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COX-2 Inhibitors Step Therapy Criteria with Medical Diagnoses Option*

* Medical diagnoses are required for implementation of this option.

Brand	generic	Dosage Form
Celebrex [®]	celecoxib	oral capsule

FDA APPROVED INDICATIONS¹

The following information is taken from individual drug prescribing information and is provided here as background information only. Not all FDA-approved indications may be considered medically necessary. All criteria are found in the section "Prior Authorization Criteria for Approval."

Celebrex¹

Carefully consider the potential benefits and risks of Celebrex and other treatment options before deciding to use Celebrex. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Celebrex is indicated

- 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, and
- To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care (e.g., endoscopic surveillance, surgery). If 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.

CLINICAL RATIONALE FOR STEP THERAPY

The intent of the step therapy criteria for COX-2 inhibitors is to accommodate their use for the treatment of labeled indications while encouraging use of cost-effective generic nonsteroidal anti-inflammatory drugs (NSAIDs) as first-line agents when possible. The cyclooxygenase-2 inhibitors (COX-2) medications were selected for the step therapy edit because there is evidence that they are overused as first-line agents when equally effective, less expensive generic agents are available within the NSAID class. [see Chapter 10.3B Anti-inflammatory Agents: COX-2 Inhibitors]² This step therapy edit may be used as a cost-savings tool by the benefit plan.

The key clinical issue is whether the reduction in ulcer complications is great enough to warrant prescribing COX-1 sparing (COX-2) agents instead of nonselective agents.³ This decision depends primarily on the individual patient's risk for developing an NSAID-induced ulcer complication.³⁻⁷ The risk of cardiovascular events has also become a factor in consideration for use of COX-2 inhibitors. [see Chapter 10.3B Anti-inflammatory Agents: COX-2 Inhibitors].² In April 2005 the Food and Drug Administration (FDA) issued a public health advisory announcing the withdrawal of Bextra[®] (valdecoxib) from the market and the addition of "black box" warnings to the Celebrex product labeling, indicating potential cardiovascular risk and encouraging avoidance in high risk individuals.² Product labeling for nonselective NSAIDs also were to be revised to indicate potential cardiovascular risk.² Studies and data analysis are on-going to further define how this risk varies with agent, dose, or duration of therapy.²

COX-2 inhibitors have not demonstrated greater efficacy than traditional NSAID comparators in relieving the signs and symptoms of osteoarthritis or rheumatoid arthritis. Published evaluations and reviews have found no clear difference in efficacy between COX-2 inhibitors and nonselective NSAIDs. [see Chapter 10.3B Anti-inflammatory Agents: COX-2 Inhibitors]²

Nonselective NSAID agents are well documented to increase the risk for upper gastrointestinal (GI) events such as ulcers, bleeding, perforation, and obstruction. [see Chapter 10.3A Anti-inflammatory Analgesics]⁷ Studies also suggest that NSAIDs may increase the risk of developing similar lower GI adverse events.⁸⁻¹⁰ In addition, studies have shown that patients with a prior history of peptic ulcer disease and/or gastrointestinal bleeding and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors.^{1,4-6,11} Previous upper GI bleed and/or peptic ulcer disease has been determined to be the single most important predictor of another upper GI bleed or another incidence of peptic ulcer disease.^{12,13}

The gastro-protective agent misoprostol and two of the proton pump inhibitors (PPIs)—esomeprazole (Nexium[®]) and lansoprazole (Prevacid[®])—are FDA-labeled for prophylaxis or treatment of NSAID-induced gastric ulcers.¹⁴⁻²³ The pharmaceutical compendia (USP/DI, AHFS-DI) list prevention and/or treatment of NSAID-induced gastric ulcers as accepted uses (labeled or unlabeled) for misoprostol, esomeprazole, lansoprazole, and omeprazole.^{18,19} An Agency for Healthcare Research and Quality (AHRQ) report on the comparative efficacy and safety of analgesics for arthritis recommends cotherapy with a PPI or misoprostol to reduce GI bleeding for people on NSAIDs.²⁰ A Cochrane review (2002) concluded that misoprostol, PPIs, and double dose H2-receptor antagonists (H2RAs) may be effective at preventing chronic NSAID-related endoscopic gastric and duodenal ulcers.²¹ Other reviews similarly concluded that misoprostol and PPIs may be effective in reducing the risk of clinically significant upper GI adverse events associated with nonselective NSAIDs; normal doses of H2RAs have not been shown to be as effective.^{14,22-24} Patients who have adverse GI effects from using nonselective NSAIDs may add misoprostol or a PPI. The step edit uses these combinations to identify patients at risk for, or with a history of, adverse GI events from nonselective NSAIDs.

Although co-therapy with a PPI and NSAID may prevent or reduce GI bleeding, the combination may not provide protection against damage caused by NSAIDs in the lower GI tract. In one study using video capsule endoscopy, celecoxib (n=120) was compared to naproxen plus omeprazole (n=118) in healthy individuals.²⁵ After two weeks of treatment the mean number of small bowel mucosal breaks per subject and the percentage with breaks were 2.99 +/- 0.51, 55% for naproxen/omeprazole compared to 0.32 +/- 0.10, 16% for celecoxib and 0.11 +/- 0.04, 7% for placebo (p<0.001, both comparisons).²⁵ In a similar double-blind, placebo-controlled trial using video capsule endoscopy in healthy adults, celecoxib use was associated with significantly fewer small bowel mucosal breaks than ibuprofen plus omeprazole.²⁶ The mean number of small bowel mucosal breaks per subject and the percentage of subjects with these mucosal breaks were 0.7/25.9% for ibuprofen/omeprazole compared to 0.2/6.4% for celecoxib and 0.1/7.1% for placebo (p < 0.001, both comparisons). There were no significant differences between celecoxib and placebo in any measure.²⁶ In a prospective, open labeled, randomized, controlled trial comparing the efficacy of celecoxib with that of PPI therapy (lansoprazole) along with an NSAID (naproxen) in the reduction of incidence of ulcer relapse in patients with a history of NSAID-related peptic ulcer, celecoxib was found to be non-inferior to combination PPI/NSAID therapy.²⁵ During a median follow-up of 24 weeks, 4 (3.7%, 95% confidence interval [CI] 0.0%-7.3%) patients in the celecoxib group,

compared with 7 patients (6.3%, 95% CI 1.6%-11.1%) in the lansoprazole group, developed recurrent ulcer complications (absolute difference -2.6%; 95% CI for the difference -9.1%-3.7%).²⁵

Therapy with COX-2 inhibitors compared to nonselective NSAIDs may be associated with a lower incidence of both upper and lower GI adverse events.^{1,4-6,8,10,27-30} For example, a comparative study of celecoxib and traditional NSAIDs determined that celecoxib, when used for 6 months in a dosage 2 to 4 times the maximum therapeutic dosage, is associated with a lower incidence of combined clinical upper GI events than the comparators, ibuprofen and diclofenac, used at standard therapeutic dosages.²⁷

Although there appears to be a synergism between *Helicobacter pylori* and the formation of peptic ulcer and bleeding,³¹ the diagnosis of *H. pylori* alone is not included in the criteria for approval. Guidelines for the treatment of *H. pylori* suggest discontinuation of NSAID agents during eradication therapy and ulcer healing, if possible.³¹ There is insufficient data indicating that use of COX-1 sparing agents instead of nonselective NSAIDs decrease the risk of an adverse GI event in *H. pylori* positive patients.³²

In addition to a past history of ulcer disease, pharmacoepidemiologic studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as treatment with oral corticosteroids, treatment with oral anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.¹ Corticosteroid drugs do not independently cause ulcer disease. The use of these drugs in conjunction with NSAIDs however increases the risk of a GI event approximately twofold.^{6,12} Patients with the diagnosis of rheumatoid arthritis (RA) may be at an increased risk for developing a GI adverse event because RA patients are likely to be prescribed corticosteroids as part of their treatment regimen.¹² The patient's previous prescription claims are used to identify the patient's potential risk for an NSAID-induced ulcer complication. Concomitant oral anticoagulant use also increases the risk of peptic ulcer bleed in the setting of NSAID therapy.¹² The increase in risk ranges from two- to 12-fold, depending upon the patient population being studied.^{4,5,6,11,13,34} Clinical literature does document that smoking and alcohol may be factors in the pathogenesis of peptic ulcer disease, but the evidence for alcohol and smoking as risk factors for NSAID-related GI events has been inconsistent.³⁵⁻⁴²

Age alone puts patients at a higher risk for developing a GI-adverse event.^{4,5,6,11,12} There does not appear to be a threshold age where the risk of a GI complication increases abruptly; rather, the risk of a complication appears to increase gradually with advancing age.^{4,5,6,11,12} Thus, the older the patient is, the greater is their risk of a GI complication.

Medical Diagnoses Criteria

The intent of the identification of patients with certain medical diagnoses is to allow coverage of COX-2 inhibitor therapy in members at high risk for adverse events from nonselective NSAID therapy or those with a diagnosis (familial adenomatous polyposis) requiring the COX-2 inhibitor celecoxib. Selected medical diagnoses are used to identify patients for pre-approval of COX-2 inhibitor therapy through the implementation process. The client identifies plan members with the ICD-9 codes included in the following table:

Table 1: Medical Diagnoses Option Detail

EVENT	ICD-9CM Code*
Ulcer and/or bleed, Duodenal	532, 532.X, 532.XX
Ulcer and /or bleed, Peptic	533, 533.X, 533.XX
Ulcer and /or bleed, Gastric	531, 531.X, 531.XX
Familial Adenomatous Polyposis	211, 211.X, 211.XX

*The Medical Diagnoses Criteria will approve ICD-9 codes of three, four, or five digits to ensure that members who have been assigned incomplete codes will be included for COX-2 therapy.

These patients would be exempt from the prior authorization process.

ELECTRONIC EDITS

The overall process for step therapy requires that another drug or drugs be tried for a specific quantity of drug in the previous time period before the claim drug. If the patient has met any of the requirements outlined below, the requested step therapy medication will be paid under the patient's current prescription benefit. If the patient does not meet the step therapy criteria, then the system will reject with the message indicating that prior authorization is necessary. The Prior Authorization (PA) criteria for approval would then be applied to requests submitted by the patients' practitioner for evaluation.

The intent of the initial step therapy edit is to electronically identify patients that may have a contraindication for the non-selective NSAID (those that inhibit both cyclooxygenase-1 and cyclooxygenase-2). The system edit reviews claims that have a days supply that begins or ends within 120 days prior to the new COX-2 claim. Contraindications to the non-selective NSAIDs are identified by detecting medications in the claims history that are indicators for a previous or future gastrointestinal (GI) adverse event.

The initial step therapy edit will electronically identify patients who are taking or have taken an oral anticoagulant or systemic corticosteroid in the 120 days prior to the current COX-2 inhibitor claim. The electronic edit will also identify patients who are taking or have taken a nonselective NSAID with misoprostol or proton pump inhibitor (PPI), including the combination products, Arthrotec[®] (diclofenac sodium/misoprostol) and Prevacid[®] NapraPac[®] (lansoprazole/naproxen), in the previous 120 days. A 120 day timeframe was selected to accommodate various treatment regimens of these medications. Some of these regimens, such as oral corticosteroids, may be taken intermittently for flairs of ulcerative colitis or atopic dermatitis. The claims system is designed to identify and count any oral anticoagulant or systemic corticosteroid claim with a days supply that overlaps into the 120-day look-back period. For claims with a 30 day supply the system would identify any claim submitted in the previous 1 to 150 days. For a 90 day supply, the system would identify any claim submitted in the previous 1 to 210 days.

The initial step therapy edit will also electronically identify patients who are 50 years of age or older and will allow use of a COX-2 inhibitor based on the patient's age alone

Patients who are currently receiving therapy with celecoxib will be allowed continuation of therapy without meeting the above edit requirements if a claim for celecoxib is identified within 90 days prior to the new claim. The claims system is designed to identify any claim with a days supply that ends within the 90-day look-back parameter.

Table 2: Summary of COX2 Step Therapy

Targeted Agent(s)	Celebrex (GPI: 661005*****)
Is auto-grandfathering implemented? (with look-back time frame)	Yes (90 days ^a)
Prerequisite Agent(s)	systemic corticosteroid (GPI 2210*****), warfarin (GPI 83200030*****), NSAID (GPI 661000*****) plus PPI (GPI 4927*****) or Zegerid (GPI 499960*****) or misoprostol (GPI 49250030*****) or Arthrotec (GPI 661099022003**) or Prevacid NapraPac (GPI 661099024264**)
Number of prerequisites required	1
Prerequisite look-back time frame	120 days ^b
Age-related edit?	Edit applied to patients < 50 years of age
Additional comments	

a - The system searches for a claim with a days supply that begins or ends in the past 90 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 120 days prior to the new claim. For claims dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 180 days.

b - The system searches for a claim with a days supply that begins or ends in the past 120 days. For claims with a 30 day supply the system would be able to identify a claim processed for payment between 1 and 150 days prior to the new claim. For claims dispensed as an extended days supply (90 days), the system would identify a claim processed between 1 and 210 days.

Celecoxib prescribed in a patient with a history of one of the diagnoses listed above (Medical Diagnoses Criteria) will require prior authorization if the medical diagnosis (ICD-9 code) has not been documented in medical claims data.

Prior Authorization (PA) Criteria for Approval

The intent of the *PA Criteria for Approval* is to ensure that patients who are at a greater risk for a GI-adverse event when using non-selective NSAIDs (by diagnoses, medications or medical history) are identified and approved. The criteria for approval repeat the electronic step therapy requirements to ensure that all previous therapies that meet the criteria are taken into account. In addition, patients with a prior history of peptic ulcer, regardless of cause, are approved through the PA review process. Patients with past or present ulcer and current *H. pylori* infection will be approved through the prior authorization process based on the ulcer history. Although a poor health status and long term disease may increase the patients' risk for a GI bleed, patients are not automatically approved because they have a chronic disease (e.g., rheumatoid arthritis) unless their medication history increases their risk. Patient smoking and alcohol use will be evaluated in the context of persistent or permanent physiologic changes. Patients prescribed celecoxib to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP) will also be granted a manual approval.

The length of the PA approval for selection elements that will not change is indefinite. Age greater than 50 years or history of GI bleed, GI obstruction, GI perforation, peptic ulcer, or use of celecoxib for colorectal polyps will be approved indefinitely through the PA process. Indefinite approvals may be subject to re-evaluation if selection criteria change or safety issues become apparent. Approvals for concurrent use of an oral anticoagulant or systemic corticosteroid or for any other condition which may change will be for 12 months.

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Celebrex (celecoxib)

Initial and Renewal Evaluation

1. Is the patient currently being treated with Celebrex?
If yes, approve for 12 months. If no, continue to 2.
2. Is the patient 50 years of age or older?
If yes, approve indefinitely. If no, continue to 3.
3. Please indicate if the patient has a history or current diagnosis of one of the following?
 - a) Peptic ulcer (includes duodenal and stomach)
 - b) Gastrointestinal (GI) bleed
 - c) GI obstruction
 - d) GI perforation
 - e) NoneIf a-d, approve indefinitely. If e, continue to 4.
4. Does the patient have a current diagnosis or medical history that puts the patient at increased risk of developing a GI adverse event?
If yes, approve for 12 months. If no, continue to 5.
5. Is the patient currently taking an oral anticoagulant [e.g., Coumadin (warfarin)]?
If yes, approve for 12 months. If no, continue to 6.
6. Is the patient currently taking systemic corticosteroids on a regular basis (i.e., long-term daily or pulse-therapy)?
If yes, approve for 12 months. If no, continue to 7.

7. Is the patient currently taking a nonselective NSAID and misoprostol or a PPI, including the combination product Arthrotec (diclofenac sodium/misoprostol) or Prevacid Naprapac (lansoprazole/naproxen)?
If yes, approve for 12 months. If no, continue to 8.
8. Is the practitioner prescribing Celebrex (celecoxib) to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP)?
If yes, approve for indefinitely. If no, deny.

SUMMARY

The COX-2 inhibitors step therapy edit is designed to identify patients electronically by their medication history and to provide automatic payment of claims when the patient's medication history indicates current or recent use of an oral anticoagulant, a systemic corticosteroid, or a nonselective NSAID with misoprostol or a PPI, including the combination product Arthrotec (diclofenac sodium/misoprostol) or Prevacid Naprapac (lansoprazole/naproxen). Claims will also automatically pay if the member is age 50 or older. The step therapy process allows for automatic payment of these agents when a medical diagnosis for a GI condition putting the member at high risk for adverse events from nonselective NSAID therapy or a diagnosis of FAP is documented. The PA review process allows for individual review of claims for COX-2 inhibitors to identify patients who have a history for, or are at a greater risk for developing, a GI adverse event that is not apparent on electronic claims history. The step therapy edit optimizes the use of first line generic agents before the COX-2 inhibitors.

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