

# *Analgesics/Anesthetics, Topical*

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## Analgesics/Anesthetics, Topical

### **FDA-Approved Indications**

<b>Drug</b>	<b>Manufacturer</b>	<b>Indication</b>
capsaicin (Qutenza <sup>®</sup> ) <sup>1</sup>	Neurogesx	◆ Management of neuropathic pain associated with post-herpetic neuralgia
diclofenac epolamine (Flector <sup>®</sup> ) <sup>2</sup>	Monarch	◆ Topical treatment of acute pain due to minor strains, sprains, and contusions
diclofenac sodium (Pennsaid <sup>®</sup> ) <sup>3</sup>	Mallinckrodt	◆ Treatment of signs and symptoms of osteoarthritis of the knee(s)
diclofenac sodium (Voltaren <sup>®</sup> Gel) <sup>4</sup>	Endo	◆ Relief of pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands
lidocaine (Lidoderm <sup>®</sup> ) <sup>5</sup>	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.<sup>6</sup> 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. The 2008 treatment guidelines from the American Association of Orthopedic Surgeons for the treatment of osteoarthritis of the knee do not specify a specific NSAID or route of administration for osteoarthritis symptoms.<sup>7</sup> If the risk of gastrointestinal adverse events is increased, though, the topical route is preferred among other treatment strategies.

Neuropathic pain is most commonly associated with painful diabetic neuropathy, post-herpetic neuralgia (PHN), or lumbar nerve root compression. PHN 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 2004 American Academy of Neurology treatment guidelines advise that tricyclic antidepressants, gabapentin, pregabalin (Lyrica<sup>®</sup>), opioids, and lidocaine (Lidoderm) can be used as the first option in treating PHN.<sup>8</sup>

**Pharmacology**

Drug	Mechanism of Action
capsaicin (Qutenza) <sup>9</sup>	◆ Capsaicin causes an initial enhanced stimulation of transient receptor potential vanilloid 1 (TRPV1), expressed on nociceptive nerve fibers in the skin. This stimulation may result in painful sensations, which are followed by pain relief thought to be mediated by a reduction in TRPV1-expressing nociceptive nerve endings.
diclofenac epolamine (Flector) <sup>10</sup>	◆ 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 (Pennsaid) <sup>11</sup>	
diclofenac sodium (Voltaren Gel) <sup>12</sup>	
lidocaine (Lidoderm) <sup>13</sup>	◆ Stabilizes neuronal membranes by inhibiting the ionic fluxes required for initiation and conduction of impulses.

**Pharmacokinetics**<sup>14,15,16,17,18</sup>

Systemic absorption of these topical agents is low. No detectable levels of capsaicin (Qutenza) metabolites were observed in treated patients.

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. Diclofenac sodium (Pennsaid) has about one-third of the systemic exposure compared to a topical diclofenac gel. 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 (± 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**<sup>19,20,21,22,23</sup>

Capsaicin (Qutenza) does not have any contraindications. The patch should not be used near eyes or mucous membranes. If irritation does occur, flush the affected area with water. Capsaicin can become aerosolized following rapid removal of the patch from the skin; inhalation

of airborne capsaicin can cause coughing or sneezing. Blood pressure may increase transiently during and after capsaicin administration and should be monitored. Patients should be prepared to treat acute pain during and following patch application with local cooling or appropriate analgesics.

Diclofenac formulations (Flector, Pennsaid, 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 formulations 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 formulations should be used cautiously in patients with these conditions.

NSAIDs, including diclofenac formulations, 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.

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.

### ***Drug Interactions***<sup>24,25,26,27,28</sup>

No drug interactions have been reported with capsaicin (Qutenza).

Diclofenac formulations (Flector, Pennsaid, 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
capsaicin (Qutenza) <sup>29</sup>	6 (4)	reported	reported	5 (2)	reported	reported
diclofenac epolamine (Flector) <sup>30</sup>	5	2	<1	3	2	1
diclofenac sodium (Pennsaid) <sup>31</sup>	4 (2)	9 (2)	nr	4 (1)	nr	reported
diclofenac sodium (Voltaren Gel) <sup>32</sup>	<1	4	nr	nr	nr	nr
lidocaine (Lidoderm) <sup>33</sup>	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 or all inclusive. Incidences for the placebo group are indicated in parentheses.

nr = not reported.

Treated areas may be sensitive to heat for a few days following capsaicin (Qutenza) treatment.

**Special Populations**<sup>34,35,36,37,38</sup>

Pediatrics

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

Pregnancy

Capsaicin (Qutenza) and lidocaine patch (Lidoderm) are Pregnancy Category B. Diclofenac formulations (Flector, Pennsaid, Voltaren Gel) are Pregnancy Category C.

Renal Impairment

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Diclofenac formulations 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 formulations. 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 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 formulations 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 formulations in the elderly, and it may be useful to monitor renal function.

**Dosages**

Drug	Adult Dosage	Special Handling and Disposal	Availability
capsaicin (Qutenza) <sup>39</sup>	Apply to the most painful skin areas, using up to four patches, then remove after 60 minutes; repeat not more frequently than every three months	Use nitrile gloves when handling patches and cleaning treatment areas (do not use on broken skin)  Apply a topical anesthetic before patch application  Apply cleansing gel (included in kit) for one minute following patch removal, then remove with a dry wipe	8% patch with cleansing gel
diclofenac epolamine (Flector) <sup>40</sup>	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 (Pennsaid) <sup>41</sup>	40 drops per knee four times daily and spread evenly around knee	Wash and dry hands after use	1.5% topical solution
diclofenac sodium (Voltaren Gel) <sup>42</sup>	Lower extremities: Apply 4 grams to the affected area four times daily  Upper extremities: Apply 2 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 8 grams daily to any one of the affected joints of the upper extremities	1% gel
lidocaine (Lidoderm) <sup>43</sup>	Apply up to 3 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.

#### capsaicin (Qutenza)

A randomized, double-blind, multicenter, parallel-group, 12-week study of the efficacy and safety of one 60-minute application of capsaicin 8% patch was performed in 402 patients with post-herpetic neuralgia.<sup>44</sup> The control group received a low-concentration (0.04%) capsaicin patch. Patients had an average baseline numeric pain rating scale (NPRS) score of 3 to 9. The primary efficacy endpoint was percentage change in NPRS score from baseline to weeks two to eight. Patients who were assigned to capsaicin 8% patch had a significantly greater reduction in pain during weeks two to eight than patients who had the control patch. The mean changes in NPRS score were -29.6 versus -19.9 percent ( $p=0.001$ ). Patients treated with capsaicin 8% patch had significant improvements in pain during weeks two to 12, as well (29.9 versus -20.4 percent,  $p=0.002$ ). Transient blood pressure changes associated with changes in pain level were reported on the day of treatment. Erythema and pain at the site of application were common, self-limited, and generally mild to moderate in the capsaicin 8% patch group and less frequent and severe in the control.

#### diclofenac patch (Flector)

A randomized, double-blind, multicenter, placebo-controlled trial was conducted in 120 patients with traumatic soft tissue injury within three hours post-injury.<sup>45</sup> 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.<sup>46</sup> 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 adverse effect measures with the diclofenac patch as compared to the placebo patch.

#### diclofenac solution (Pennsaid)

Patients ( $n=248$ ) with osteoarthritis of the knee and at least moderate pain were randomly assigned to apply one solution to their painful knee for four weeks: diclofenac solution 1.5%, vehicle solution, or placebo solution.<sup>47</sup> The primary efficacy endpoint was pain relief, measured by the Western Ontario and McMaster Universities (WOMAC) LK3.0 Osteoarthritis Index pain subscale. In the intent-to-treat group, the mean change in pain score from baseline to final assessment was significantly greater for the patients who applied the diclofenac solution ( $-3.9$ , 95% Confidence Interval [CI],  $-4.8$  to  $-2.9$ ) than for those who applied the vehicle solution ( $-2.5$ , 95% CI,  $-3.3$  to  $-1.7$ ,  $p=0.023$ ) or the placebo solution ( $-2.5$ , 95% CI,  $-3.3$  to  $-1.7$ ,  $p=0.016$ ). The diclofenac solution also showed superiority to the vehicle and placebo solutions in physical function, stiffness, and in pain on walking. The Patient Global Assessment scores were significantly better for the patients who applied the diclofenac solution than for those who applied the other solutions ( $p=0.039$  and  $0.025$ , respectively). The diclofenac solution caused some skin irritation in 36 percent of patients. In a similarly designed six-week study, diclofenac solution was again found to be superior to vehicle in 216 patients with osteoarthritis of the knee.<sup>48</sup> A 12-week trial in 216 patients with osteoarthritis of the knee came to the same conclusions.<sup>49</sup>

A 12-week, double-blind, double-dummy, randomized controlled trial was performed in 775 subjects with symptomatic primary osteoarthritis of the knee.<sup>50</sup> This study compared diclofenac solution with a placebo solution, the vehicle solution, oral diclofenac, and the combination of oral diclofenac and diclofenac solution. Subjects applied study solutions 40 drops four times daily and took one study tablet daily for 12 weeks. Co-primary efficacy variables were WOMAC pain and physical function and a patient overall health assessment. Diclofenac solution was superior to placebo for pain ( $-6.0$  versus  $-4.7$ ,  $p=0.015$ ), physical function ( $-15.8$  versus  $-12.3$ ,  $p=0.034$ ), overall health ( $-0.95$  versus  $-0.37$ ,  $p<0.0001$ ), and Patient Global Assessment ( $-1.36$  versus  $-1.01$ ,  $p=0.016$ ), and was superior to vehicle for all efficacy variables. The most common adverse event associated with diclofenac solution was dry skin. Fewer digestive system and laboratory abnormalities were observed with diclofenac solution than with oral diclofenac.

#### diclofenac gel (Voltaren Gel)

In a randomized, double-blind, placebo-controlled trial, 385 patients with primary osteoarthritis in the dominant hand were assigned to diclofenac 1% gel or vehicle to both hands four times daily for eight weeks.<sup>51</sup> Primary outcome measures included osteoarthritis pain intensity (100 mm visual analog scale), total Australian/Canadian Osteoarthritis Hand Index (AUSCAN) score, and global rating of disease activity at four and six weeks. Diclofenac gel decreased pain intensity scores by 42-45 percent, total AUSCAN scores by 35-40 percent, and global rating of disease by 36-40 percent. Significant differences favoring diclofenac gel over vehicle were observed at week four for pain intensity and AUSCAN. At week six, diclofenac gel significantly improved each primary outcome measure compared with vehicle. Secondary outcomes generally supported the primary outcomes. The most common adverse event was application site paresthesia.



In a randomized, double-blind, vehicle-controlled trial, 492 adults with symptomatic knee osteoarthritis were randomized to diclofenac gel 1% or vehicle four times daily for 12 weeks.<sup>52</sup> Primary efficacy outcomes at week 12 were the WOMAC pain subscale, WOMAC physical function subscale, and global rating of disease. At week 12, the diclofenac gel group had significant decreases versus the vehicle group in mean WOMAC pain ( $p=0.01$ ), mean WOMAC physical function ( $p=0.001$ ), and mean global rating of disease ( $p<0.001$ ). Efficacy outcomes significantly favored diclofenac gel versus vehicle beginning at week one. Application site reactions occurred in 5.1 and 2.5 percent of patients in the diclofenac gel and vehicle groups, respectively.

#### lidocaine patch (Lidoderm)

In a double-blind, crossover trial with 35 patients with post-herpetic neuralgia, lidocaine patch was compared to no treatment for a single dose.<sup>53</sup> Lidocaine performed statistically better than vehicle patch in terms of pain intensity from four to 12 hours. A two-week trial of lidocaine patch versus vehicle patch was performed in a double-blind manner in 32 patients with constant pain who had been considered responders in an open-label lead-in. Lidocaine patch was statistically significantly better than vehicle in terms of time to exit from trial, daily average pain relief, and patient's preference of treatment. Half of the patients also took oral medication commonly used in the treatment of post-herpetic neuralgia, but use was similar between groups.

#### **Meta Analysis**

A Cochrane Review was conducted to examine the efficacy and safety of topical lidocaine (Lidoderm) in the treatment of postherpetic neuralgia.<sup>54</sup> 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, Pennsaid, Voltaren Gel) provides an alternative method of drug delivery.

Professional guidelines suggest that lidocaine (Lidoderm) is amongst the first line treatments for PHN, but supporting data are lacking in this area. Capsaicin patch (Qutenza) was not available during the time of these evaluations. More evaluation is needed in the area of neuropathic pain to determine the most effective treatments.

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