This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Health Insurance Marketplace and KeyRx formularies.

This is a FlexRx standard and GenRx standard step therapy program.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

**FDA APPROVED INDICATIONS AND DOSAGE**¹⁻³⁻⁷

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosage and Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Flector®</strong> (diclofenac epolamine)</td>
<td>Topical treatment of acute pain due to minor strains, sprains, and contusions</td>
<td>One patch to the most painful area twice a day</td>
</tr>
<tr>
<td>180 mg topical patch (1.3% in aqueous base)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pennsaid®</strong> (diclofenac sodium)</td>
<td>Treatment of signs and symptoms of osteoarthritis of the knee(s)</td>
<td>40 drops per knee, 4 times daily; apply 10 drops at a time;</td>
</tr>
<tr>
<td>1.5% topical solutionᵃ</td>
<td></td>
<td>40 mg (2 pump actuations) per knee, 2 times daily.</td>
</tr>
<tr>
<td>2% topical solution</td>
<td></td>
<td>Application of Pennsaid in an amount exceeding or less than the recommended dose has not been studied and is therefore not recommended</td>
</tr>
<tr>
<td><strong>Voltaren Gel®</strong> (diclofenac sodium)</td>
<td>Relief of the pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands. Voltaren Gel has not been evaluated for use on the spine, hip, or shoulder</td>
<td>Apply gel to affected area 4 times daily</td>
</tr>
<tr>
<td>1% topical gelᵃ</td>
<td></td>
<td>Lower extremities: (knees, ankles, feet)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose is 4 grams per joint;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum daily dose is 16 grams to any single joint</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Upper extremities: (elbows, wrists, hands)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose is 2 grams per joint;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maximum daily dose is 8 grams to any single joint</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total dose should not exceed 32 grams/day over all affected joints</td>
</tr>
</tbody>
</table>

ᵃ – available as generic

**CLINICAL RATIONALE:**
Efficacy

Acute Pain

The American Family Physician review suggest that data were insufficient to make conclusions regarding comparisons of topical vs. oral NSAIDs, a specific topical NSAID vs. another, or different formulations of the same topical NSAID.¹¹

A 2016 review suggests topical NSAIDs are good options for acute musculoskeletal pain in patients at risk of adverse effects from oral NSAIDs who present with a focal area pain. Topical agents are only effective for treating more superficial structures.⁶

A Cochrane Review (2015) evaluating topical NSAIDs for acute pain due to strains, sprains, or sports/overuse type injuries found there were insufficient data to reliably compare individual topical NSAIDs with each other or the same oral NSAID.⁵

Osteoarthritis (OA)

A review on treatment of OA (American College of Physicians, 2014) suggests management should always begin with non-pharmacologic and nonsurgical strategies. Two major reasons substantiate this initial approach. First, there is a large body of evidence on the therapeutic efficacy of non-pharmacologic interventions. Second, pharmacologic interventions, particularly NSAID-related injury to the GI, renal, and central nervous systems, have the potential for toxicity. Pharmacologic agents should be offered only when more conservative efforts have failed to improve function. Many prescription and OTC agents are available for medical management of OA. Surgery should be a last resort.⁹

- There are several recommended first-line agents for OA, depending on comorbid conditions, age, and level of pain. Acetaminophen in doses up to 4 g/day is often the first choice for mild to moderate pain associated with OA. Advocacy for its front-line role stems from comparable efficacy to NSAIDs with a safer GI profile. NSAIDs may be added or substituted in patients who respond inadequately to acetaminophen.
- NSAIDs are also considered by many physicians to be the preferred first-line agents in medical management of OA. However, routine use of NSAIDs in OA has disadvantages. All NSAIDs, both non-selective and cyclo-oxygenase (COX)-2 selective, are associated with significant potential toxicity, particularly among the elderly.
- Topical NSAIDs have been found to be effective in relieving pain compared with placebo for both OA of the hand and knee joints. An attractive feature of this approach is reduced adverse GI reactions by maximizing local delivery and minimizing systemic toxicity. Although these topical agents can be associated with local side effects, such as rash, itching, and burning, they are usually minimal. These medications are attractive first-line agents for patients wishing to avoid systemic therapy.

The American Academy of Orthopedic Surgeons (2013) recommended the following for treatment of OA of the knee.⁸

- NSAIDs (oral or topical) or tramadol are recommended for patients with symptomatic OA of the knee. [Strong recommendation; high level evidence]
- The panel was unable to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic OA of the knee. (Inconclusive recommendation)

The American College of Rheumatology (ACR, 2012) recommended the following treatments for OA of the hands and knees.⁴

- For initial treatment of hand OA, ACR recommended use of one or more of the following- topical capsaicin, topical NSAIDs (including trolamine salicylate), oral NSAIDs (including COX2 selective inhibitors), or tramadol. They recommended not using intraarticular therapies, or opioid analgesics. They recommend persons age >75
years use topical rather than oral NSAIDs. In persons age <75 years, they have no preference for using topical rather than oral NSAIDs.

- For initial treatment of knee OA, ACR recommended use of one of the following: acetaminophen, oral NSAIDs, topical NSAIDs, tramadol, or intraarticular corticosteroid injections. They recommend not using the following: chondroitin sulfate, glucosamine, and topical capsaicin. They have no recommendations regarding intraarticular hyaluronates, duloxetine, and opioid analgesics. If patients lack satisfactory response to full-dose acetaminophen, the panel strongly recommends oral or topical NSAIDs or intraarticular corticosteroid injections. Do not use oral NSAIDs in patients with contraindications to these agents and be aware of their warnings/precautions. For persons age >75 years, the panel strongly recommends the use of topical rather than oral NSAIDs.

A 2016 review suggests topical NSAIDs are as effective as oral NSAIDs and generally safer, but only effective for OA of more superficial joints such as hands and knees. Topical NSAIDs may be preferred over oral NSAIDs in patients age >75 for hand and knee OA. For multiple or deep arthritic joints, oral NSAIDs are easier to use and more efficacious. 6

Up to Date recommends that pharmacologic therapy should only be used during periods when symptoms are present, since none of the interventions have been shown to be disease-modifying. In patients with one or a few joints affected, especially knee and/or hand OA, initiate pharmacotherapy with topical NSAIDs due to their similar efficacy compared with oral NSAIDs and their better safety profile. Use of oral NSAIDs is recommended in patients with inadequate symptom relief from topical NSAIDs, symptomatic OA in multiple joints, and/or patients with hip OA. Use the lowest dose required to control the patient’s symptoms on an as needed basis.10

**Safety**
Flector, Pennsaid, and Voltaren contain the following black box warning:1-3

- Cardiovascular risk
  - Non steroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
  - NSAIDs are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

- Gastrointestinal Risk
  - NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

For additional clinical information see the Prime Therapeutics Formulary Chapters 10.3A: Anti-inflammatory Analgesics and 14.5FF: Topical Anti-inflammatory Agents.

**REFERENCES**
2. Pennsaid (1.5%) prescribing information. Horizon Pharma Inc. May 2016.
5. Cochrane Data System Review 2015;6: CD007402
Topical NSAID (Non-Steroidal Anti-Inflammatory Drug; Flector, Pennsaid, Voltaren Gel) Step Therapy

OBJECTIVE
The intent of the Topical NSAID Step Therapy (ST) criteria is to encourage the use of cost-effective generic oral or topical non-steroidal anti-inflammatory drug (NSAID) agents before the target topical agents, and to accommodate for the use of target agents due to previous trial, documented intolerance, FDA labeled contraindication or hypersensitivity to generic oral and topical NSAIDs. Requests for target agents will be reviewed when patient-specific documentation has been provided.

TARGET AGENTS – STEP THERAPY
Flector® (diclofenac patch)
Pennsaid® 1.5% (diclofenac solution)b
Pennsaid® 2% (diclofenac solution)
Voltaren Gel® (diclofenac gel)a
a – generic available and is prerequisite in step therapy program
b – only available as generic and is prerequisite in step therapy program

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Target Agents will be approved when ONE of the following are met:
1. The patient’s medication history includes use of any generic oral or topical NSAID (non-steroidal anti-inflammatory drug) agent in the past 90 days
   OR
2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to generic oral and topical NSAID agent that is not expected to occur with the requested agent

Length of approval: 12 months

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents.
Step Therapy Supplement

This program applies to FlexRx Closed, FlexRx Open, GenRx Closed, GenRx Open, Health Insurance Marketplace, FocusRx and KeyRx formularies.

Please note, this does not include or apply to quantity limit questions.

STEP THERAPY SUPPLEMENT

OBJECTIVE

The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

CONDITIONS FOR APPROVAL

The requested agent will be approved when ONE of the following are met:

1. The patient is currently being treated with the requested agent as indicated by ALL of the following:
   a. A statement by the prescriber that the patient is currently taking the requested agent
      AND
   b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
      AND
   c. The prescriber states that a change in therapy is expected to be ineffective or cause harm


2. The patient's medication history include the required prerequisite/preferred agent(s) as indicated by:
   a. Evidence of a paid claim(s) within the past 999 days
   OR
   b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event

3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm

Length of Approval: As per program specific criteria