

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 2017*).
- 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.
- Solaraze (diclofenac sodium gel) is the only topical NSAID indicated for actinic keratoses. Actinic keratosis is a common cutaneous lesion, usually found on sun-exposed areas such as the head, neck, forearms, and hands in older, fair-skinned patients. Actinic keratosis is considered a potential premalignant lesion that may progress to squamous cell carcinoma. For patients with a single lesion, a few low-risk lesions, or thin lesions, treatment with cryotherapy, topical 5-fluorouracil, imiquimod, diclofenac, or ingenol mebutate may be considered (*de Berker et al 2017, Shoimer et al 2010*).
- 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.
 - Licart (diclofenac epolamine topical system, 1.3%), which shares the same indication as Flector, is a topical system comprised of an adhesive material containing 1.3% diclofenac epolamine which is applied to a non-woven polyester felt backing and covered with a polypropylene film release liner. Licart differs from Flector in that it is applied once daily, while Flector is applied twice daily.
 - 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.
 - Solaraze (diclofenac sodium topical gel, 3%) is indicated for the topical treatment of actinic keratoses. In addition to sun avoidance measures, diclofenac sodium topical gel (3%) is effective for lesions of the scalp, forehead, face, arm, forearm, and back of the hand. Solaraze provides diclofenac sodium in a gel base including benzyl alcohol, hyaluronate sodium, 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.
- A number of therapy packs, compounding products, and compounding kits (ie, EnovaRx, Rexaphenac, etc) are available; however, these products are excluded from this review.
- Medispan class: Anti-inflammatory Agents – Topical; Diclofenac sodium (actinic keratoses)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
diclofenac sodium topical solution 1.5%*	✓
diclofenac sodium topical gel 3%†	✓

Drug	Generic Availability
Flector (diclofenac epolamine patch) 1.3%	✓
Licart (diclofenac epolamine topical system) 1.3%	⬇️‡
Pennsaid (diclofenac sodium topical solution) 2%	-
Voltaren (diclofenac sodium topical gel) 1%	✓

*Pennsaid 1.5% solution is no longer marketed; however, branded generic (ie, Klofensaid II, etc) and generic formulations are available.

‡Solaraze 3% topical gel is no longer marketed; however, generic formulations are available.

⬇️Launch plans are pending.

(Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Flector (diclofenac epolamine patch)	diclofenac sodium topical solution 1.5%	diclofenac sodium topical gel 3%	Licart (diclofenac epolamine) system 1.3%	Pennsaid (diclofenac sodium topical solution) 2%	Voltaren (diclofenac sodium topical gel) 1%
Treatment of acute pain due to minor strains, sprains and contusions	✓			✓		
Treatment of actinic keratoses*			✓			
Relief of the pain of OA of joints amenable to topical treatment, such as 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)					✓	

*Sun avoidance is indicated during therapy.

(Prescribing information: Flector 2018, diclofenac 1.5% 2016, Licart 2018, Pennsaid 2% 2016, Solaraze 2016, Voltaren 2018)

- 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 vs -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 safety and efficacy of diclofenac epolamine topical system 1.3% (Licart) was based on 2 placebo- and active-controlled studies in patients with minor sprains, strains, and/or contusions. Patients were randomized to receive Licart, placebo, or Flector (diclofenac epolamine patch 1.3%) once daily for 7 or 14 days. The primary efficacy endpoint was the mean change from baseline in pain on movement to day 3 of treatment. In both studies, Licart demonstrated a statistically significant difference vs placebo for the reduction in pain on movement at day 3. Conclusions regarding comparative efficacy of Licart vs Flector cannot be made because Flector was not administered according to its approved twice daily dosing regimen (*Licart prescribing information 2018*).
- 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 (relative risk [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*).
- The clinical effectiveness of diclofenac sodium topical gel (3%) was evaluated in 427 patients, of whom 213 were treated with diclofenac sodium topical gel (3%) and had actinic keratosis lesions. In trials, significantly more patients treated with diclofenac sodium topical gel (3%) had complete clearing of lesions on the scalp (36% vs 13%; $p = 0.09$), forehead (39% vs 19%; $p = 0.001$), and face (47% vs 20%; $p = 0.002$) vs a vehicle alone. However, results were not significantly different for application to the arm/forearm ($p = 0.20$) or the back of hand ($p = 0.36$). Overall rates of clearing ranged from 18 to 47% in trials (*Solaraze prescribing information 2016*).
- One Cochrane review evaluated topical, oral, mechanical, and chemical interventions (totaling 24 different treatments) for actinic keratosis across 83 RCTs with 10,036 patients. A total of 60 trials evaluated 18 topical creams or gels. In those trials that evaluated topical diclofenac sodium 3% gel compared to a vehicle, diclofenac was associated with a significant improvement in complete clearance of lesions (32% vs 13%; RR, 2.46; 95% CI, 1.66 to 3.66) in 3 studies with 420 patients. There was also a significant increase in number of patients who withdrew from trials due to adverse events (RR, 3.59; 95% CI, 1.92 to 6.70) in 4 trials with 592 patients (*Gupta et al 2012*).

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 (updated guidelines are due to be published later in 2019):
 - 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).
- The British Association of Dermatologists (BAD) guidelines for the management of actinic keratoses recommend the following:
 - Treatment needs to address a wide range of variables including the nature of the actinic keratosis, the body site, patient preference, the premorbid state of the patient and previous treatments tried.
 - For mild actinic keratosis, treatment options include no treatment or emollient only.
 - Depending on severity, location, and other factors, topical and oral treatment options include 5-fluorouracil (strength of recommendation A), imiquimod (strength of recommendation A), diclofenac gel (strength of recommendation A), ingenol mebutate (strength of recommendation A), topical retinoids (strength of recommendation B), and systemic therapies (strength of recommendation C).
 - Overall, data with diclofenac gel indicate moderate efficacy with low morbidity in mild actinic keratoses. Treatment was well tolerated and reported adverse effects were mainly pruritus (41% estimated after 30 days' treatment) and rash (40% estimated after 60 days) (*de Berker et al 2017*).

SAFETY SUMMARY

- Diclofenac sodium topical solution, Flector, **Licart**, Pennsaid, Solaraze, 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. These events were also observed in the first 10 to 14 days following coronary artery bypass graft (CABG) surgery via 2 large clinical trials. All agents are contraindicated in the setting of coronary artery bypass graft surgery. 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 or **Licart topical system**. Even a used Flector patch or **Licart topical system** contains a large amount of diclofenac. It is important for patients to store and dispose of the patch or **topical system** 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	1.5% solution	Topical	Four times daily	Apply to clean, dry skin; do not

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
sodium topical solution				apply heat or occlusive dressings
diclofenac sodium topical gel	3% gel	Topical	Twice daily	The recommended duration of therapy is from 60 to 90 days. Complete healing or optimal therapeutic effect may not be evident for up to 30 days following the cessation of therapy. Therapy may be interrupted for severe dermal reactions until the condition subsides.
Flector (diclofenac epolamine)	1.3% patch	Topical	Twice daily	Should not be applied to non-intact or damaged skin; should not be worn while bathing or showering
Licart (diclofenac epolamine)	1.3% topical system	Topical	Once daily	Do not apply Licart to nonintact or damaged skin resulting from any etiology (eg, exudative dermatitis, eczema, infected lesion, burns or wounds). Do not wear when bathing or showering.
Pennsaid (diclofenac sodium)	2% solution	Topical	Twice daily	Apply to clean, dry skin; do not apply heat or occlusive dressings
Voltaren (diclofenac sodium)	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.

Note: The lowest effective dosage of topical product should be used for the shortest duration consistent with individual patient treatment goals.

CONCLUSION

- NSAIDs are commonly used for the treatment of pain due to OA, actinic keratosis, 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 and Licart are available as 1.3% topical patch and topical system, respectively. These products are 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. A higher strength formulation of Solaraze (3%) has also been made available; it is indicated for the treatment of actinic keratoses. Of the topical NSAIDs, Solaraze 3%, Pennsaid 1.5% and Voltaren 1% are available generically. Branded Solaraze 3% and Pennsaid 1.5% solution are 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.

- Treatment guidelines from BAD recommend topical diclofenac as a viable option for the treatment of actinic keratosis (de Berker et al 2017). 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).

REFERENCES

- Altman RD, Dreiser RL, Fisher CL, et al. Diclofenac sodium gel in patients with primary hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. *J Rheumatol*. 2009 Sep;36(9):1991-9.
- American Academy of Orthopedic Surgeons. Treatment of osteoarthritis of the knee; Evidence-based guideline; 2nd edition. Rosemont (IL): 2013. Available at: <http://www.aaos.org/research/guidelines/TreatmentofOsteoarthritisoftheKneeGuideline.pdf>. Accessed March 22, 2019.
- Barthel HR, Haselwood D, Longley S, et al. Randomized controlled trial of diclofenac sodium gel in knee osteoarthritis. *Semin Arthritis Rheum* 2009;39:203-12.
- Centers for Disease Control and Prevention. Osteoarthritis Fact Sheet. Atlanta (GA): 2018. Available at: <https://www.cdc.gov/arthritis/basics/osteoarthritis.htm>. Accessed March 22, 2019.
- de Berker D, McGregor JM, Mohd Mustapa MF, et al. British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. *Br J Dermatol*. 2017;176(1):20-43
- Deng Z, Zeng C, Yang Y, et al. Topical diclofenac therapy for osteoarthritis: a meta-analysis of randomized controlled trials. *Clin Rheumatol*. 2016;35:1253-61.
- Derry S, Moore RA, Gaskell H. Topical NSAIDs for acute musculoskeletal pain in adults. *Cochrane Database Syst Rev*. 2015;6:CD007402. doi: 10.1002/14651858.CD007402.pub3.
- Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev*. 2016;4:CD007400. doi: 10.1002/14651858.CD007400.pub3.
- Diclofenac 1.5% topical solution prescribing information. Apotex, Inc. Weston, FL. October 2016.
- Doherty M, Abhishek A. Clinical manifestations and diagnosis of osteoarthritis. UpToDate Web Site. <http://www.uptodate.com>. Updated October 30, 2017. Accessed March 22, 2019.
- Drugs@FDA [database on the Internet]. Rockville (MD):U.S. Food and Drug Administration; 2019. Available at: <http://www.accessdata.fda.gov/scripts/cder/daf/>. Accessed March 22, 2019.
- Flector Patch prescribing information. Pfizer Inc. New York, NY. August 2018.
- Galer BS. A comparative subjective assessment study of Pennsaid and Voltaren Gel, two topical formulations of diclofenac sodium. *Pain Pract*. 2011 May-Jun;11(3):252-60.
- Galer B, Rowbotham M, Perander J, et al. Topical diclofenac patch relieves minor sports injury pain: results of a multicenter controlled clinical trial. *Journal of Pain Symptom Management*. 2000;19:287-94.
- Gupta AK, Paquet M, Villanueva E, et al. Interventions for actinic keratoses. *Cochrane Database Syst Rev*. 2012;12:CD004415. doi: 10.1002/14651858.CD004415.pub2.
- Hochberg MC, Altman RD, April KT, 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 Apr;64(4):455-74.
- Kuehl K, Carr W, Yanchick J, et al. Analgesic efficacy and safety of the diclofenac epolamine topical patch 1.3% (DETP) in minor soft tissue injury. *Int J Sports Med*. 2011 Aug;32(8):635-43.
- **Licart prescribing information. IBSA Institut Biochimique. Lugano, Switzerland. December 2018.**
- McAlindon ET, Bannuru RR, Sullivan MC, et al. OARSJ guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22:363-88.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed March 22, 2019.
- Peniston JH, Gold MS, Alwine LK. An open-label, long-term safety and tolerability trial of diclofenac sodium 1% gel in patients with knee osteoarthritis. *Phys Sports Med*. 2011 Sep;39(3):31-8.
- Pennsaid 2% prescribing information. Horizon Pharma USA Inc. Lake Forest, IL. May 2016.
- Shoimer I, Rosen N, Muhn C. Current management of actinic keratoses. *Skin Therapy Lett*. 2010;15(5):5-7
- Simon LS, Grierson LM, Naseer Z, et al. Efficacy and safety of topical diclofenac containing dimethyl sulfoxide (DMSO) compared to those of topical placebo, DMSO vehicle and oral diclofenac for knee osteoarthritis. *Pain*. 2009 Jun;143(3):238-45.
- Solaraze prescribing information. PharmaDerm and Fougere Pharmaceuticals. Melville, NY. April 2016.
- Suri P, Morgenroth DC, Hunter DJ. Epidemiology of Osteoarthritis and Associated Comorbidities. *PM&R*. 2012;4:S10-S19.
- Veterans Affairs/Department of Defense clinical practice guideline for the non-surgical management of hip & knee osteoarthritis. Version 1.0 – 2014. Available at: <https://www.healthquality.va.gov/guidelines/CD/OA/VADoDOACPGFINAL090214.pdf>. Accessed March 22, 2019.
- Voltaren prescribing information. Endo Pharmaceuticals. Malvern, PA. **September 2018.**
- Wadsworth LT, Kent JD, Holt RJ. Efficacy and safety; of diclofenac sodium 2% topical solution for osteoarthritis of the knee: a randomized, double-blind, vehicle-controlled, 4 week study. *Curr Med Res Opin*. 2016;32(2):241-50.
- Zacher J, Altman R, Bellamy N, et al. Topical diclofenac and its role in pain and inflammation: an evidence-based review. *Curr Med Res Opin*. 2008 Apr;24(4):925-50.

Publication Date: April 2, 2019