

Analgesics/Anesthetics, Topical

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Analgesics/Anesthetics, Topical

FDA-Approved Indications

Drug	Manufacturer	Indication
diclofenac epolamine (Flector [®]) ¹	Monarch	◆ Topical treatment of acute pain due to minor strains, sprains, and contusions
diclofenac sodium (Voltaren [®] Gel) ²	Endo	◆ Relief of pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands
lidocaine (Lidoderm [®]) ³	Endo	◆ Relief of pain associated with post-herpetic neuralgia

Overview

Among the latest innovations of the pharmaceutical industry is the technology of drug delivery that overcomes the disadvantages of oral drug administration. Oral administration can be impacted by first pass metabolism and has the potential for systemic adverse effects.⁴ A route of administration that bypasses the systemic exposure would provide an alternative that might improve patient adherence, minimize adverse effects, allow for a longer treatment interval, and serve as a substitute to conventional therapy.

Non-steroidal anti-inflammatory drugs (NSAIDs) reduce swelling and ease inflammation that can cause pain. NSAIDs are commonly used to treat osteoarthritis and pain from different etiologies. Local anesthetics are substances used to reduce or eliminate pain in a limited area of the body. These work by blocking the transmission of nerve impulses.

Neuropathic pain is most commonly associated with painful diabetic neuropathy, post-herpetic neuralgia (PHN), or lumbar nerve root compression. Post-herpetic neuralgia is a long-lasting pain disorder that causes pain from stimuli that are not normally painful. There are a number of oral medications available to treat neuropathic pain. The lidocaine patch (Lidoderm) is the only FDA-approved topical treatment for PHN. The American Academy of Neurology advises that tricyclic antidepressants, gabapentin, pregabalin (Lyrica[®]), opioids, and lidocaine can be used as the first option in treating PHN.⁵

Pharmacology^{6,7,8}

Drug	Mechanism of Action
diclofenac epolamine (Flector)	<ul style="list-style-type: none"> ◆ Similar to other NSAIDs, diclofenac inhibits cyclooxygenase, an early component of the arachidonic acid cascade, resulting in the reduced formation of prostaglandins, thromboxane, and prostacyclin.
diclofenac sodium (Voltaren Gel)	
lidocaine (Lidoderm)	<ul style="list-style-type: none"> ◆ Stabilizes neuronal membranes by inhibiting the ionic fluxes required for initiation and conduction of impulses.

Pharmacokinetics^{9,10,11}

Systemic absorption of these topical agents is low. Following a single application of diclofenac epolamine (Flector) to the upper inner arm, the peak plasma concentrations were noted within 10 to 20 hours. Diclofenac epolamine is 99 percent protein bound. Diclofenac sodium (Voltaren Gel) has 17 times less systemic exposure than the orally administered diclofenac. The amount of diclofenac sodium that is absorbed is on average six percent of that from oral diclofenac. The elimination half-life for topical diclofenac is approximately 12 hours. Diclofenac is metabolized through glucuronidation and eliminated through subsequent urinary and biliary excretion.

Lidocaine (Lidoderm) has varied absorption depending on the duration of application and the surface area over which it is applied. Only three percent (\pm two percent) of the applied dose is expected to be systemically absorbed. At least 95 percent of lidocaine within the patch system will remain in a used patch. Lidocaine is approximately 70 percent protein bound. However, at higher concentrations, the binding becomes concentration-dependent. Metabolism in the skin is unknown; however, lidocaine is metabolized rapidly by the liver to a number of metabolites which are then renally excreted.

Contraindications/Warnings^{12,13,14}

Used lidocaine patches (Lidoderm) contain a large amount of lidocaine (at least 665 mg). To avoid accidental exposure of children, pets, and others, proper storage and disposal of lidocaine patches is highly recommended.

Avoid excessive dosing of lidocaine patch by avoiding extended duration of application, application of more than the recommended number of patches, use in smaller patients, or use in patients with impaired elimination. These uses may lead to increased blood concentrations of lidocaine and serious adverse effects.

Diclofenac epolamine patch (Flector) and diclofenac sodium gel (Voltaren Gel) should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. They should also be avoided in patients with the aspirin triad (a nasal symptom complex typically occurring in asthmatic patients who experience rhinitis with or without nasal polyps or who have severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs).

Diclofenac epolamine patch and diclofenac sodium gel are also contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. These should not be applied to damaged skin or skin that is not intact.

Patients should be informed of the potential for adverse cardiovascular effects associated with all NSAIDs (e.g. risk of cardiovascular thrombotic events, new onset or worsening of hypertension, congestive heart failure, and edema). Diclofenac epolamine patch and diclofenac sodium gel should be used cautiously in patients with these conditions.

NSAIDs, including diclofenac epolamine patch and diclofenac sodium gel, can cause serious gastrointestinal adverse events, including inflammation, ulceration, and bleeding and perforation of the stomach, small intestine, or large intestine, which can be fatal.

Drug Interactions^{15,16,17}

Diclofenac epolamine (Flector) and diclofenac sodium (Voltaren Gel) have a similar profile to other NSAIDs and may interact with ACE inhibitors, aspirin, diuretics, lithium, methotrexate, and warfarin.

Lidocaine patch (Lidoderm) should be used with caution in patients receiving Class I antiarrhythmics (e.g. tocainide and mexiletine) since the toxic effects are additive and potentially synergistic. In addition, caution should also be exercised when using lidocaine patch with other products containing local anesthetics.

Adverse Effects

Drug	Pruritis	Dermatitis	Burning	Nausea	Dysgeusia	Headache
diclofenac epolamine (Flector) ¹⁸	5	2	<1	3	2	1
diclofenac sodium (Voltaren Gel) ¹⁹	<1	4	nr	nr	nr	nr
lidocaine (Lidoderm) ²⁰	reported	reported	reported	reported	reported	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. Incidences for the placebo group are indicated in parentheses. nr = not reported.

Special Populations^{21,22,23}

Pediatrics

Safety and effectiveness in pediatric patients for the topical products in this review have not been established.

Pregnancy

Lidocaine patch (Lidoderm) is Pregnancy Category B. Diclofenac epolamine (Flector) and diclofenac sodium gel (Voltaren Gel) are Pregnancy Category C.

Renal Impairment

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Diclofenac epolamine patch and diclofenac sodium gel are not recommended for use in patients with advanced renal disease.

Hepatic Impairment

Elevations of one or more liver tests may occur in up to 15 percent of patients taking NSAIDs including diclofenac epolamine and diclofenac sodium gel. Notable elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (approximately three times the upper limit of normal) have been reported in about one percent of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis, and hepatic failure, some of them with fatal outcomes, have been reported.

Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine because of their inability to metabolize lidocaine normally.

Geriatrics

Diclofenac, as with any NSAID, is known to be substantially excreted by the kidney, and the risk of toxic reactions to diclofenac epolamine and diclofenac sodium gel may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken when using diclofenac epolamine or diclofenac sodium gel in the elderly, and it may be useful to monitor renal function.

Dosages

Drug	Adult Dosage	Special Handling and Disposal	Availability
diclofenac epolamine (Flector) ²⁴	Apply one patch to the most painful area twice daily	Hand washing is recommended after applying, handling, or removing this patch	1.3% patch
diclofenac sodium (Voltaren Gel) ²⁵	Lower extremities: Apply four grams to the affected area four times daily Upper extremities: Apply two grams to the affected area four times daily	Do not apply more than 16 grams daily to any one of the affected joints of the lower extremities Do not apply more than eight grams daily to any one of the affected joints of the upper extremities	1% gel
lidocaine (Lidoderm) ²⁶	Apply up to three patches to affected area once daily for up to 12 hours within a 24-hour period	Hand washing required after handling, and eye contact should be avoided Used patches should be folded on the adhesive side and discarded out of the reach of children and pets	5% patch

Clinical Trials

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, comparative, controlled trials comparing agents within this class for the approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

diclofenac patch (Flector)

A randomized, double-blind, multi-center, placebo-controlled trial was conducted in 120 patients with traumatic soft tissue injury within three hours post-injury.²⁷ Patients were randomized to twice daily treatment with either diclofenac patch or placebo over a period of seven days. The primary efficacy endpoint was the area under the curve (AUC) for tenderness over the first three days. The diclofenac patch was significantly more effective than placebo ($p < 0.0001$). The diclofenac patch produced rapid pain relief as reflected by the time to reach resolution of pain at the injured site, which was significantly shorter compared to placebo ($p < 0.0001$). The most frequently observed adverse events with the use of diclofenac patch were mild, local cutaneous adverse events, occurring at the same frequency as placebo.

A multicenter, randomized, placebo-controlled, parallel-design study was conducted to assess the efficacy and safety of diclofenac patch applied directly to the injury site for the treatment of acute minor sports injury pain in 222 adult patients within 72 hours of the injury.²⁸ Either a diclofenac or placebo topical patch was applied directly to the skin overlying the injured site twice daily for two weeks. Measures of pain intensity were performed in a daily diary and at clinic visits on days three, seven, and 14. Diclofenac patch was superior to placebo patch in relieving pain. Statistical significance was seen on clinic days three ($p = 0.036$) and 14 ($p = 0.048$), as well as the daily diary pain ratings at days three, seven, and 14 ($p \leq 0.044$). No statistically significant differences were seen in any safety or side effect measures with the diclofenac patch as compared to the placebo patch.

Meta Analysis

A Cochrane Review was conducted to examine the efficacy and safety of topical lidocaine (Lidoderm) in the treatment of postherpetic neuralgia.²⁹ Three trials involving 182 topical lidocaine treated participants and 132 control participants were included. Two trials gave data on pain relief, and the remaining study provided data on secondary outcome measures. A meta-analysis combining two of the three studies identified a significant difference between the topical lidocaine and control groups for the primary outcome measure: a mean improvement in pain relief according to a pain relief scale. Topical lidocaine relieved pain better than placebo ($p = 0.003$). There were a similar number of adverse skin reactions in both treatment and placebo groups.

Summary

NSAIDs are useful in acute pain conditions including strains and sprains as well as chronic pain conditions like arthritis. Long-term administration of oral NSAIDs can result in adverse events such as gastrointestinal ulcers and cardiovascular events. For patients at risk for these events, topical administration of diclofenac (Flector, Voltaren Gel) provides an alternative method of drug delivery.

Lidocaine (Lidoderm) has been prescribed for many uses other than its indication for PHN. Professional guidelines suggest that lidocaine is amongst the first line treatments for PHN, but supporting data are lacking in this area. More evaluation is needed in the area of neuropathic pain to determine the most effective treatments.

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