STEP THERAPY POLICY

POLICY: Cycloxygenase-2 Inhibitor Step Therapy Policy
- Celebrex® (celecoxib capsules – Pfizer, generic)

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OVERVIEW

Celebrex is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the following conditions:
- Osteoarthritis (OA);
- Rheumatoid arthritis;
- Juvenile rheumatoid arthritis in patients ≥ 2 years of age;
- Ankylosing spondylitis;
- Acute pain; and
- Primary dysmenorrhea.

Celecoxib works primarily by inhibiting prostaglandin synthesis by way of cyclooxygenase-2 (COX-2) and at therapeutic concentrations in humans, celecoxib does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.[1] Overall, it appears that celecoxib and NSAIDs have similar clinical efficacy at equipotent doses for the management of acute and chronic pain and other conditions associated with pain; however, individual responses to NSAIDs vary among patients for reasons that are not well understood.

Safety

Like other NSAIDs, celecoxib labeling includes Boxed Warnings related to risk of serious cardiovascular (CV) and gastrointestinal (GI) adverse events.[1] Various studies have attempted to characterize relative differences between celecoxib and other NSAIDs regarding CV and GI risks. In the PRECISION trial (published) [n = 24,801], celecoxib, ibuprofen, and naproxen were similar regarding rate of major adverse CV events when used chronically for osteoarthritis or rheumatoid arthritis.[2] In addition, clinically significant GI adverse events occurred at similar rates across treatment groups. Of note, patients with CV disease or at high risk of CV disease were excluded from the study.

Celecoxib is also contraindicated in the setting of coronary artery bypass graft surgery. Additionally, it is contraindicated if a patient has a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs.[1] Although some data have suggested that COX-2 inhibitors may be used safely in patients with asthma-exacerbated respiratory disease, most of these trials have involved rofecoxib (not commercially available in the US) rather than celecoxib. In a 2014 meta-analysis, only four of the 14 included studies involved celecoxib and all of the trials were very small (< 40 patients with aspirin-exacerbated respiratory disease each).[3] Additionally, the duration of exposure was short across all studies (up to 7 days).

Guidelines/Consensus Statements

In 2019, the American College of Rheumatology (ACR) updated recommendations for management of OA of the hand, hip, and knee.[4] Oral NSAIDs as a class are strongly recommended, although the guideline does not address relative merits of different NSAIDs. Doses should be as low as possible and for as short a time as possible to mitigate AE potential. Older ACR guidelines (2012) provide more specific recommendations.[5] Regarding knee OA, the guidelines recommend that in patients with a history of a symptomatic or complicated upper GI ulcer but no history of an upper GI bleed in the past year, a COX-2 inhibitor or a nonselective NSAID in combination with a proton pump inhibitor (PPI) should be the choice

if an NSAID has to be used. If patients have had an upper GI bleed within the past year and an oral NSAID is still recommended, it is suggested to use a COX-2 inhibitor in combination with a PPI. Whenever an NSAID is utilized for the management of knee or hip OA chronically, a PPI should be considered to reduce the risk of symptomatic or complicated upper GI events. If a patient with OA is taking low-dose aspirin (≤ 325 mg per day) for cardioprotection and an oral NSAID is needed, it is recommended to use a nonselective NSAID other than ibuprofen in combination with a PPI; a COX-2 inhibitor should not be used in this situation.

OA Research Society International guidelines (2019) for non-surgical management of knee, hip, and polyarticular OA also comment on the role of COX-2 inhibitors.[6] In the setting of knee OA, COX-2 inhibitors and other NSAIDs are given equal support (Level 1B) for patients without comorbidities. For patients with GI comorbidities, COX-2 inhibitors are preferred (Level 1B) over non-selective NSAIDs + PPI (Level 2). Recommendations are overall similar for hip and polyarticular OA.

In 2019, the American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults.[7] The Beers Criteria lists sixteen non-COX selective NSAIDs (e.g., ibuprofen, naproxen, diclofenac) where chronic use should be avoided. The rationale is that these NSAIDs increase the risk of GI bleeding or peptic ulcer disease in high-risk groups, which includes patients > 75 years of age or taking parenteral corticosteroids, anticoagulants or antiplatelet agents. The quality of evidence is moderate and the strength of the recommendation is strong. The Beers Criteria also notes that in patients with a history of gastric or duodenal ulcers, non-COX-2 selective NSAIDs should be avoided because it may exacerbate existing ulcers or cause new or additional ulcers.

Effect on Platelets

In two studies in healthy volunteers, and in patients with OA and established heart disease, respectively, celecoxib (200 mg to 400 mg daily) has demonstrated a lack of interference with the cardioprotective antiplatelet effect of aspirin (100 mg to 325 mg). Celebrex is not a substitute for aspirin for CV prophylaxis.[1] Other NSAIDs have demonstrated variable effects on COX-1 inhibition; reports of COX-2 selectivity are confounded by study methods and assay used, and studies conducted in vitro are not always well correlated with COX selectivity in humans.[8,9] Differences in pharmacokinetic profiles of NSAIDs also result in heterogeneous effects on COX inhibition across the dosing interval for the respective products.[10] In 2006, the FDA issued a science paper regarding the concomitant use of ibuprofen and aspirin and the potential for attenuation of the antiplatelet effect of aspirin.[11] Patients who may be adversely affected by reduced platelet function (e.g., patients with coagulation disorders, patients receiving anticoagulants) should be carefully monitored.

Surgery

Some data are available that describe the effects of celecoxib short-term in settings related to surgery (the preoperative/perioperative/postoperative setting) and noted favorable effects (e.g., reduced low bleeding risk, decreased opioid use).[12-16] Guidelines on the management of postoperative pain from the American Pain Society (2016) recommend acetaminophen and/or NSAIDs as part of multimodal analgesia for management of postoperative pain in patients without contraindications.[17] It is noted that GI risks are thought to be lower with celecoxib vs. nonselective NSAIDs. Celecoxib is also recommended preoperatively for patients who are undergoing major surgery; association with reduced opioid requirements is noted in the guideline. The evidence was considered insufficient to recommend a preoperative dose of nonselective NSAIDs.

POLICY STATEMENT

This program has been developed to encourage the use of two Step 1 drugs (oral NSAIDs) prior to the use of the Step 2 drug (generic celecoxib). Approval for a Step 3 drug (brand Celebrex) may be authorized if the patient has tried two Step 1 drugs (oral NSAIDs) and has tried the Step 2 drug (generic celecoxib). If the Step Therapy rule is not met for the requested drug at the point of service, coverage will be determined by the Step Therapy criteria below. All approvals are provided for the duration noted below.

Automation: A patient with a history of two Step 1 drugs (oral NSAIDS) within the 130-day look-back period can receive the Step 2 drug (generic celecoxib). A patient can receive the Step 3 drug (brand Celebrex) if the patient has a history of two Step 1 drugs (oral NSAIDS) and the Step 2 drug (generic celecoxib) within the 130-day look back period. Also, this policy contains automation for patients receiving warfarin, clopidogrel, Effient® (prasugrel tablets), Brilinta™ (ticagrelor tablets), Xarelto® (rivaroxaban tablets), Pradaxa® (dabigatran capsules), Eliquis® (apixaban tablets), and Savaysa™ (edoxaban tablets).

Step 1 (oral NSAIDs):

- diclofenac potassium
- diclofenac sodium (IR and ER)
- diclofenac sodium and misoprostol
- etodolac (IR and ER)
- flurbiprofen
- ibuprofen
- indomethacin (IR and ER)
- ketoprofen IR 50 mg and 75 mg
- ketorolac (tablets)
- meclofenamate
- mefenamic acid
- meloxicam
- nabumetone
- naproxen**
- oxaprozin
- piroxicam
- sulindac
- tolmetin**

**Some generic naproxen and tolmetin products are not Step 1 products

Step 2: generic celecoxib capsules

Step 3: brand Celebrex capsules

CRITERIA

1. Approve the Step 2 drug (generic celecoxib) for 1 year if the patient meets one of the following (A, B, C, D, or E):
   A) Patient has tried two Step 1 drugs (oral NSAIDs), either as prescription products or as over-the-counter (OTC) products, at prescription-strength doses for the current condition; OR
   B) Patient is currently taking chronic systemic corticosteroid therapy (e.g., prednisone), warfarin, clopidogrel, Effient® (prasugrel tablets), Brilinta™ (ticagrelor tablets), Xarelto® (rivaroxaban tablets), Pradaxa® (dabigatran capsules), Eliquis® (apixaban tablets), Savaysa™ (edoxaban tablets), chronic aspirin therapy, fondaparinux injection or a low molecular weight heparin product (i.e., enoxaparin injection, Fragmin® [dalteparin injection]); OR
   C) Patient has reduced platelet counts or other coagulation disorders; OR
   D) Patient is > 75 years of age and is using celecoxib for a chronic condition; OR
   E) Patient has had a documented upper gastrointestinal bleed from a duodenal or gastric ulcer.

2. Approve the Step 2 drug (generic celecoxib) for 30 days if the patient is using the drug during the preoperative/perioperative/postoperative period.

3. Approve the Step 3 drug (brand Celebrex) for 1 year if the patient meets the following (A and B):
   A) Patient meets one of the following (i, ii, iii, iv, or v):

i. Patient has tried two Step 1 products (oral NSAIDs) either as prescription products or as over-the-counter (OTC) products at prescription-strength doses, for the current condition; OR
ii. Patient is currently taking chronic systemic corticosteroid therapy (e.g., prednisone), warfarin, clopidogrel, Effient® (prasugrel tablets), Brilinta™ (ticagrelor tablets), Xarelto® (rivaroxaban tablets), Pradaxa® (dabigatran capsules), Eliquis® (apixaban tablets), Savaysa™ (edoxaban tablets), chronic aspirin therapy, fondaparinux injection or a low molecular weight heparin product (i.e., enoxaparin injection, Fragmin® [dalteparin injection]); OR
iii. Patient has reduced platelet counts or other coagulation disorders; OR
iv. Patient is > 75 years of age and is using celecoxib for a chronic condition; OR
v. Patient has had a documented upper gastrointestinal bleed from a duodenal or gastric ulcer; AND

B) Patient has tried the Step 2 drug (generic celecoxib).

4. Approve the Step 3 drug (brand Celebrex) for 30 days if the patient meets both of the following (A and B):
A) Patient is using the drug during the preoperative/perioperative/postoperative period.
B) Patient has tried the Step 2 drug (generic celecoxib).

REFERENCES

1. Celebrex® capsules [prescribing information]. New York, NY: Pfizer, Inc.; May 2019.
2. Nissen SE, Yeomans ND, Solomon DH, et al, for the PRECISION Trial Investigators. Cardiovascular safety of celecoxib, naproxen, or ibuprofen for arthritis. *N Engl J Med*. 2016;375(26):2519-29.
3. Morales DR, Lipworth BJ, Guthrie B, et al. Safety risks for patients with aspirin-exacerbated respiratory disease after acute exposure to selective nonsteroidal anti-inflammatory drugs and COX-2 inhibitors: meta-analysis of the controlled clinical trials. *J Allergy Clin Immunol*. 2014;134(1):40-45.
4. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guidelines for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2020;72(2):149-162.
5. Hochberg MC, Altman RD, Toupin K, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken)*. 2012;64(4):465-474.
6. Bannuru RR, Osani MC, Baysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage. 2019;27(11):1578-1589. Available at: https://www.oarsijournal.com/article/S1063-4584(19)31116-1/pdf. Accessed on August 12, 2020.
7. The American Geriatric Society 2019 Beers Criteria Update Expert Panel. American Geriatric Society 2019 Updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019;67:674-594.
8. Kerola M, Vuolteenaho K, Kosonen O, et al. Effects of nimesulide, acetylsalicylic acid, ibuprofen and nabumetone on cyclooxygenase-1- and cyclooxygenase-2-mediated prostanoid production in healthy volunteers ex vivo. *Basic Clin Pharmacol Toxicol*. 2009;104(1):17-21.
9. Blain H, Boileau C, Lapicque F, et al. Limitation of the in vitro whole blood assay for predicting the COX selectivity of NSAIDs in clinical use. *Br J Clin Pharmacol*. 2002;53(3):255-265.
10. Grosser T, Ricciotti E, FitzGerald GA. The cardiovascular pharmacology of nonsteroidal anti-inflammatory drugs. *Trends Pharmacol Sci*. 2017;38(8):733-748.
11. Food and Drug Administration Science Paper. Concomitant use of ibuprofen and aspirin: potential for attenuation of the anti-platelet effect of aspirin. September 8, 2006.
12. Teerawattananon C, Tantayakom P, Suwanawiboon B, Katchamart W. Risk of perioperative bleeding related to highly selected cyclooxygenase-2 inhibitors: a systematic review and meta-analysis. *Semin Arthritis Rheum*. 2017;46(4):520-528.
13. Zhou F, Du Y, Huang W, et al. The efficacy and safety of early initiation of preoperative analgesia with celecoxib in patients underwent arthroscopic knee surgery: a randomized, controlled study. *Medicine* (*Baltimore*). 2017;96(42):e8234.
14. Carpenter PS, Shepherd HM, McCrary H, et al. Association of celecoxib use with decreased opioid requirements after head and neck cancer surgery with free tissue reconstruction. *JAMA Otolaryngol Head Neck Surg*. 2018;144(11):988-994.
15. Bergstrom JE, Scott ME, Alimi Y, et al. Narcotics reduction, quality, and safety in gynecologic oncology surgery in the first year of enhanced recovery after surgery protocol implementation. *Gynecol Oncol*. 2018;149(3):554-559.
16. Nelson G, Dowdy SC, Lasala J, et al. Enhanced recovery after surgery (ERAS®) in gynecologic oncology – Practical considerations for program development. *Gynecol Oncol*. 2017;147:617-620.
17. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guidelines from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of

Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. 2016;17(2):131-157.