cyclobenzaprine HCl | CYCLOBENZAPRINE HCL | TABLET | N |
| cyclobenzaprine HCl | FEXMID | TABLET | N |
| dantrolene sodium | DANTRIUM | CAPSULE | N |
| dantrolene sodium | DANTROLENE SODIUM | CAPSULE | N |
| metaxalone | METAXALL | TABLET | N |
| metaxalone | METAXALONE | TABLET | N |
| metaxalone | SKELAXIN | TABLET | N |
| methocarbamol | METHOCARBAMOL | TABLET | N |
| methocarbamol | ROBAXIN-750 | TABLET | N |
| orphenadrine citrate | ORPHENADRINE CITRATE ER | TABLET ER | N |
| orphenadrine/aspirin/caffeine | NORGESIC FORTE | TABLET | N |
| orphenadrine/aspirin/caffeine | ORPHENGESIC | TABLET | N |
| tizanidine HCl | TIZANIDINE HCL | CAPSULE | N |
| tizanidine HCl | ZANAFLEX | CAPSULE | N |
| baclofen | BACLOFEN | TABLET | |
| chlorzoxazone | CHLORZOXAZONE | TABLET | |

**Appendix 2:** New Comparative Clinical Trials

A total of twenty citations were manually reviewed from the initial literature search. After further review, twenty citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

**Appendix 3:** Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to July Week 2 2019

Search Strategy:

| # | Searches | Results |
|---|---|---|
| 1 | Carisoprodol/ | 380 |
| 2 | Chlorzoxazone/ | 432 |
| 3 | cyclobenzaprine.mp. | 264 |
| 4 | dantrolene.mp. or Dantrolene/ | 2714 |
| 5 | metaxalone.mp. | 38 |
| 6 | methocarbamol.mp. or Methocarbamol/ | 258 |
| 7 | orphenadrine.mp. or Orphenadrine/ | 617 |
| 8 | tizanidine.mp. | 500 |
| 9 | baclofen.mp. or Baclofen/ | 7261 |
| 10 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 | 12105 |
| 11 | limit 10 to (english language and humans) | 5084 |
| 12 | limit 11 to yr="2017 -Current" | 339 |
| 13 | limit 12 to (clinical trial, phase iii or meta analysis or practice guideline or "systematic review") | 22 |

**Appendix 4:** Key Inclusion Criteria

| | |
|---|---|
| **Population** | Patients with an indication for skeletal muscle relaxants |
| **Intervention** | Muscle relaxant |
| **Comparator** | Active control or placebo |
| **Outcomes** | Pain relief, alcohol abstinence, reduced muscle spasticity |
| **Timing** | As indicated |
| **Setting** | Outpatient |

# Skeletal Muscle Relaxants

**Goal(s):**

- Cover non-preferred drugs only for funded conditions.
- Restrict carisoprodol to short-term use due to lack of long-term studies to assess safety or efficacy and high potential for abuse.

**Length of Authorization:**

- Up to 3 - 6 months

**Requires PA:**

- Non-preferred agents

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

| Approval Criteria | | |
|---|---|---|
| 1. What diagnosis is being treated? | Record ICD10 code | |
| 2. Is the diagnosis funded by the Oregon Health Plan? | **Yes:** Go to #3 | **No:** Pass to RPh. Deny; not funded by the OHP |
| 3. Will the prescriber consider a change to a preferred product?<br><br>Message:<br>• Preferred products do not require PA<br>• Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee. | **Yes:** Inform prescriber of covered alternatives in class | **No:** Go to #4 |
| 4. Is drug requested carisoprodol? | **Yes:** Go to #5 | **No:** Approve for up to 3 months |
| 5. Has an opioid been prescribed within the past 30 days? | **Yes:** Deny; medical appropriateness | **No:** Go to #6 |

| Approval Criteria | | |
|---|---|---|
| 6. Does total quantity of carisoprodol exceed 56 tablets in 90 days?<br><br>From claims, document product, dose, directions, and amount used during last 90 days. | **Yes:** Go to #7 | **No:** Approve for up to 3 months |
| 7. Does patient have a terminal illness (e.g. metastatic cancer, end stage Parkinson's disease, ALS)? | **Yes:** Approve for 6 months. | **No:** Pass to RPh. Go to #8 |
| 8. Pharmacist's statement:<br><br>• Carisoprodol cannot be approved for long term usage.<br>• Patients are limited to 56 tablets in a 90 day period.<br>• It is recommended that the patient undergo a "taper" of the carisoprodol product of which a supply may be authorized for this to occur.<br>• The amount and length of taper depends upon the patient's condition. Does the patient meet one or more of the following:<br>  ○ >65 years of age; or<br>  ○ renal failure; or<br>  ○ hepatic failure; or<br>  ○ take > 1400 mg per day? | **Yes:** Document reason and approve long taper:<br><br>• Authorize 18 tablets<br>• Reduce dose over 9 days<br>• 350 mg TID X 3 days, then<br>• 350 mg BID X 3 days, then<br>• 350 mg daily x 3 days then evaluate | **No:** Approve short taper:<br><br>• Authorize 10 tablets<br>• Reduce dose over 4 days<br>• 350 mg TID x 1 day, then<br>• 350 mg BID x 2 days, then<br>• 350 mg daily x1 day, then evaluate |

*P&T Review:* *9/19 (KS); 3/17 (DM); 3/17; 11/14; 9/09; 2/06; 2/04; 11/01; 2/01; 9/00; 5/00; 2/00*
*Implementation:* *4/1/17; 1/1/15, 1/1/14, 1/1/10, 11/18/04*