



BlueCross BlueShield of Nebraska

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COX-2 INHIBITORS

Preauthorization Criteria for Approval

Medications and Dosage Forms Included in Criteria

Generic Name	Brand Name	Dosage Form(s)
Celecoxib	Celebrex [®]	Oral capsules

FDA Approved Indications

Carefully consider the potential benefits and risks of Celebrex[®] (celecoxib) and other treatment options before deciding to use Celebrex. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals¹.

Celebrex is indicated¹:

- For relief of the signs and symptoms of osteoarthritis
- For relief of the signs and symptoms of rheumatoid arthritis
- 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[®] (diclofenac sodium/misoprostol), or nonselective NSAID with a proton-pump inhibitor (PPI) which includes the combination product Prevacid[®] Naprapac[®] (lansoprazole/naproxen). 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. Does the patient have 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. Does the patient have a history or current diagnosis that may put the patient at increased risk for developing a GI adverse event as indicated by use of an oral anticoagulant [e.g., Coumadin[®] (warfarin sodium)] or systemic corticosteroids on a regular basis (i.e., long-term daily, weekly, or pulse-therapy)?
If yes, approve 12 months.
If no, continue to 4.
4. Is Celebrex[®] (celecoxib) being prescribed to reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis (FAP)?
If yes, approve indefinitely.
If no, continue to 5.
5. Is the patient currently taking a nonselective NSAID and misoprostol, including the combination product Arthrotec[®] (diclofenac sodium/misoprostol), or taking a nonselective NSAID and a PPI, including the combination product Prevacid[®] Naprapac[®] (lansoprazole/naproxen)?
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.^{2,3} Pain and inflammation is mediated by the inhibition of COX-2.^{2,3} The use of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of pain, inflammation, and fever is widespread across the globe.^{3,4} 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.⁵⁻¹² 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[®]). Rofecoxib (Vioxx[®]) was voluntarily withdrawn from the market in 2004¹³ and valdecoxib (Bextra[®]) was voluntarily withdrawn in 2005.¹⁴ 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.^{14,15} The “black box” warning indicates the potential for cardiovascular risk and encourages avoiding NSAIDs in high risk individuals.^{14,15} 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.¹⁴⁻²⁰

Studies have shown there is an increased risk for upper gastrointestinal (GI) events due to nonselective NSAID use^{1,2,6,21} and some evidence shows a possible increase in lower GI adverse events.²²⁻²⁴ COX-2 inhibitors may lower the incidence of upper and lower GI adverse events when compared to nonselective NSAIDs.^{1,2,6-8,10,22,23,25} 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.¹⁰ 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.^{10,26} 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.²⁶ 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.^{1,26}

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.^{20,27} The decision depends primarily on a patients' individual risk factors for developing NSAID-induced GI complications.^{2,6,7,27} 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.^{1,2,6,7,21} The most important risk factor for developing peptic ulcer disease and/or an upper GI bleed is having a medical history of either condition.^{28,29} Misoprostol (Cytotec[®]) 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.^{30,31} Patients with GI adverse effects while utilizing nonselective NSAIDs may add misoprostol or use the diclofenac sodium/misoprostol medication (Arthrotec[®]). 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. Patients with GI adverse effects while utilizing a nonselective NSAID and a PPI (including the combination product Prevacid[®] Naprapac[®]) will also be reviewed for candidates for celecoxib.

Peptic ulcer disease is strongly correlated with *Helicobacter pylori* infection, however, this association has not been confirmed in NSAID-induced ulcer patients.³² However, if the patient is *H. pylori* positive the NSAID should be discontinued if possible to assist in eradication and healing.^{32,33} 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.³³

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.^{1,2,6,7,21} Systemic corticosteroids do not cause ulcer disease alone, however, their use with NSAID therapy may increase the risk of GI adverse events two-fold.^{2,28} Concomitant use of an anticoagulant and NSAIDs increases the risk of peptic ulcer bleeding two- to twelve-fold.^{2,6,7,21,28,29} 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.^{32,34-41}

A patient's age alone can confer a higher-risk for GI complications due to NSAID use.^{2,6,25,28-30,32,35,37,39-42} The risk for GI complications increases gradually with increasing age²⁸, however, the data does suggest that the elderly population is at increased risk from NSAID utilization.^{2,6,25,28-30,32,35,37,39-42} Studies vary in the age range used to assess GI complication rates for the elderly and range from 60 years of age and older^{28,29,32,35,39-41}, 65 years of age and older^{2,6,37,39,41-43}, 66 years and older²⁵, and 75 years of age and older.³⁰ 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.^{1,2,25,41,43}

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 (≤ 325 mg/day). Some COX-2/NSAID comparator trials have included aspirin utilizing participants.^{10,12,44} 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.⁸ 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.⁸

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.⁴⁵ 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.⁴⁵ Other pharmacodynamic studies have shown diclofenac, sulindac, celecoxib, and meloxicam may not interfere with aspirin at the COX-1 binding site.^{46,47} Without a randomized controlled trial the clinical implication of this interaction is uncertain, however, is important considering the cardioprotective effect of aspirin.⁴⁵

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[®] (warfarin sodium)];
- c. A prescription for a systemic corticosteroid;
- d. A prescription for a nonselective NSAID and misoprostol (Cytotec[®]), including the combination product diclofenac sodium/misoprostol (Arthrotec[®]);
- e. A prescription for a nonselective NSAID and a PPI, including the combination product lansoprazole/naproxen (Prevacid[®] Naprapac[®]).

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, lansoprazole (including the combination product Prevacid[®] Naprapac[®]) or misoprostol (including the combination product Arthrotec[®]) 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 [†]
➤ 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

[†]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

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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
05/28/09	Update PA Criteria	Annual review – updated references and provided NSAIDs that can be used with aspirin that do not interfere with the cardioprotective effects of aspirin.
04/23/10	Update PA Criteria	Annual review – updated language around other NSAID/PPI combinations that allow for Celebrex approval similar to the diclofenac/misoprostol edit

Preauthorization Criteria History

06/26/08	Reviewed by QMC
07/01/08	Preauthorization criteria original effective date
05/28/09	Updated criteria reviewed and approved by QMC
04/23/10	Updated criteria reviewed and approved by MPC
Nov. 2010	Next Review