



STEP THERAPY POLICY

POLICY: Nonsteroidal Anti-Inflammatory Drugs Step Therapy Policy

REVIEW DATE: 04/12/2023

NSAID	Product	Manufacturer
Diclofenac	Cataflam® tablets (brand obsolete 11/17/2022), generic	Novartis, generic
	diclofenac sodium delayed-release tablets (generic only)	Generic only
	Lofena™ tablets, generic	Carwin, generic
	Voltaren® XR extended-release tablets (obsolete 03/01/2021), generic	Novartis, generic
	Zorvolex® capsules, authorized generic (35 mg only)	Iroko
	Zipsor® capsules, generic	Assertio
	Cambia® powder for oral solution, generic	Assertio, generic
	Arthrotec® (diclofenac and misoprostol tablets), generic	Pfizer, generic
	diclofenac 1.5% solution (generic only)	Generic only
	Flector® (diclofenac epolamine 1.3% topical patch), authorized generic	Institut Biochimique SA, generic
	Licart™ (diclofenac epolamine 1.3% topical system)	Institut Biochimique SA
	Pennsaid® (diclofenac sodium 2% topical solution, generic)	Horizon, generic
	Voltaren® Gel (diclofenac sodium 1% topical gel [brand obsolete 3/1/2021]), generic [OTC topical gel available]	Endo, generic
Etodolac	Lodine® tablets, generic	Sallus, generic
	etodolac capsules (generic only)	Generic only
	etodolac extended-release tablets (generic only)	Generic only
Fenoprofen	Nalfon® capsules and tablets (generic to tablets only)	Xspire, generic
	Fenortho® capsules	Sterling Knight
	Fenoprofen capsules (brand)	Various
Flurbiprofen	flurbiprofen tablets (generic only)	Generic only
Ibuprofen	ibuprofen capsules, tablets, and oral suspension [OTC capsules, tablets, chewable tablets, oral suspension available]	Generic only
	Duexis® (ibuprofen and famotidine tablets, generic)	Horizon, generic
Indomethacin	indomethacin capsules and extended-release capsules (generic only)	Generic only
	Indocin® oral suspension	Iroko
	Tivorbex® capsules, authorized generic	Iroko
Ketoprofen	ketoprofen capsules and extended-release capsules (generic only)	Generic only
Ketorolac	ketorolac tablets (generic only)	Generic only
	Sprix® (ketorolac nasal spray, authorized generic)	Egalet
Meclofenamate	meclofenamate capsules (generic only)	Generic only
Mefenamic acid	mefenamic acid capsules (generic only)	Generic only
Meloxicam	Mobic® tablets (brand obsolete 4/1/2022), generic	Boehringer Ingelheim, generic
	Vivlodex™ capsules, generic	Iroko, generic
	meloxicam oral suspension (generic)	Generic only

Nabumetone	Relafen® tablets (brand obsolete 11/17/2022), generic	Blucrest, generic
	Relafen® DS tablets	Carwin
Naproxen	Naprosyn® tablets and oral suspension, generic [OTC tablets available]	Canton, generic
	EC-Naprosyn® delayed-release tablets, generic	Canton, generic
	Anaprox DS® controlled-release tablets, generic	Canton, generic
	Naprelan® controlled-release tablets, generic	Almatica, generic
	Vimovo® (naproxen and esomeprazole delayed-release tablets, generic)	Horizon, generic
Oxaprozin	Daypro® tablets, generic	Pfizer, generic
Piroxicam	Feldene® capsules, generic	Pfizer, generic
Sulindac	sulindac tablets (generic only)	Generic only
Tolmetin	tolmetin capsules and tablets (product obsolete 11/8/2022)	Generic only

NSAID – Nonsteroidal anti-inflammatory drug; OTC – Over-the-counter.

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Cigna National Formulary Coverage:

OVERVIEW

Nonsteroidal anti-inflammatory drugs (NSAIDs) are indicated primarily for the **treatment of acute and chronic conditions that require an agent with analgesic and anti-inflammatory activity**, although other uses exist.¹ For example, Cambia® (diclofenac potassium oral solution) is the only NSAID indicated for the acute treatment of migraine attacks with or without aura in adults ≥ 18 years of age²; however, other NSAIDs are also supported in clinical practice guidelines.³

Overall, it appears that NSAID products have similar clinical efficacy when given at equipotent doses for the management of acute pain and other pain-related conditions; however, individual responses to NSAIDs may vary among patients for reasons that are not well understood. No one product can be distinguished from

another on a consistent basis. All of the products have Boxed Warnings outlining cardiovascular (CV) and gastrointestinal (GI) risks.

Guidelines and Recommendations

The American College of Rheumatology (ACR)/Arthritis Foundation hand, hip, and knee osteoarthritis (OA) guidelines (2019) strongly recommend topical NSAIDs for knee OA and conditionally recommend topical NSAIDs for hand OA.⁴ Topical NSAIDs are not expected to be efficacious in hip OA due to the depth of the affected joint. Oral NSAIDs are strongly recommended in hand, hip, and knee OA and are recommended over all other oral therapies. These agents are the mainstay of pharmacological management of OA. Safe use of NSAIDs is recommended, including utilization of the lowest possible doses for the shortest period of time.. The relative merits of different oral NSAIDs were considered outside the scope of the guideline review.

The European League Against Rheumatism (EULAR) hand OA guidelines (2018) state that optimal management of hand OA generally requires a multidisciplinary approach, including non-pharmacological therapies and pharmacological therapies.⁵ The guidelines specifically recommend topical treatments as preferred over oral therapies because of safety reasons. Topical NSAIDs are the first pharmacological topical treatment of choice for hand OA. The guidelines cite pooled safety data comparing topical diclofenac gel with placebo, which showed similar low rates of AEs in subgroups of low-risk versus high-risk patients (≥ 65 years of age with comorbid hypertension, type 2 diabetes or cerebrovascular and/or CV disease). The guidelines additionally note that when a large number of joints are affected, oral pharmacological treatment may be preferred.

OA Research Society International guidelines for non-surgical management of knee, hip, and polyarticular OA (2019) comment on oral and topical NSAID use in a variety of settings.⁶ For knee OA, topical NSAIDs are strongly recommended (Level 1A) for patients without comorbidities, as well as for patients with GI or CV comorbidities. For patients with GI comorbidities, selective COX-2 inhibitors and nonselective oral NSAIDs, in combination with a PPI, were conditionally recommended due to their benefits on pain and functional outcomes. Topical and oral NSAIDs are both conditionally recommended in the setting of widespread pain; it is noted that for topical NSAIDs, the number of joints being treated should be monitored due to potential risk of exceeding recommended doses. Oral NSAIDs, but not topical NSAIDs, are conditionally recommended in the setting of hip OA.

Beers Criteria

In 2019, the American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults.⁴⁹ The Beers Criteria acknowledge that many nonselective NSAIDs increase the risk of GI bleeding or peptic ulcer disease in high-risk groups, which include patients > 75 years of age or taking parenteral corticosteroids, anticoagulants, or antiplatelet agents. It is noted that use of a proton pump inhibitor (PPI) or misoprostol reduces but does not eliminate the risks.

The Beers Criteria also note that in patients with a history of gastric or duodenal ulcers, non-cyclooxygenase-2 selective NSAIDs should be avoided because they may exacerbate existing ulcers or cause new or additional ulcers. The quality of evidence is moderate and the strength of the recommendation is strong. Indomethacin and ketorolac (including the parenteral formulation) should be avoided due to the GI risks and acute kidney injury in older adults. Indomethacin is more likely to cause central nervous system AEs and appears to have the most AEs among the NSAIDs. In patients with kidney or urinary tract disease (creatinine clearance < 30 mL/min) it is noted that NSAIDs (non-COX and COX selective, oral and parenteral, nonacetylate salicylates) may increase the risk of acute kidney injury and further decline in renal function. It is recommended to avoid these agents.

POLICY STATEMENT

This program has been developed to encourage the use of two Step 1a Products prior to the use of a Step 2a Product. Of note, naproxen/esomeprazole delayed-release tablets (Vimovo, generic) and ibuprofen/famotidine tablets (Duexis, generic) are not included in Step 2a. A trial of one prescription naproxen product (Step 1b) and one prescription proton pump inhibitor (PPI) [Step 1b] is required prior to the use of naproxen/esomeprazole delayed-release tablets (Vimovo, generic) [Step 2b]. A trial of one prescription oral ibuprofen product (Step 1c) and one prescription oral histamine₂ receptor antagonist (H₂RA) [Step 1c] is required prior to the use of ibuprofen/famotidine tablets (Duexis, generic) [Step 2c]. If the Step Therapy rule is not met for a Step 2 Product (a, b or c) at the point of service, coverage will be determined by the Step Therapy criteria below. All approvals are provided for 1 year in duration.

Nonsteroidal Anti-Inflammatory Drug product(s) is(are) covered as medically necessary when the following step therapy criteria is(are) met. Any other exception is considered not medically necessary.

Step 1a/2a

Step 1a NSAIDs:

- | | | |
|---------------------|---------------------|-----------------------|
| • Cataflam | • diclofenac sodium | • ketorolac (tablets) |
| • diclofenac | topical solution | • meclofenamate |
| potassium 50 mg | 1.5%* | • mefenamic acid |
| • diclofenac | • etodolac (IR and | • meloxicam tablets |
| potassium 25 mg | ER) | • nabumetone |
| capsules | • flurbiprofen | • naproxen** |
| • diclofenac sodium | • ibuprofen | • oxaprozin |
| (IR and ER) | • indomethacin (IR | • piroxicam |
| • diclofenac sodium | and ER) | • sulindac |
| and misoprostol | • ketoprofen IR 50 | • tolmetin 200 mg |
| | mg and 75 mg | |

Step 2a NSAIDs:

- | | | |
|--|---|--|
| • Anaprox DS | epolamine 1.3% patch* | • Pennsaid 2%* |
| • Arthrotec | • Indocin | • Qmiiz |
| • Cambia, diclofenac potassium powder packet | • ketoprofen ER 200 mg | • Relafen |
| • Daypro | • ketoprofen IR 25 mg | • Relafen DS |
| • diclofenac potassium 25 mg tablets | • Licart* | • Sprix, ketorolac nasal spray |
| • diclofenac sodium 1% topical gel* | • Lodine | • Tivorbex, indomethacin 20 mg capsule |
| • diclofenac sodium 2% topical solution* | • Lofena | • tolmetin 400 mg, 600 mg |
| • Feldene | • meloxicam capsules | • Vivlodex |
| • Fenoprofen (brand), fenoprofen 600 mg | • meloxicam suspension | • Voltaren Gel 1%* |
| • Fenortho | • Mobic | • Voltaren XR |
| • Flector patch, diclofenac | • Nalfon | • Zipsor |
| | • Naprelan and generics | • Zorvolex, diclofenac 35 mg capsule |
| | • Naprosyn, EC-Naprosyn, and generic suspension | |

IR – Immediate-release; ER – Extended-release

* Denotes topical product

** Some generic naproxen products are Step 2a

Step 1b/2b**Step 1b (brand or generic):**

- Prescription naproxen sodium
- Prescription naproxen

AND

- | | |
|---------------------------------------|--|
| • Prescription dextlansoprazole | • Prescription omeprazole magnesium |
| • Prescription esomeprazole magnesium | • Prescription omeprazole/sodium bicarbonate |
| • Prescription esomeprazole strontium | • Prescription pantoprazole (oral) |
| • Prescription lansoprazole | • Prescription rabeprazole |
| • Prescription omeprazole | |

Step 2b NSAID:

- Vimovo
- naproxen/esomeprazole delayed-release tablets

Step 1c/2c**Step 1c (brand or generic):**

- Prescription ibuprofen (oral)

AND

- Prescription cimetidine (oral)
- Prescription famotidine (oral)
- Prescription nizatidine (oral)
- Prescription ranitidine (oral)

Step 2c NSAID:

- Duexis
- ibuprofen/famotidine tablets

CRITERIA

Step 2a NSAIDs

1. If the patient has tried two different Step 1a prescription-strength NSAIDs for the current condition, approve a Step 2a NSAID.

Note: Celecoxib is accepted as a generic NSAID. Also, over-the-counter (OTC) NSAIDs count as alternatives if the patient used prescription-strength doses.

2. If the patient has tried ibuprofen suspension, approve naproxen suspension, meloxicam suspension, or Indocin suspension.

Note: OTC ibuprofen suspension would count as an alternative.

3. If the patient has tried generic diclofenac sodium topical solution 1.5% and the patient has difficulty swallowing or cannot swallow tablets or liquid dosage forms (solution/suspension), approve ketorolac nasal spray (Sprix, authorized generic), Pennsaid 2%, diclofenac sodium 2% topical solution, Flector Patch, diclofenac epolamine 1.3% patch, Licart topical system, diclofenac sodium 1% topical gel, or Voltaren Gel.

4. If the patient has tried generic diclofenac sodium topical solution 1.5% and the patient has a chronic musculoskeletal pain condition (e.g., osteoarthritis) and is at risk of NSAID-associated toxicity, approve Pennsaid 2%, diclofenac sodium 2% topical solution, diclofenac sodium 1% topical gel, or Voltaren Gel.

Note: Examples of risk factors of NSAID-associated toxicity include patients with a previous gastrointestinal bleed, history of peptic ulcer disease, impaired renal function, cardiovascular disease, hypertension, heart failure, elderly patients with impaired hepatic function, or taking concomitant anticoagulants.

5. If the patient has tried generic diclofenac sodium topical solution 1.5% and the patient has hand or knee osteoarthritis, approve Pennsaid 2%, diclofenac sodium 2% topical solution, diclofenac sodium 1% topical gel, or Voltaren Gel.

Step 2b NSAID (Vimovo, generic)

1. If the patient has tried one prescription proton pump inhibitor (PPI) [e.g., omeprazole, lansoprazole, pantoprazole] and one prescription naproxen product (brand or generic), approve naproxen/esomeprazole delayed-release tablets (Vimovo, generic).

Note: Do not approve naproxen/esomeprazole delayed-release tablets (Vimovo, generic) if the patient has only tried over-the-counter (OTC) naproxen, NSAIDs other than naproxen, a COX-2 inhibitor (celecoxib), or OTC PPIs.

Note: Separate trials of a prescription PPI and a prescription naproxen product are required; a previous trial of Vimovo or generic naproxen/esomeprazole does not count.

Step 2c NSAID (Duexis, generic)

1. If the patient has tried one prescription histamine₂ receptor antagonist (H₂RA) [e.g., famotidine, ranitidine, nizatidine] and one prescription ibuprofen product (brand or generic), approve ibuprofen/famotidine tablets (Duexis, generic).

Note: Do not approve ibuprofen/famotidine tablets (Duexis, generic) if the patient has only tried over-the-counter (OTC) ibuprofen, NSAIDs other than ibuprofen, a COX-2 inhibitor (celecoxib), or OTC H₂RAs.

Note: Separate trials of a prescription H₂RA and a prescription ibuprofen product are required; a previous trial of Duexis or generic ibuprofen/famotidine does not count.

REFERENCES

1. Facts and Comparisons Online®. Wolters Kluwer Health, Inc.; Last updated August 10, 2021. Available at: <http://fco.factsandcomparisons.com/action/home>. Accessed on April 7, 2023. Search term: Nonsteroidal anti-inflammatory agents.
2. Cambia® oral solution [prescribing information]. Lake Forest, IL: Assertio; April 2021.
3. American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019; 59:1-18.
4. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020; 72(2):220-233.
5. Kloppenburg M, Kroon F, Blanco FJ, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. *Ann Rheum Dis*. 2019; 78:16-24.
6. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. *Osteoarthritis Cartilage*. 2019; 27(11):1578-1589.
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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	<p>Cataflam: The policy was clarified to note that Cataflam is a Step 1a product. Previously, this was listed in Step 2a.</p> <p>Diclofenac potassium: Clarification was added to note that diclofenac potassium 25 mg tablets are Step 2a; diclofenac potassium 50 mg remains Step 1a.</p> <p>Lofena: Lofena was added to Step 2a.</p> <p>Motrin: Brand Motrin was removed from Step 2a; this product has been obsolete > 3 years.</p> <p>Sprix: Clarified that authorized generic ketorolac nasal spray is also Step 2a.</p> <p>Tivorbex: Clarified that authorized generic indomethacin 20 mg capsule is also Step 2a.</p> <p>Tolmetin: Clarified that the Step 1a strength is 200 mg.</p> <p>Zorvolex: Clarified that authorized generic diclofenac 35 mg capsule is also Step 2a.</p>	04/13/2022
Selected Revision	<p>Diclofenac potassium 25 mg capsules: Diclofenac potassium 25 mg capsules were added to Step 1a (diclofenac potassium 25 mg tablets remain Step 2a).</p>	05/04/2022
Update	<p>06/21/2022: No criteria changes. In criteria for naproxen/esomeprazole tablets (Vimovo, generic), a Note was added to clarify that the required trials of a prescription proton pump inhibitor and prescription naproxen product must be separate trials; a previous trial of Vimovo or generic naproxen/esomeprazole does not count. In criteria for ibuprofen/famotidine tablets (Duexis, generic), a Note was added to clarify that the required trials of a prescription histamine-2 receptor antagonist and prescription ibuprofen product must be separate trials; a previous trial of Duexis or generic ibuprofen/famotidine does not count.</p>	--
Selected Revision	<p>Diclofenac sodium 2% topical solution: This product was added to Step 2a.</p> <p>Criteria: In the exception regarding difficulty swallowing, it was noted that the same exception which applies to Sprix also applies to the authorized generic ketorolac nasal spray. Additionally, the same exceptions which apply to Pennsaid 2% also apply to generic diclofenac sodium 2% topical solution.</p>	06/29/2022
Selected Revision	<p>Meloxicam suspension: Meloxicam suspension was added to Step 2a. In exception criteria, it was added that meloxicam suspension can be approved if the patient has tried ibuprofen suspension.</p>	08/10/2022
Selected Revision	<p>Diclofenac potassium powder packets: Diclofenac potassium powder packet (generic to Cambia) was added to Step 2a.</p>	01/11/2023
Annual Revision	No criteria changes.	04/12/2023

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