

Therapeutic Class Overview

Topical Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

INTRODUCTION

- Osteoarthritis (OA) is a key area where topical formulations of nonsteroidal anti-inflammatory drugs (NSAIDs) are used. OA, the most common form of arthritis, causes signs and symptoms such as pain, tenderness, reduced range of motion, bony swelling, joint deformity, and instability. Symptoms typically appear in one or a few joints in a middle-aged or older person, and are often progressive (*Doherty et al 2016*).
- The number of U.S. adults affected by OA has increased in the last several decades due to aging of the population and the increasing prevalence of obesity. Approximately 30 million U.S. adults are affected by OA, up from 21 million in 1995 (*Centers for Disease Control and Prevention 2017, Suri et al 2012*).
- Oral NSAIDs are effective for the treatment of moderate to severe pain, but are associated with an increased risk of several gastrointestinal (GI) and cardiovascular adverse events. The NSAID products as a class, including topical products, carry a Boxed Warning regarding the risk of cardiovascular and GI adverse events associated with their use. However, the use of topical NSAIDs applied directly to the affected area reduces overall systemic absorption and minimizes the risk of severe adverse events (*Galer 2011*). The adverse events associated with the topical NSAIDs are typically dermatologic in nature and are self-limiting in most cases.
- Diclofenac is the only NSAID commercially available in topical formulations. There are currently 3 formulations available, and Food and Drug Administration (FDA)-approved indications vary among products.
- The following products are included within this review:
 - Flector (diclofenac epolamine patch, 1.3%) is indicated for the topical treatment of acute pain due to minor strains, sprains, and contusions. Flector is composed of an adhesive material containing 1.3% diclofenac epolamine applied to a polyester felt backing.
 - Pennsaid (diclofenac sodium topical solution, 1.5%) is indicated for the treatment of signs and symptoms of OA of the knee(s); and higher strength Pennsaid (diclofenac sodium topical solution, 2%) is indicated for the treatment of pain of OA of the knees. Pennsaid contains diclofenac sodium as well as the penetration enhancer dimethyl sulfoxide (DMSO) and other inactive ingredients.
 - Voltaren (diclofenac sodium topical gel, 1%) is indicated for the relief of pain of OA of joints amenable to topical treatment, such as the knees and those of the hands. Voltaren provides diclofenac sodium in a white gel base.
- Medispan class: Anti-inflammatory Agents - Topical

Table 1. Medications Included Within Class Review

Drug	Generic Availability
diclofenac sodium topical solution 1.5%*	✓
Flector (diclofenac epolamine patch) 1.3%	-
Pennsaid (diclofenac sodium topical solution) 2%	-
Voltaren (diclofenac sodium topical gel) 1%	✓

*Pennsaid 1.5% solution is no longer marketed; however, generic formulations are available.

(*Drugs@FDA 2017, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2017*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Flector (diclofenac epolamine patch)	diclofenac sodium topical solution 1.5%	Pennsaid (diclofenac sodium topical solution) 2%	Voltaren (diclofenac sodium topical gel)
Treatment of acute pain due to minor strains, sprains and contusions	✓			
Relief of the pain of OA of joints amenable to topical treatment, such as				✓

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Indication	Flector (diclofenac epolamine patch)	diclofenac sodium topical solution 1.5%	Pennsaid (diclofenac sodium topical solution) 2%	Voltaren (diclofenac sodium topical gel)
the knees and those of the hands				
Treatment of signs and symptoms of OA of the knee(s)		✓		
Treatment of the pain of OA of the knee(s)			✓	

(Prescribing information: Flector 2016, diclofenac 1.5% 2016, Pennsaid 2% 2016, Voltaren 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Two studies evaluated the use of diclofenac patch vs placebo patch in patients with acute injuries.
 - Patients who had experienced a sports-related sprain, strain, or contusion experienced a statistically significant improvement in scores for pain and functioning following application of the diclofenac epolamine patch over 14 days ($p = 0.036$ and $p = 0.048$, respectively) (Galer et al 2000).
 - Patients with a minor soft tissue injury experienced an 18.2% reduction in visual analog scale (VAS) pain scores following twice-daily application of the diclofenac epolamine patch over 14 days ($p = 0.002$) (Kuehl et al 2011).
- The efficacy and safety of diclofenac gel have been evaluated in patients with OA of the hands and knees in an 8-week study. Study results demonstrated greater pain relief, Australian/Canadian Osteoarthritis Hand Index (AUSCAN) score improvement, and global rating of disease with diclofenac sodium gel compared to placebo in patients with OA of the hand (Altman et al 2009). In patients with OA of the knee, treatment with diclofenac gel for 12 weeks led to greater improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score, WOMAC physical function score, and global rating of disease (Barthel et al 2009). Additionally, a 12-month, open-label study in patients with OA of the knee demonstrated sustained long-term improvement compared to baseline for WOMAC pain scores, stiffness, and physical function (Peniston et al 2011).
- In a study by Simon et al, patients with OA of the knee treated with topical diclofenac sodium 1.5% solution achieved statistically significant reductions in pain scores compared to patients treated with placebo (-6 vs -4.7; $p = 0.015$) and dimethyl sulfoxide alone (-6 vs -4.7; $p = 0.009$). There was no statistically significant difference in pain scores compared to patients receiving diclofenac tablets (-6 v. -7; $p = 0.429$) (Simon et al 2009).
- The safety and efficacy of diclofenac 2% solution were evaluated in a phase 2, randomized, double-blind, parallel-group, placebo-controlled, 4-week clinical trial in patients with osteoarthritis of the knee (N = 260). A reduction of 4.5 in the WOMAC pain score was noted in the diclofenac 2% group as compared to a 3.6 reduction in the placebo vehicle group ($p = 0.04$) (Wadsworth et al 2016).
- The clinical effectiveness of the gel and solution formulations has not been compared in any head-to-head trials. However, a single-dose patient preference trial in 24 healthy volunteers demonstrated a preference for the solution formulation on several characteristics, including odor/smell, oiliness/greasiness, and stickiness/tackiness (Galer et al 2011).
- A systematic review of 19 trials summarized the benefits of diclofenac solution, gel, and patch based on clinical studies comparing the topical diclofenac products to placebo or oral NSAIDs. Key reported outcomes included:
 - Superiority of diclofenac patch and gel over placebo for the treatment of acute pain due to blunt impact injuries or ankle sprains
 - Superiority of diclofenac gel and solution over placebo for pain due to OA of the knee
 - Superiority of diclofenac gel over placebo for pain relief due to epicondylitis and peri-arthritis, and superiority of diclofenac patch over placebo for epicondylitis
 - Similar efficacy of diclofenac gel and/or diclofenac liquid with DMSO compared to oral NSAIDs for several outcomes including pain relief due to OA of the hand and knee and acute musculoskeletal injury (Zacher et al 2008)
- A recent meta-analysis of 9 randomized trials evaluated topical diclofenac therapy (patch, solution, or gel) compared to placebo or vehicle for the treatment of OA. The combined data demonstrated significantly improved pain scores with

topical diclofenac compared to the control group (standard mean difference, 0.4; 95% confidence interval [CI], 0.19 to 0.62; $p = 0.0003$). The data also suggested an improvement in function scores, but further studies on this endpoint would be required to confirm the results (*Deng et al 2016*).

- In a Cochrane review, data from an analysis of 39 double-blind, randomized controlled trials comparing topical NSAIDs to placebo, oral NSAIDs, or other topical treatments demonstrated a small benefit of topical NSAIDs compared to a placebo vehicle in patients with chronic musculoskeletal conditions. Treatment success was achieved in 60% of patients treated with topical diclofenac vs 50% of patients treated with a placebo vehicle. The analysis also demonstrated similar efficacy with topical NSAIDs and oral NSAIDs, with treatment success in 55% and 54% of patients, respectively (*Derry et al 2016*).
- Another Cochrane review focused on the use of topical NSAIDs for acute musculoskeletal pain, including sprains, strains, contusions, tendinitis, and acute low back pain. A total of 61 double-blind, randomized controlled trials comparing topical NSAIDs to topical placebo or an oral NSAID were included. Overall, topical NSAID formulations provided good levels of pain relief in acute conditions. The majority of the recent data is for topical diclofenac, and this recent data is of higher quality than earlier data. Based on 10 studies, 74% of patients treated with topical diclofenac experienced a successful treatment outcome, compared to 47% with placebo (RR, 1.6; 95% CI, 1.5 to 1.7). Data was not sufficient to compare the efficacy of different topical NSAIDs or of oral vs topical formulations of the same NSAID.
 - Topical NSAIDs were not associated with an increase in local or systemic adverse events compared to topical placebo. There were fewer systemic adverse events with topical vs oral treatment; however, this was based on limited data (*Derry et al 2015*).

CLINICAL GUIDELINES

- According to the American College of Rheumatology (ACR) 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in OA of the hand, hip, and knee:
 - For the initial management of OA pain of the hand, topical capsaicin, oral or topical NSAIDs, or tramadol may be used. In patients > 75 years of age, topical NSAIDs are preferred over oral formulations.
 - For the initial management of OA pain of the knee, acetaminophen, NSAIDs (oral or topical), tramadol, or intraarticular corticosteroid injections may be used. In patients > 75 years of age, topical NSAIDs are preferred over oral formulations.
 - No one topical NSAID product is recommended over another within the guidelines (*Hochberg et al 2012*).
- According to the American Academy of Orthopedic Surgeons (AAOS) 2013 Guidelines for the treatment of OA of the knee:
 - Acupuncture, lateral wedge insoles, and glucosamine and chondroitin are not recommended.
 - NSAIDs (oral or topical) or tramadol are recommended.
 - There is inconclusive evidence to recommend either for or against the use of acetaminophen, opioids, pain patches, or intraarticular corticosteroids.
 - No one topical NSAID product is recommended over another within the guidelines (*AAOS 2013*).
- According to the Osteoarthritis Research Society International (OARSI) 2014 guidelines for the non-surgical management of knee OA:
 - Appropriate treatments vary based on patient-specific comorbidities and whether patients have knee-only OA or multi-joint OA.
 - Topical NSAIDs are recommended as appropriate in patients with knee-only OA, but their use in patients with multi-joint OA is uncertain and will depend on an assessment of individual patients' risks and benefits.
 - No one topical NSAID product is recommended over another within the guidelines (*McAlindon et al 2014*).
- According to the Veterans Affairs (VA)/Department of Defense (DOD) clinical practice guideline for the non-surgical management of hip and knee OA:
 - In patients with no contraindications to pharmacologic therapy, clinicians should consider acetaminophen or oral NSAIDs as first-line treatment.
 - The recommendation to use topical NSAID therapy as an alternative to oral NSAIDs is supported by evidence from studies that have compared various topical and oral NSAIDs in patients with knee OA. The results have consistently shown that the topical and oral formulations of any given NSAID are similar in terms of improvement in pain and function in patients with knee OA.

- For topical NSAIDs collectively, the reduction in the incidence of GI events has been shown to be 36% relative to the oral formulations. However, there is insufficient evidence to compare topical and oral NSAIDs in terms of serious GI adverse events (perforation, ulcers or bleeding).
- The decision to use a topical NSAID (vs oral NSAID with or without proton pump inhibitor) should be based on consideration of patient preference, adverse event potential (including GI adverse events), and resource utilization.
- No studies have directly compared the solution and gel formulations in patients with OA (VA/DOD 2014).

SAFETY SUMMARY

- Flector, Pennsaid, and Voltaren carry a boxed warning for:
 - Cardiovascular thrombotic events
 - NSAIDs cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
 - GI risk
 - NSAIDs cause an increased risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These reactions can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.
- Despite low systemic blood levels relative to oral NSAIDs, the topical NSAIDs carry a number of warnings and precautions related to potential systemic events, including:
 - Anaphylactic reactions
 - Exacerbation of asthma related to aspirin sensitivity
 - Heart failure and edema; avoid use in patients with severe heart failure
 - Hematologic toxicity
 - Hepatotoxicity
 - Hypertension
 - Premature closure of fetal ductus arteriosus; avoid use in pregnant women starting at 30 weeks gestation
 - Renal toxicity and hyperkalemia; avoid use in patients with advanced renal disease
 - Serious skin reactions
- The most common adverse reactions for the topical NSAIDs are application site reactions, such as dermatitis, pruritus, burning, dryness, and erythema.
- Warnings specific to the topical administration of NSAID products include the following:
 - The potential exists for a small child or pet to suffer serious adverse effects from chewing or ingesting a Flector patch. Even a used Flector patch contains a large amount of diclofenac. It is important for patients to store and dispose of the patch out of the reach of children and pets.
 - Avoid contact of diclofenac with eyes and mucosa.
 - Avoid exposure to natural or artificial sunlight on treated areas because studies in animals indicated topical diclofenac treatment resulted in earlier onset of ultraviolet light-induced skin tumors.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
diclofenac sodium topical solution	1.5% topical solution	Topical	Four times daily	Apply to clean, dry skin; do not apply heat or occlusive dressings
Flector (diclofenac epolamine patch)	1.3% topical patch	Topical	Twice daily	Should not be applied to non-intact or damaged skin; should not be worn while bathing or showering
Pennsaid (diclofenac sodium topical)	2% topical solution	Topical	Twice daily	Apply to clean, dry skin; do not apply heat or occlusive dressings

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Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
solution)				
Voltaren (diclofenac sodium topical gel)	1% gel	Topical	Four times daily	Use enclosed dosing card to measure dose Apply to clean, dry, intact skin; do not apply heat or occlusive dressings.

See the current prescribing information for full details.

CONCLUSION

- NSAIDs are commonly used for the treatment of pain due to OA or minor strains, sprains, and contusions. The topical application of NSAIDs may reduce the risk of severe adverse events associated with oral NSAID use. Diclofenac is currently the only NSAID available in topical formulations.
- Flector is available as a 1.3% patch and is indicated for acute pain due to minor strains, sprains, and contusions. Pennsaid is available as a 1.5% topical solution and is indicated for the treatment of signs and symptoms of OA of the knee(s). A higher strength formulation of Pennsaid (2%) has also been made available; it is indicated for the treatment of pain of OA of the knees. Voltaren is available as a 1% topical gel and is indicated for the relief of pain of OA of joints amenable to topical treatment, such as the knees and those of the hands. Of the topical NSAIDs, Pennsaid 1.5% and Voltaren 1% are available generically. Branded Pennsaid 1.5% solution is no longer marketed.
- The topical products carry many of the same warnings as their respective orally-administered products; however, systemic absorption is generally low, and the most frequent adverse events are administration site reactions.
- Guidelines from ACR, AAOS, ORSI, and VA/DOD recommend the use of topical NSAIDs for the treatment of OA (for specific joints), however, they do not recommend one topical NSAID product over another (*Hochberg et al 2012*).

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