**Medication Policy Manual**

**Policy No:** dru041

**Topic:** celecoxib-containing products
- Celebrex®, celecoxib
- Generic celecoxib

**Date of Origin:** September 2001

**Committee Approval Date:** December 11, 2015

**Next Review Date:** December 1, 2016

**Effective Date:** January 1, 2016

**IMPORTANT REMINDER**

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

*Benefit determinations should be based in all cases on the applicable contract language.* To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce pain and inflammation.
Policy/Criteria
I. Most contracts require prior authorization approval of celecoxib prior to coverage. Celecoxib may be considered medically necessary when treatment with at least three low-cost generic prescription NSAIDs were ineffective or not tolerated. At least one of the previously used NSAIDs must be diclofenac, etodolac, meloxicam, or nabumetone. (see Appendix 1).

II. Administration, Quantity Limitations, and Authorization Period
A. OmedaRx considers celecoxib to be a self-administered medication.
B. When prior authorization is approved, celecoxib may be authorized in doses up to 400 mg daily.
C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective.

Position Statement
Summary
- The intent of the policy is to allow coverage of celecoxib when lower cost generic nonsteroidal antiinflammatory drugs (NSAIDs) are not effective or not tolerated.
- Celecoxib is a non-steroidal antiinflammatory drug (NSAID) that is selective for the COX-2 enzyme subtype.
- All NSAIDs, including COX-2 selective NSAIDs, are equally effective treatments for pain and/or inflammation.
- Celecoxib has not demonstrated clinically significant safety advantages when compared with other NSAIDs.
- Please note: two other COX-2 selective NSAIDS, rofecoxib (Vioxx®) and valdecoxib (Bextra®), have been removed from the market due to safety concerns.

Clinical Efficacy
- Celecoxib 200 mg daily is efficacious for arthritis pain and inflammation. Higher doses are generally not more effective. However, some patients with rheumatoid arthritis may derive additional benefit from 200 mg twice daily.

Other Uses
- There is limited prospective, randomized, controlled trial data evaluating the use of celecoxib for the prevention of capecitabine-related hand-foot syndrome.
- A retrospective study concluded that celecoxib may reduce the frequency of capecitabine-related hand-foot syndrome in patients with metastatic colorectal cancer.\[1\]
- A randomized, open-label trial supported these conclusions by demonstrating that celecoxib combined with capecitabine can prevent hand-foot syndrome in patients receiving treatment for colorectal cancer.\[2\]
* Grade 1 and grade 2 hand-foot syndrome were significantly more common in the
capcitabine group (n = 68) than in the capcitabine plus celecoxib group (n = 71); however, the difference in the incidence of grade 3 hand-foot syndrome was not significant.

**Insufficient evidence to establish effectiveness or safety**

* There are insufficient clinical data to conclude that NSAIDs are safe and
effective as anticancer agents or agents to prevent Alzheimer’s disease.[3-12]

* There are insufficient clinical data to conclude that celecoxib is effective:
  -- as adjunctive therapy in schizophrenia.[13]
  -- in the prevention of restenosis after coronary angioplasty.[14]
  -- in the prevention of Barrett’s Esophagus.[15]
  -- in the treatment of cervical dysplasia.[16]
  -- in the prevention of heterotopic ossification.[17]
  -- in the treatment of metastatic, advanced or unresectable colorectal
cancer.[10-12,18]
  -- in the treatment or prevention of non-small cell lung cancer.[5]
  -- in the treatment or prevention of breast cancer.[9]
  -- in the treatment or prevention of pancreatic cancer.
  -- in the treatment or prevention of hepatocellular carcinoma.
  -- in the treatment or prevention of gastric cancer.
  -- in the treatment or prevention of oral cancer.[8]
  -- in the treatment or prevention of meningiomas.
  -- in the treatment or prevention of pituitary macroadenomas.
  -- in the treatment or prevention of malignant mesotheliomas.
  -- in the treatment or prevention of other advanced malignancies.
  -- as adjunctive therapy in bipolar disorder.[19]
  -- as adjunctive treatment in chronic periodontitis.[20]
  -- in the treatment of proteinuria in patients with diabetic nephropathy.[21]
  -- as adjunctive treatment in gastric bypass or gastric banding.
  -- as adjunctive treatment in inflammatory bowel disease.[22,23]
  -- as adjunctive treatment in postoperative spinal fusion.[24,25]

**Safety**

**GI Safety/Tolerability**

- Celecoxib has not demonstrated overall superiority over other NSAIDs in avoiding upper
gastrointestinal (GI) events.
Systematic reviews consider the risk of GI complications with the NSAIDs based on the relative COX-2 selectivity of the medications. The NSAIDs are divided into three groups: non-selective NSAIDs (e.g., ibuprofen, naproxen), partially selective NSAIDs (e.g., etodolac, meloxicam, and nabumetone), and COX-2 selective medications (e.g., celecoxib).[26-28]

* Short-term use (less than three to six months) of celecoxib may be associated with fewer ulcer complications than non-selective NSAIDs; however, it is not known how it compares to generic lower cost partially selective NSAIDs.

* It is unclear whether celecoxib is associated with fewer GI harms when used for longer than three to six months.

- The scientific evidence to date is not sufficient to conclude that celecoxib has potential benefits that are greater than other NSAIDs.

- Celecoxib may not be safe in patients who have a history of gastrointestinal bleeding. In patients with recent history of ulcer bleeding, the rate of recurrent bleeding after treatment with celecoxib for 6 months is 4.9%.[29]

- Concomitant use of aspirin and celecoxib resulted in a four-fold increase in the rate of complicated ulcers when compared with celecoxib alone.

- Celecoxib has not demonstrated improved safety over other NSAIDs when used in patients with inflammatory bowel disease (such as Crohn’s disease or ulcerative colitis).[22,23]

**Bone remodeling risk**

- There is no reliable evidence that bones heal more quickly when celecoxib is used as compared to other NSAIDs[24,25,30,31]. Common flaws of the trials are:
  * Retrospective studies.
  * Non-randomized, open label studies.
  * Small study populations.

**Thrombotic/Cardiovascular Risk**

- Current evidence indicates that selective COX-2 inhibitors have important adverse cardiovascular effects that include increased risk for myocardial infarction, stroke, heart failure, and hypertension.[32]

- The American Heart Association has stated that COX-2 inhibitors should be the last line of treatment for chronic pain in patients with known heart disease or who have cardiovascular risk.[32]

- Selective COX-2 inhibitors in all dosages and nonselective NSAIDs in high dosages increase mortality in patients with previous myocardial infarction (MI) and should therefore be used with particular caution in these patients.[33]

- Celecoxib does not affect platelet aggregation and is not a substitute for aspirin in patients requiring cardiovascular prophylaxis.
- All NSAIDs, including COX-2 selective NSAIDs, may increase the risk of serious bleeding when given concomitantly with warfarin.[34-37]

* The relative safety of celecoxib versus other NSAIDs when given concomitantly with anticoagulants such as warfarin is inconclusive[26]

* Although COX-2 selective NSAIDs do not inhibit platelet function like nonselective NSAIDs, interactions that increase bleeding risk are possible and have been reported when they are given concomitantly with warfarin. [34-37]

* Post-marketing experience has uncovered serious bleeding events, some fatal, with concomitant use of celecoxib and warfarin.

* Prescribing information for all NSAIDs, including celecoxib, warns of the potential of drug-drug interactions with warfarin which may result in increased bleeding.[35,37]

- Celecoxib has not demonstrated a more favorable safety profile over non-selective NSAIDs in patients with renal failure or heart failure.
### Appendix 1: Lower-cost generically available prescription nonsteroidal anti-inflammatory drugs (NSAIDs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac**</td>
<td>Arthrotec®, Cambia™, Cataflam®, Flector® patch, Pennsaid®, Solaraze® gel, Voltaren®, Voltaren® XR, Voltaren® gel, Zipsor®</td>
</tr>
<tr>
<td>Diflunisal</td>
<td>Dolobid®</td>
</tr>
<tr>
<td>Etodolac**</td>
<td>Lodine®, Lodine XL®</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>Nalfon®</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Ansaid®</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>Advil®, Motrin®, Nuprin® (Also available without prescription)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Indocin®</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Oruvail®, Orudis®, Orudis KT® (Also available without prescription)</td>
</tr>
<tr>
<td>Meclofenamate**</td>
<td>Meclomen®</td>
</tr>
<tr>
<td>Meloxicam**</td>
<td>Mobic®</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>Relafen®</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Aleve®, Anaprox®, Naprelan®, Naprosyn® (Also available without prescription)</td>
</tr>
<tr>
<td>Oxaprozin</td>
<td>Daypro®</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Feldene®</td>
</tr>
<tr>
<td>Sulindac</td>
<td>Clinoril®</td>
</tr>
<tr>
<td>Tolmetin</td>
<td>Tolectin 600®</td>
</tr>
</tbody>
</table>

**More "COX-2 selective" than celecoxib.**[38]
# Appendix 2: Low-cost COX-1 and COX-2 Selectivity charts for nonsteroidal anti-inflammatory drugs (NSAIDs)[26]

## More COX 2 Selective (towards top)

<table>
<thead>
<tr>
<th>COX-2 selectivity</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>more diclofenac</td>
<td>Arthrotec®, CambiaTM, Cataflam®, Flector® patch, Pennsaid®, Solaraze® gel, Voltaren®, Voltaren® XR, Voltaren® gel, Zipsor®</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>more mefenamic acid</td>
<td>Meclomen®</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>more meloxicam</td>
<td>Mobic®</td>
<td>0.09</td>
<td></td>
</tr>
<tr>
<td>more celecoxib</td>
<td>Celebrex</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>more etodolac</td>
<td>Lodine®, Lodine® XL</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>more nabumetone</td>
<td>Relafen®</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>more piroxicam</td>
<td>Feldene®</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>more ketorolac</td>
<td>Toradol®</td>
<td>1.64</td>
<td></td>
</tr>
<tr>
<td>more ibuprofen</td>
<td>Motrin®, Tab-Profen®, Vicoprofen** (combined with hydrocodone), Combunox® (combined with oxycodone)</td>
<td>1.69</td>
<td></td>
</tr>
<tr>
<td>more indomethacin</td>
<td>Indocin®, Indocin® SR, Indo Lemmon®, Indomethagan®, Tivorbex®</td>
<td>1.78</td>
<td></td>
</tr>
<tr>
<td>more naproxen</td>
<td>Naprosyn®, Anaprox®, Anaprox® DS, Naprelan®</td>
<td>1.79</td>
<td></td>
</tr>
<tr>
<td>more oxaprozin</td>
<td>Daypro oxaprozin</td>
<td>2.52</td>
<td></td>
</tr>
<tr>
<td>less aspirin</td>
<td></td>
<td>3.12</td>
<td></td>
</tr>
<tr>
<td>less tolmetin</td>
<td>Tolectin®, Tolectin® DS, Tolectin® 600</td>
<td>3.93</td>
<td></td>
</tr>
<tr>
<td>less fenoprofen</td>
<td>Nalfon®, Nalfon® 200</td>
<td>5.14</td>
<td></td>
</tr>
<tr>
<td>less ketoprofen</td>
<td>Oruvail®</td>
<td>8.16</td>
<td></td>
</tr>
<tr>
<td>less flurbiprofen</td>
<td>Ansaid®</td>
<td>10.27</td>
<td></td>
</tr>
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</table>

* Expressed as the ratio of the 50% inhibitory concentration of cyclooxygenase-2 to the 50% inhibitory concentration of cyclooxygenase-1 in whole blood. NSAIDs with a ratio of < 1.00 indicate selectivity for cyclooxygenase-2. Note: different assay methods will give different results and no assay method will predict what will happen when the drug is given to patients.
**Cross References**

<table>
<thead>
<tr>
<th>Code</th>
<th>Cross Reference</th>
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<tbody>
<tr>
<td>Flector®, diclofenac topical patch, RegenceRx Medication Policy Manual, Policy No. dru286</td>
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<tr>
<td>Pennsaid®, diclofenac topical solution, RegenceRx Medication Policy Manual, Policy No. dru287</td>
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<tr>
<td>Sprix®, ketorolac nasal spray, RegenceRx Medication Policy Manual, Policy No. dru288</td>
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<table>
<thead>
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<th>Code</th>
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**References**


<table>
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<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
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<tbody>
<tr>
<td>12/11/2015</td>
<td>- Generic celecoxib added to policy.</td>
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<tr>
<td></td>
<td>- Clarified that step therapy with low-cost generic NSAIDs is required.</td>
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