



# BlueCross BlueShield of Nebraska

An Independent Licensee of the Blue Cross and Blue Shield Association.

## COX-2 INHIBITORS

### Preauthorization Criteria for Approval

#### Medications and Dosage Forms Included in Criteria

Generic Name	Brand Name	Dosage Form(s)
Celecoxib	Celebrex <sup>®</sup>	Oral capsules

#### FDA Approved Indications

Carefully consider the potential benefits and risks of Celebrex<sup>®</sup> (celecoxib) and other treatment options before deciding to use Celebrex. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals<sup>1</sup>.

Celebrex is indicated<sup>1</sup>:

- For relief of the signs and symptoms of osteoarthritis
- For relief of the signs and symptoms of rheumatoid arthritis in adults
- For relief of the signs and symptoms of juvenile rheumatoid arthritis in patients 2 years and older
- For the relief of signs and symptoms of ankylosing spondylitis
- For the management of acute pain in adults
- For the treatment of primary dysmenorrhea
- To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). It is not known whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients. It is also not known whether the effects of Celebrex treatment will persist after Celebrex is discontinued. The efficacy and safety of Celebrex treatment in patients with FAP beyond six months have not been studied.

#### Description

The COX-2 inhibitors were developed to provide another pain reliever option in the NSAID class that decreases the gastrointestinal adverse effects of nonselective NSAIDs. The COX-2 inhibitors have not been shown to be more effective in analgesic properties than nonselective NSAIDs, however, nonselective NSAIDs have been shown to increase GI complications (bleeding, stricture, and perforations). The COX-2 PA program ensures clinically appropriate use of these products based on established risk factors. The COX-2 PA criteria has been established to identify patients electronically by prescription claims history that have recently used or are currently using other medications that can potentially increase their risk for a serious GI complication while also taking a nonselective NSAID. Claims for a COX-2 inhibitor will automatically adjudicate if at least one of the following classes of medication is identified in the prescription claims history: anticoagulant, systemic corticosteroid, nonselective NSAID with misoprostol which includes the combination product Arthrotec<sup>®</sup> (diclofenac sodium/misoprostol). The risk for NSAID related GI complications increases with age, therefore, claims for a COX-2 inhibitor will automatically adjudicate for patients 65 years of age or older. Automatic adjudication is also allowed upon identification of patients with a documented medical diagnosis of a GI complication that may place that patient at high risk for GI adverse events and patients with a documented medical diagnosis of FAP. If previous documentation is not available or other conditions may place the patient at a high risk for GI complications on NSAID therapy the PA process is utilized to review these occurrences.

## Criteria

1. Is the patient 65 years of age or older?  
If yes, approve indefinitely.  
If no, continue to 2.
2. Is the patient at increased risk for a gastrointestinal (GI) adverse event by having a history or current diagnosis of one of the following?
  - a. Peptic ulcer (including duodenal and stomach)
  - b. GI bleed
  - c. GI obstruction
  - d. GI perforation
  - e. None of the aboveIf a-d, approve indefinitely. If e, continue to 3.
3. Is Celebrex<sup>®</sup> (celecoxib) being prescribed to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP)?  
If yes, approve indefinitely.  
If no, continue to 4.
4. Is the patient currently taking an oral anticoagulant [e.g., Coumadin<sup>®</sup> (warfarin sodium)]?  
If yes, approve for 12 months.  
If no, continue to 5.
5. Is the patient currently taking systemic corticosteroids on a regular basis (i.e., long-term daily, weekly, or pulse-therapy)?  
If yes, approve for 12 months.  
If no, continue to 6.
6. Is the patient currently taking daily aspirin?  
If yes, deny.  
If no, continue to 7.
7. Is the patient currently taking a nonselective NSAID and misoprostol, including the combination product Arthrotec<sup>®</sup> (diclofenac sodium/misoprostol)?  
If yes, approve for 12 months.  
If no, deny.

## Rationale

The NSAIDs consists of different classes of medications based on their preference for inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Nonselective NSAIDs inhibit both isoenzymes while COX-2 inhibitors inhibit the COX-2 isoenzyme at a greater extent than the COX-1 isoenzyme.<sup>2,3</sup> Pain and inflammation is mediated by the inhibition of COX-2.<sup>2,3</sup> The use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of pain, inflammation, and fever is widespread across the globe.<sup>3,4</sup> COX-2 inhibitors have been selected for preauthorization (PA) because evidence has proven that the COX-2 inhibitor class is no more effective at reducing pain and inflammation in rheumatoid arthritis or osteoarthritis than less-expensive, nonselective NSAIDs.<sup>5-12</sup> The intent of the PA criteria is to accommodate the use of COX-2 inhibitors for the treatment of labeled indications while encouraging the use of cost-effective generic NSAIDs as first-line agents when possible.

The only available COX-2 inhibitor on the market is celecoxib (Celebrex<sup>®</sup>). Rofecoxib (Vioxx<sup>®</sup>) was voluntarily withdrawn from the market in 2004<sup>13</sup> and valdecoxib (Bextra<sup>®</sup>) was voluntarily withdrawn in 2005.<sup>14</sup> An FDA Public Health Advisory in 2005 outlined the reasoning for the withdrawal of valdecoxib and also stated the addition of “black box” warnings to the product labeling of all NSAIDs currently on the market.<sup>14,15</sup> The “black box” warning indicates the potential for cardiovascular risk and encourages avoiding NSAIDs in high risk individuals.<sup>14,15</sup> Due to the voluntary withdrawals of two COX-2 inhibitors,

the risk of cardiovascular events has become a factor in considering the use of these agents while on-going studies further evaluate the risk variation based on medication, dose, and/or duration of therapy.<sup>14-20</sup>

Studies have shown there is an increased risk for upper gastrointestinal (GI) events due to nonselective NSAID use<sup>1,2,6,21</sup> and some evidence shows a possible increase in lower GI adverse events.<sup>22-24</sup> COX-2 inhibitors may lower the incidence of upper and lower GI adverse events when compared to nonselective NSAIDs.<sup>1,2,6-8,10,22,23,25</sup> The CLASS study has provided confusion on the true benefits of the only COX-2 inhibitor available (celecoxib) and its ability to decrease GI adverse events compared to nonselective NSAIDs.<sup>10</sup> The CLASS study was a long-term trial (at least 12 months) to evaluate the differences in GI complications (GI bleeding, perforation, or obstruction) between celecoxib, ibuprofen, and diclofenac. As reported by Jüni, et al, published in the CLASS study was the first 6 months of 2 different trials with different protocols and length of follow-up.<sup>10,26</sup> The trial included data from 12 and 15 month follow-up studies. The full length trial data sets were only submitted to the FDA and not published elsewhere.<sup>26</sup> Based on the full length trials, there were no differences in ulcer complications between the three treatment groups and is reported in the celecoxib product labeling.<sup>1,26</sup>

Based on the potential for GI complications with the NSAIDs class the clinical issue is whether the modest reduction in ulcer complications is great enough to warrant prescribing COX-2 inhibitors in place of less expensive nonselective NSAIDs with a potential for increased risk of cardiovascular events.<sup>20,27</sup> The decision depends primarily on a patients' individual risk factors for developing NSAID-induced GI complications.<sup>2,6,7,27</sup> Patients who use NSAIDs and have a prior history of peptic ulcer disease or GI bleeding have a greater than 10-fold risk for developing another GI bleed than patients without these risk factors.<sup>1,2,6,7,21</sup> The most important risk factor for developing peptic ulcer disease and/or an upper GI bleed is having a medical history of either condition.<sup>28,29</sup> Misoprostol (Cytotec<sup>®</sup>) has been shown to reduce serious upper GI complications by 40% and is FDA approved for reducing the risk of gastric ulcers caused by NSAIDs.<sup>30,31</sup> Patients with GI adverse effects while utilizing nonselective NSAIDs may add misoprostol or use the diclofenac sodium/misoprostol medication (Arthrotec<sup>®</sup>). The use of either product is included in the edit to identify patients at an increased risk for or a history of GI adverse events.

Peptic ulcer disease is strongly correlated with *Helicobacter pylori* infection, however, this association has not been confirmed in NSAID-induced ulcer patients.<sup>32</sup> However, if the patient is *H. pylori* positive the NSAID should be discontinued if possible to assist in eradication and healing.<sup>32,33</sup> A diagnosis of *H. pylori* is not included in the criteria due to little evidence supporting COX-2 specific NSAIDs lowering the risk of GI adverse events in these patients.<sup>33</sup>

Other conditions and medications that can increase the risk for GI complications include treatment with systemic corticosteroids or oral anticoagulants, long duration of NSAID use, older age, poor health status, smoking and alcoholism.<sup>1,2,6,7,21</sup> Systemic corticosteroids do not cause ulcer disease alone, however, their use with NSAID therapy may increase the risk of GI adverse events two-fold.<sup>2,28</sup> Concomitant use of an anticoagulant and NSAIDs increases the risk of peptic ulcer bleeding two- to twelve-fold.<sup>2,6,7,21,28,29</sup> A patient's prescription claims history is evaluated for medications just described to identify potential risk increases for GI adverse effects. The evidence supporting smoking and alcohol as potential risk factors for NSAID-induced GI complications are conflicting.<sup>32,34-41</sup>

A patient's age alone can confer a higher-risk for GI complications due to NSAID use.<sup>2,6,25,28-30,32,35,37,39-42</sup> The risk for GI complications increases gradually with increasing age<sup>28</sup>, however, the data does suggest that the elderly population is at increased risk from NSAID utilization.<sup>2,6,25,28-30,32,35,37,39-42</sup> Studies vary in the age range used to assess GI complication rates for the elderly and range from 60 years of age and older<sup>28,29,32,35,39-41</sup>, 65 years of age and older<sup>2,6,37,39,41-43</sup>, 66 years and older<sup>25</sup>, and 75 years of age and older.<sup>30</sup> The COX-2 inhibitor criteria includes the age of 65 and older based on the age for the geriatric population used by multiple sources, including the Celebrex product labeling.<sup>1,2,25,41,43</sup>

It is possible that patients requiring treatment for pain and inflammation from a nonselective NSAID or COX-2 inhibitor will also be recommended to take low- or regular-strength aspirin ( $\leq 325$  mg/day). Some COX-2/NSAID comparator trials have included aspirin utilizing participants.<sup>10,12,44</sup> These trials reported no

difference in ulcer complications in patients taking aspirin along with either a nonselective NSAID or COX-2 inhibitor. The use of aspirin was also evaluated in a systematic review examining the use of celecoxib and nonselective NSAIDs.<sup>8</sup> The review included unpublished data from Pharmacia which showed no statistical difference in ulcer occurrence which is consistent with previous estimates. The benefit of celecoxib was determined to be less in aspirin users than non-users.<sup>8</sup>

The clinical benefits of aspirin in primary and secondary prevention of cardiovascular events are well known. Aspirin exhibits beneficial outcomes by irreversible inhibition of the COX-1 isoenzyme. Nonselective NSAIDs reversibly bind to COX-1 which can inhibit the binding of aspirin to the same site. An FDA Science Paper advised of a possible interaction between concomitant use of ibuprofen and aspirin.<sup>45</sup> The paper only makes reference to one other NSAID, naproxen sodium, that when given two hours before or after aspirin administration shows no interference with aspirin's antiplatelet activity.<sup>45</sup> Other pharmacodynamic studies have shown diclofenac and meloxicam may not interfere with aspirin at the COX-1 binding site.<sup>47,46</sup> Without a randomized controlled trial the clinical implication of this interaction is uncertain, however, is important considering the cardioprotective effect of aspirin.<sup>45</sup>

### **Automatic Claims History Edit**

The automatic electronic edit process will identify and approve patients that may have a contraindication or have a high-risk for developing serious GI complications (by medical diagnoses, medications, or medical history) to a nonselective NSAID. The edit requires that other medication(s) of a specific quantity be tried in a designated time period prior to a claim adjudicating for a COX-2 inhibitor medication. If the patient has met at least one of the following requirements the COX-2 inhibitor medication claim will automatically adjudicate under the patient's current prescription benefit.

The patient has evidence of one or more of the below in the previous 120 days:

- a. Patient is 65 years of age or older;
- b. A prescription for an oral anticoagulant [e.g., Coumadin<sup>®</sup> (warfarin sodium)];
- c. A prescription for a systemic corticosteroid;
- d. A prescription for a nonselective NSAID and misoprostol (Cytotec<sup>®</sup>), including the combination product diclofenac sodium/misoprostol (Arthrotec<sup>®</sup>)

Evidence of the above medications filled prior to the COX-2 inhibitor medication must be documented in the electronic prescription drug history. If there is no documentation that the patient has met the electronic edit criteria, the claim will reject with a Point of Sale message indicating that preauthorization is necessary. The Criteria documented previously may then be applied to requests submitted by the patient's practitioner. These criteria are similar to account for previous therapies that meet the PA criteria.

Patients with a history of or present peptic, duodenal, or gastric ulcers and/or bleeds and current *H. pylori* infection are approved through the PA process based on medical diagnoses of the current or past ulcer history. Other potential risk factors for GI complications are poor health status, chronic disease, smoking, and alcohol use. Although these can increase the risk they do not qualify for automatic approval. Medication history will be evaluated for health status and chronic disease matters and may be approved if the history increases their risk. Smoking and alcohol use and history will be evaluated based on medical documentation of persistent or permanent physiologic changes. Approval will be granted for patients that are prescribed celecoxib in the treatment of adenomatous colorectal polyps from familial adenomatous polyposis (FAP).

Approvals are granted for different lengths of time based on the medical and pharmacy claims history provided either electronically or through the PA evaluation process. Patient's that are 65 years of age or older, have a history of GI complications as outlined in the Criteria, or are using celecoxib to reduce the number of adenomatous colorectal polyps are approved for an indefinite length of time. Indefinite preauthorizations are subject to review based on new information, changes in criteria, or identified safety concerns. Patient's that are currently taking an oral anticoagulant (e.g., warfarin sodium), systemic corticosteroid, or misoprostol (including the combination product Arthrotec<sup>®</sup>) will be approved for 12 months.

The electronic edit employs a 120 day look-back period prior to the COX-2 inhibitor prescription claim for certain medications outlined above. The electronic edit will identify claims in these classes that have a

day supply that overlaps with 120 day look-back period. A 120 day period was selected to accommodate various treatment regimens of these medications.

### Medical Diagnoses

A component of the PA criteria is the inclusion of medical diagnoses as part of the approval process. Certain medical diagnoses predispose patients to a high-risk of developing an adverse event to the nonselective NSAIDs. The intent of using medical diagnoses is to identify those patients at high-risk for GI complications or other diagnoses specific for Celebrex (familial adenomatous polyposis), and pre-approve those patients for COX-2 inhibitor therapy during the implementation process. Patients that qualify for pre-approval are identified by the following ICD-9 diagnosis codes:

Event	ICD-9-CM Code <sup>†</sup>
➤ Gastric ulcer and/or bleed	531.xx
➤ Duodenal ulcer and/or bleed	532.xx
➤ Peptic ulcer and/or bleed	533.xx
➤ Familial adenomatous polyposis	211.xx

<sup>†</sup>Approval is based on either 3, 4, or 5 digit ICD-9-CM codes provided

Patients with these medical diagnoses will be identified through the PA review process if the ICD-9-CM codes are not documented in the medical claims file.

### References

1. Celebrex<sup>®</sup> (celecoxib) [package insert]. New York, NY: G.D. Searle, LLC, January 2008.
2. Dubois RW, Melmid GY, Henning JM, Bernal M. Risk of upper gastrointestinal injury and events in patients treated with cyclooxygenase (COX)-1/COX-2 nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 selective NSAIDs, and gastroprotective cotherapy; an appraisal of the literature. *J Clin Rheumatol* 2004;10:178-89.
3. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000;343(21):1520-8.
4. Laine, L. Approaches to nonsteroidal anti-inflammatory drug use in the high-risk patient. *Gastroenterology* 2001;120(3):594-606.
5. Hur C, Chan AT, Tramontano AC, Gazelle GS. Coxibs versus combination NSAID and PPI therapy for chronic pain: an exploration of the risk, benefits, and costs. *Ann Pharmacother* 2006;40:1052-63.
6. Chou R, Helfand M, Peterson K, Dana T. Drug Class Review of Cyclo-oxygenase (COX)-2 Inhibitors and Non-steroidal Anti-inflammatory Drugs (NSAIDs). Final Report Update 3. November 2006. Available at: <http://www.ohsu.edu/drugeffectiveness>. Accessed May 2008.
7. Chou R, Helfand M, Peterson K, Dana T, Roberts C. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis. Comparative Effectiveness Review No. 4 (prepared by the Oregon Evidence-based Practice Center under Contract No. 290-02-0024). Rockville, MD: Agency for Healthcare Research and Quality. September 2006. Available at: <http://www.effectivehealthcare.ahrq.gov/reports/final.cfm>. Accessed May 2007.
8. Deeks JJ, Smith LA, Bradley. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. *BMJ* 2002;325:619.
9. Goldstein J, Silverstein F, Agrawal N, et al. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. *Am J of Gastroenterol* 2000;95(7):1681-90.
10. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib versus non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS Study: A randomized controlled trial. *JAMA* 2000;284(10):1247-55.
11. Bensen W, Fiechtner JJ, McMillen JI, et al. Treatment of osteoarthritis with celecoxib a cyclooxygenase-2 inhibitor: A randomized controlled trial. *Mayo Clin Proc* 1999;74:1095-1105.
12. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA* 1999;282(20):1921-8.
13. FDA Public Health Advisory: Safety of Vioxx. September 30, 2004. Available at: [http://www.fda.gov/cder/drug/infopage/vioxx/PHA\\_vioxx.htm](http://www.fda.gov/cder/drug/infopage/vioxx/PHA_vioxx.htm). Accessed June 2008.

14. FDA Public Health Advisory: FDA Announces Important Changes and Additional Warnings for COX-2 Selective and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs). April 7, 2005. Available at: <http://www.fda.gov/cder/drug/advisory/COX2.htm>. Accessed June 2008.
15. American College of Rheumatology. ACR Hotline-The Safety of COX-2 inhibitors. Available at: [www.rheumatology.org](http://www.rheumatology.org). Accessed May 2008.
16. Andersohn F, Suissa S, Garbe E.; Henry D, McGettigan. Cyclooxygenase inhibitors and cardiovascular risk [letter & reply]. *JAMA* 2007;29(6)7:586-8.
17. Graham DJ. COX-2 inhibitors, other NSAIDs, and cardiovascular risk [editorial]. *JAMA* 2006;296(13):1653-6.
18. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA* 2006;296(13):1633-44.
19. Solomon SD, Pfeffer MA, McMurray JJV, et al. Effect of celecoxib on cardiovascular events and blood pressure in two trials for the prevention of colorectal adenomas. *Circulation* 2006;114:1028-35.
20. Wright JM. The double-edged sword of COX-2 selective NSAIDs. *CMAJ* 2002;167(10):1131-7.
21. Nielsen OH, Ainsworth M, Csillag C, Rask-Madsen J. Systematic review: coxibs, non-steroidal anti-inflammatory drugs or no cyclooxygenase inhibitors in gastroenterological high-risk patients? *Aliment Pharmacol Ther* 2006;23:27-33.
22. Lehmann FS, Beglinger C. Impact of COX-2 inhibitors in common clinical practice a gastroenterologist's perspective. *Curr Top Med Chem* 2005;5(5):449-64.
23. Laine L, Connors LG, Reicin A, et al. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. *Gastroenterology* 2003;124(2):288-92.
24. Wilcox CM, Alexander LN, Cotsonis GA, Clark WS. Nonsteroidal anti-inflammatory drugs are associated with both upper and lower gastrointestinal bleeding. *Dig Dis Sci* 1997;42(5):990-7.
25. Mamdani M, Rochon PA, Juurlink DN, et al. Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs. *BMJ* 2002;325:624.
26. Jüni P, Rutjes AWS, Dieppe PA. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? *BMJ* 2002;324:1287-8.
27. Peterson WL, Cryer B. COX-1-sparing NSAIDs—Is the enthusiasm justified? *JAMA* 1999;282(2):1961-3.
28. Bjorkman DJ. Current status of non-steroidal anti-inflammatory Drug (NSAID) use in the United States: Risk factors and frequency of complications. *Am J Med* 1999;107(6a):3s-10s.
29. Garcia-Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet* 1994;343:769-772.
30. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs: A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1995;123(4):241-9.
31. Cytotec® (misoprostol) [package insert]. New York, NY: G.D. Searle, LLC, September 2006.
32. Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcers. *Am J Gastroenterol* 1998;93(11):2037-46.
33. The Pharmacologic Management of *Helicobacter pylori* in Peptic Ulcer Disease and Dyspepsia. Department of Veteran's Affairs. Veterans Health Administration. Publication No. 98-0009. Updated 1998. Available at [www.pbm.va.gov/archive/dsmpud.pdf](http://www.pbm.va.gov/archive/dsmpud.pdf). Accessed May 2008.
34. Rosenstock S, Jorgensen T, Bonnevie O, Andersen L. Risk factors for peptic ulcer disease: a population based prospective cohort study comprising 2416 Danish adults. *Gut* 2003;52:186-93.
35. Konturek SJ, Bielanski W, Plonka M, et al. *Helicobacter pylori*, non-steroidal anti-inflammatory drugs and smoking in risk pattern of gastroduodenal ulcers. *Scand J Gastroenterol* 2003;38(9):923-30.
36. Stack WA, Atherton JC, Hawkey GM, Logan RFA, Hawkey CJ. Interactions between *Helicobacter pylori* and other risk factors for peptic ulcer bleeding. *Aliment Pharmacol Ther* 2002;16:497-506.
37. Straus WL, Ofman JJ. Gastrointestinal toxicity associated with nonsteroidal anti-inflammatory drugs. *Gastroenterol Clin North Am* 2001;30(4):895-920.
38. Weil J, Langman MJS, Wainwright P, et al. Peptic ulcer bleeding: accessory risk factors and interactions with non-steroidal anti-inflammatory drugs. *Gut* 2000;46:27-31.

39. Hernandez-Diaz S, Rodriguez LAG. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation. *Arch Intern Med* 2000;160:2093-99.
40. Kurata J, Nogawa AH. Meta-analysis of risk factors for peptic ulcer: nonsteroidal anti-inflammatory drugs, *Helicobacter pylori*, and smoking. *J Clin Gastroenterol* 1997;24(1):2-17.
41. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. *Ann Intern Med* 1991;115(10):787-96.
42. Laine L, Bombardier C, Hawkey CJ, et al. Stratifying the risk of NSAID-related upper gastrointestinal clinical events: Results of a double-blind outcomes study in patients with rheumatoid arthritis. *Gastroenterology* 2002;123(4):1006-12.
43. Cebollero-Santamaria, Smith J, Gioe S, et al. Selective outpatient management of upper gastrointestinal bleeding in the elderly. *Am J Gastroenterol* 1999;94(5):1242-7.
44. Schnitzer TJ, Burmester GR, Mysler E, et al. Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomized controlled trial. *Lancet* 2004;364:665-74.
45. FDA Science Paper. Concomitant use of ibuprofen and aspirin: Potential for attenuation of the anti-platelet effect of aspirin. September 8, 2006. Available at: [http://www.fda.gov/cder/drug/infopage/ibuprofen/science\\_paper.htm](http://www.fda.gov/cder/drug/infopage/ibuprofen/science_paper.htm). Accessed May 2008.
46. Van Ryn J, Kink-Eiband M, Kuritsch I, et al. Meloxicam does not affect the antiplatelet effect of aspirin in healthy male and female volunteers. *J Clin Pharmacol* 2004;44(7):777-84.
47. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med* 2001;345(25):1809-17.

## Billing/Coding

CODES	NUMBER	DESCRIPTION
GPI	661005*****	Cyclooxygenase-2 (COX-2) Inhibitors
Type of Service	Prescription Drug	
Place of Service	Outpatient	

## Update Information

Date	Action	Reason
07/01/08	Replace PA criteria	New PA criteria

## Preauthorization Criteria History

06/26/08	Reviewed by QMC
07/01/08	Preauthorization criteria original effective date
May 2009	Next Review