

Injectable Diclofenac (Dyloject) National Drug Monograph February 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Diclofenac (DYLOJECT®) is a non-steroidal anti-inflammatory drug (NSAID). The mechanism of action is not fully understood but likely involves inhibition of the cyclooxygenase (COX-1 and COX-2) pathways and may also be related to inhibition of prostaglandin synthetase.
Indication(s) Under Review in this document (may include off label)	Diclofenac (DYLOJECT®) is approved for use in adults for the: <ul style="list-style-type: none">• Management of mild to moderate pain• Management of moderate to severe pain alone or in combination with opioid analgesics FDA approved in December 2014
Dosage Form(s) Under Review	Injection, single use vial containing 37.5 mg/mL
REMS	<input type="checkbox"/> REMS <input checked="" type="checkbox"/> No REMS <input type="checkbox"/> Postmarketing Requirements <i>See Other Considerations for additional REMS information</i>
Pregnancy Rating	Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation; further explanation is detailed in Special Populations

Executive Summary

Efficacy	<ul style="list-style-type: none">• IV diclofenac was evaluated for the short-term management of moderate to severe postoperative pain in two double-blind, placebo and active controlled, multiple-dose clinical trials.<ul style="list-style-type: none">○ Injectable diclofenac was consistently better in improving standard measures of acute pain (Summed pain intensity difference [SPID], pain intensity difference [PID], etc.) and reduced the dose, time to administration, and overall need for rescue opioid therapy when compared to placebo.○ There were no consistent differences between IV diclofenac and IV ketorolac as assessed by a number of pain measures including SPID, PID, percentage of patients with reduced pain intensity $\geq 30\%$ from baseline, patient global assessment or consumption of rescue opioids. In the study of patients having orthopedic surgery, there was a statistical difference in favor of diclofenac over ketorolac in total morphine consumed over 5 days (11.8 mg vs. 18.1 mg, respectively). However, the clinical significance of a difference of 6 mg of morphine consumed over 5 days is not clear. Additionally, time for PID to become significant vs. placebo was 10 minutes for diclofenac and 30 minutes for ketorolac.○ Differences in length of stay were not reported.○ There are no studies comparing IV diclofenac to IV acetaminophen or IV ibuprofen.• There was a single study in patients having third molar extraction comparing IV diclofenac to IV ketorolac and placebo. No differences were noted between active treatment groups and both groups were statistically better in improving pain measures vs. placebo.
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Safety	<ul style="list-style-type: none"> The incidence and type of treatment-related adverse events in all trials were similar with IV diclofenac when compared to intravenous ketorolac. The most common adverse events include gastrointestinal (GI)-related events (nausea, vomiting, constipation), headache, injection site pain, and bleeding. There was more injection site pain with injectable diclofenac and ketorolac when compared to placebo. <i>Included in the labeling is an adverse event of special interest: Data from a pooled analysis of multiple-dose, controlled trials in postoperative patients showed a higher incidence of adverse events related to wound healing in the IV diclofenac group (7.5%) vs. placebo (4%).</i> Other adverse events are similar to agents in the NSAID class. Boxed Warning for Cardiovascular and Gastrointestinal Risk (CONSISTENT WITH LABELING FOR ALL NSAIDS)
Other Considerations	<ul style="list-style-type: none"> The recommended dose of injectable diclofenac is 37.5mg intravenous bolus given over 15 seconds. May be repeated every 6 hours not to exceed a maximum dose of 150mg/day. Patients should be well hydrated prior to receiving diclofenac injection. IV ketorolac can be administered over 15 seconds. IV ibuprofen over 30 minutes and IV acetaminophen over 15 minutes.
Potential Impact	<ul style="list-style-type: none"> Projected place in therapy <ul style="list-style-type: none"> In clinical trials, there were no consistent or substantive advantages or disadvantages in terms of efficacy or safety between IV diclofenac and IV ketorolac in managing acute postoperative pain. However, IV ketorolac is available generically and therefore is significantly less expensive compared to IV diclofenac. There are currently no studies comparing IV diclofenac to other parenteral non-opioid analgesics for managing acute pain including IV acetaminophen or IV ibuprofen. Injectable diclofenac may be an alternative to ketorolac in patients with a hypersensitivity to ketorolac or who require a longer duration of treatment with parenteral analgesics since use of ketorolac is limited to 5 days. However, parenteral acetaminophen or ibuprofen could also be used in these patients. Because of the lack of substantive differences between IV diclofenac and ketorolac, the use of IV diclofenac will be limited in VA. Patient/Provider convenience <ul style="list-style-type: none"> Bolus dosing allows for shorter infusion time with either IV diclofenac or ketorolac when compared to IV ibuprofen and IV acetaminophen

Background

Purpose for review

Issues to be Determined:

- Is there a need for additional parenteral therapeutic alternatives in patients with varied intensities of acute pain?
- Does injectable diclofenac offer advantages to currently available parenteral alternatives?
- Does injectable diclofenac offer advantages over current VANF agents?
- What safety issues need to be considered?
- Does injectable diclofenac have specific characteristics best managed by the non-formulary process, prior authorization, and criteria for use?

Other therapeutic options	Alternatives	Other Considerations
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Ibuprofen	IV (NF) and oral NSAID. Boxed warnings for cardiovascular and gastrointestinal risk. IV formulation associated with skin irritation, renal insufficiency. <i>IV FDA Approved: mild to moderate pain or moderate to severe pain as an adjunct to opioids. Also for fever reduction. Given over 30 min.</i>
Naproxen	Oral, rectal NSAID. Boxed warnings for cardiovascular and gastrointestinal risk. Other safety concerns include renal insufficiency, fluid retention, and dyspnea.
Meloxicam	Oral NSAID. Boxed warnings for cardiovascular and gastrointestinal risk. Safety concerns include arthralgias, headache, upper respiratory tract infections.
Oral Diclofenac	Oral NSAID, topical (NF). Boxed warnings for cardiovascular and gastrointestinal risk. Safety concerns. Oral analgesic dose is 50mg three times daily. Other safety concerns include respiratory infections, pruritis, and increased liver enzymes.
IV/IM Ketorolac	IV/IM NSAID. Boxed warnings for cardiovascular, bleeding, renal and gastrointestinal risk, intrathecal and epidural administration, hypersensitivity, and concomitant use with NSAIDs. 30mg IV/IM single dose or 30mg IV/IM every 6 hours. Maximum duration of 5 days use. Maximum daily dose of 120mg. <i>FDA Approved: moderate to severe pain that requires analgesia at the level of opioids, not to exceed 5 days. Generally post-op use. Given over 15 seconds.</i>
Inj Acetaminophen	Oral, IV (restricted to use post-op and post anesthesia care unit, other uses non formulary), and rectal non-NSAID analgesic. Boxed warning for hepatotoxicity. IV dosing for patients <50kg: 15mg/kg every 6 hours or 12.5mg/kg every 4 hours. IV dosing for patients >50kg: 650mg every 4 hours or 1000mg every 6 hours. Other safety concerns, nausea and vomiting, pruritus/rash, headache. <i>FDA Approved: mild to moderate pain or moderate to severe pain as an adjunct to opioids. Also for fever reduction. Given over 15 min.</i>

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed in PubMed (2005 to September 2015) using the search terms “Dyloject”, “injectable diclofenac”, “efficacy” and “safety”. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. All randomized clinical trials evaluating the efficacy and safety of injectable diclofenac published in peer-reviewed journals were included.

Review of Efficacy

- Grading of evidence quality: please refer to Appendix A for interpretation
- The FDA approval of injectable diclofenac was based on two double-blind, placebo and active-controlled, multiple dose clinical trials in patients with moderate to severe postoperative pain. In both trials, intravenous morphine was permitted as rescue medication for pain management and injectable ketorolac was used as the active control. Patients were requested to wait 30 minutes to an hour after study medication was administered to request rescue medication; allowing ample time for the study medication to take effect.
- In these two studies, there were a number of exclusions including recent cardiovascular event, renal or liver impairment, history of gastric ulcers, recent use of other analgesics, etc.
- A third double-blind, placebo and comparator-controlled parallel group study evaluated the use of injectable diclofenac in patients with postoperative third molar extraction pain.

	<i>Gan TJ (2012)²</i>	<i>Daniels (2013)³</i>	<i>Christensen (2011)⁴</i>
Number of participants	N=331	N=277	N=353
Study Design	Multiple-dose,	Multiple-dose,	Single-dose, randomized,

	randomized, double-blind, active- and placebo-controlled, parallel-group phase 3 study in patients having abdominal or pelvic surgery.	randomized, double-blind, active- and placebo-controlled, parallel-group study in patients having orthopedic surgery.	double-blind, comparator- and placebo-controlled, parallel group study in patients having third molar extraction.
Age	16-65 years Mean: 43 Approx. 80% female Baseline pain intensity (VAS): 68.4 mm	18-85 years Mean: 55 Approx 65% female Baseline pain intensity (VAS): 69 mm	18-75 years Mean: 23.7
Primary Efficacy Measure	SPID over 0-48 hours after the first dose of study drug.	SPID over 5 intervals: 0-24, 0-48, 0-72, 0-96, and 0-120 hours.	TOTPAR6 for the intention-to-treat population.
Duration of Follow-Up	At least 48 hours from study drug initiation up to 5 days post-surgery	At least 24 hours from study drug initiation up to 5 days post-surgery	0-24 hours post-surgery
Dyloject Dose and Formulation/Active control and dose	18.75mg or 37.5mg IV/30 mg IV ketorolac	18.75mg, 37.5mg, 50mg (all IV)/15-30 mg IV ketorolac *higher risk pts allocated to lower doses of active treatments.	3.75mg, 9.4mg, 18.75mg, 37.5mg, 75mg (all IV)/ Ketorolac dose: 30mg
SPID and TOTPAR6 scores	Over the first 48 hours after drug administration, mean SPID scores were greater in injectable diclofenac doses of 18.75mg(p=0.032), 37.5mg(p=0.0001) and ketorolac (p<0.0001) compared to placebo. No specific scores provided. No difference noted in any endpoint between active groups.	Mean SPID scores w/ injectable diclofenac and ketorolac were significantly better than placebo (p<0.0001). No specific scores provided. Total pain relief was better with diclofenac and ketorolac at all time intervals tested vs. placebo (p<0.0001). In a subgroup of pts with severe pain at baseline, total pain relief was better with diclofenac and ketorolac vs. placebo (≤0.05).	Mean SPID scores better with injectable diclofenac and ketorolac compared to placebo (p<0.0001) and were similar to one another (p=0.0003). TOTPAR6: IV diclofenac was statistically superior to placebo (p<0.001) in providing pain relief over the 0-6 hour period following IV treatment.
Rescue Medication Used	Bolus IV morphine 5mg titrated up to 7.5mg after 30 min if necessary. Every 3 hrs.	IV morphine as needed in 2.5mg increments not to exceed a total of 7.5mg every three hours.	Oral ibuprofen 400-600mg or oral hydrocodone/APAP 5/325mg
Amount of Rescue Medication Used	Mean total cumulative morphine dose 0-72 hours post-surgery: -Placebo: 15.9mg -Ketorolac: 8.5mg -Diclofenac 18.75mg: 8.8mg -Diclofenac 37.5mg: 7.4mg	Patients treated with diclofenac required statistically less morphine than those treated with placebo or ketorolac over a period of 5 days. <i>Whether a difference of 6 mg over 5 days is clinically important between the</i>	Median time from administration of study drug to administration of morphine: -Diclofenac 75mg: 360 min -Diclofenac 37.5mg: 372 min -Diclofenac 18.75mg:

	No difference between active groups.	<p><i>active treatments is unknown. The authors do not separate rescue doses by study drug dose since both 15 and 30 mg of ketorolac were used.</i></p> <p>-Diclofenac: 11.8 mg -Ketorolac: 18.1 mg -Placebo: 20.5 mg</p> <p>Median time from administration of study drug to administration of morphine: -Diclofenac: 220.0 min -Ketorolac: 137.0 min -Placebo: 51.0 min</p>	<p>~240 min -Diclofenac 9.4mg: ~240 min -Diclofenac 3.75mg: ~180 min -Placebo: 69 min</p> <p>-Median time to morphine administration not listed for ketorolac.</p>
Meaningful pain relief (>30% reduction)	<p>Within 6 hours: -Placebo (n=42): 55.3% -Ketorolac (n=63): 76.8% -Diclofenac 18.75mg (n=54): 64.3% -Diclofenac 37.5mg (n=60): 69.8%</p> <p>No differences between active groups.</p>	<p>Within 6 hours: -Placebo (n=72): 43% -Ketorolac (n=60): 75% -Diclofenac (n=145): 81%</p>	<p>A statistically greater number of patients receiving diclofenac 75mg and 37.5mg reported a 30% reduction in pain intensity after 5 min compared to placebo. For ketorolac, a statistically greater number of patients reporting a 30% reduction in pain intensity from baseline was reported at 15 minutes vs. placebo.</p>
Time to pain reduction	<p>Mean time to >30% pain intensity reduction 27-33 minutes; did not differ between active treatment groups and placebo</p>	<p>Diclofenac had a faster onset of action when measured by PID; was significantly greater than placebo at 10min for diclofenac (P=0.03) whereas ketorolac required 30min (P=0.006) for significance vs. placebo.</p>	<p>Statistically significant separation in mean pain relief scores from placebo occurred at 5 minutes following drug administration for patients in diclofenac 37.5mg and 75mg groups and at 15min following administration of ketorolac 30mg. IV diclofenac 37.5mg had the greatest mean pain relief scores from 30-120 min post dose, and ketorolac 30mg had greatest mean pain relief scores 180-600 min post dose.</p>
Patient Global Evaluation	<p>No difference between active groups, both better than placebo (p<0.001)</p>	<p>No difference between active groups, both better vs. placebo (p<0.0001).</p>	<p>82.4% of patients who received IV diclofenac 37.5mg indicated “good” or better on global evaluation compared to 89.3% of patients who received ketorolac. Patients who received IV diclofenac 75mg indicated</p>

			“good” or better in 78.4% of cases on global evaluation.
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PID: Pain Intensity Difference, SPID: Sum of Pain Intensity Differences (Greater values reflect more reduction in pain from baseline), TOTPAR6: Total Pain Relief over 0-6 Hours, VAS=visual analog scale (0-100 mm)

Summary of Efficacy

- In two postoperative populations, IV diclofenac was similar to IV ketorolac and superior to placebo in reducing various measures of acute pain (SPID, PID and pain reduction >30% from baseline, use of rescue morphine, patient global evaluation, etc.).
- IV diclofenac and ketorolac performed similarly in all three trials with the exception a lower consumption of rescue morphine in the diclofenac vs. ketorolac (11.8 mg vs. 18.1 mg, respectively) group over a period of 5 days in the trial by Gan, et. al.² However, it is not clear whether a difference of 6 mg of morphine over a 5 day period is clinically significant.
- In the two trials that the FDA based its approval for IV diclofenac, the quality of evidence for the efficacy and the safety are moderate. Although the studies reported fairly consistent results across both trials, they were conducted in a younger population of patients that were primarily female which may not be entirely representative of the VA population. Additionally, differences in length of stay were not reported.

Potential Off-Label Use

- N/A

Safety

(For more detailed information refer to the product package insert)

	Comments
Boxed Warning	<p>Cardiovascular risk:</p> <ul style="list-style-type: none"> • NSAIDs may increase the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. Risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. • IV diclofenac is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. <p>Gastrointestinal Risk:</p> <ul style="list-style-type: none"> • NSAIDs increase the risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. Events can occur at any time without warning symptoms. Elderly patients are at greater risk.
Contraindications	<ul style="list-style-type: none"> • Patients with known hypersensitivity to diclofenac. • Patients with history of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. • Use in the perioperative pain in the setting of coronary artery bypass graft (CABG) surgery. • Patients with moderate to severe renal insufficiency in the perioperative period and those who are at risk for volume depletion.
Warnings/Precautions	<ul style="list-style-type: none"> • Serious and potentially fatal cardiovascular (CV) thrombotic events, MI, and stroke have been reported in patients taking NSAIDs. Patients with known CV disease or risk factors may be at greater risk. Use at the lowest dose for the shortest possible duration. • Serious GI adverse events including bleeding, ulceration, and perforation may occur and can be fatal. Use at the lowest possible dose for the shortest possible duration. Use caution in patients with prior history of ulcer disease or GI bleeding. • Renal papillary necrosis and other renal injury can occur with long-term administration of NSAIDs. Use caution in patients at greatest risk for this

potential adverse reaction including the elderly, those with renal or liver impairment, heart failure and those taking diuretics or angiotensin converting enzyme (ACE) inhibitors.

- Elevation of one or more liver tests or severe hepatic reactions can occur with diclofenac. These elevations may remain; they may progress or may be transient with continued therapy. If abnormal liver tests persist or worsen or if signs and symptoms of liver impairment appear, stop IV diclofenac immediately.
- New onset or worsening of hypertension can occur with NSAIDs. Monitor blood pressure closely during treatment with diclofenac.
- Fluid retention and edema can occur with all NSAIDs, including diclofenac. Use diclofenac with caution in patients with fluid retention or heart failure.
- Anaphylactic reactions can occur with NSAIDs, including diclofenac. Avoid use of diclofenac or other NSAIDs in patients with aspirin triad. Discontinue diclofenac immediately if an anaphylactic reaction occurs.
- Serious skin reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN) can occur with NSAIDs and can be fatal. Diclofenac should be discontinued if rash or other sign of local skin reaction occur.

Safety Considerations

The clinical trial development program for IV diclofenac involved 1,156 patients who received IV diclofenac. In these trials, IV diclofenac was administered every six hours up to five days. See selected details from Gan, et al.² and Daniels, et al.³ below:

GAN, et al.²: (See Table 1 for summary of adverse events)

- 84.6% (280/331) of patients experienced one or more adverse events, however, a majority of the events were mild-to-moderate in severity.
- The most common adverse reactions were nausea, flatulence and injection site pain/irritation.
- 20.2% of patients experienced at least one adverse event that was considered related to treatment by the investigators (23.2% ketorolac 30 mg, 19.8% diclofenac 18.75 mg, 18.4% diclofenac 37.5 mg and 19.7% in the placebo group).
- Moderate-to-severe pain is known to be a risk factor for postoperative nausea and vomiting which was reported most frequently in the placebo group.
- One serious adverse event that was possibly treatment related was reported in the ketorolac group (abdominal hematoma). Of the 9 events that led to discontinuation of treatment, only one was considered to related to treatment with diclofenac (moderate peripheral edema).
- No differences were reported in bleeding and no reports of renal or hepatic events.

Table 1. Summary of Adverse Events²

Adverse Event	Placebo (n=76)	Ketorolac (n=82)	Diclofenac 18.75mg (n=86)	Diclofenac 37.5mg (n=87)
Nausea	29 (38.2%)	22 (26.8%)	26 (30.2%)	22 (25.3%)
Flatulence	19 (25.0%)	22 (26.8%)	22 (25.6%)	12 (13.8%)
Injection site pain	5 (6.6%)	17 (20.7%)	19 (22.1%)	14 (16.1%)
Constipation	11 (14.5%)	8 (9.8%)	17 (19.8%)	16 (18.4%)
Headache	15 (19.7%)	14 (17.1%)	9 (10.5%)	7 (8.0%)
Insomnia	9 (11.8%)	7 (8.5%)	9 (10.5%)	7 (8.0%)

Vomiting	11 (14.5%)	7 (8.5%)	7 (8.1%)	5 (5.7%)
Increased CPKb	3 (3.9%)	12 (14.6%)	7 (8.1%)	6 (6.9%)
Pyrexia	8 (10.5%)	9 (11.0%)	2 (2.3%)	6 (6.9%)
Thrombophlebitis	9 (11.8%)	6 (7.3%)	6 (7.0%)	3 (3.4%)
Pruritus	5 (6.6%)	3 (3.7%)	4 (4.7%)	6 (6.9%)
Tachycardia	5 (6.6%)	4 (4.9%)	2 (2.3%)	2 (2.3%)
Diarrhea	3 (3.9%)	6 (7.3%)	2 (2.3%)	0 (0.0%)

Daniels, et al.³ (See Tables 2 and 3 for a summary of adverse events)

- 78% (216/277) patients reported at least one adverse event. There were no difference between active treatment groups in incidence of adverse events and no difference observed in risk cohorts.
- The majority of events were mild to moderate in severity with nausea being the most commonly reported event in each risk cohort.
- 17% (47/277) events were considered to be related to treatment.
- There were 5 CV adverse events that were not considered to be treatment related.
- Incidence of bleeding did not differ between active groups or placebo.
- No differences were noted for renal or hepatic tests between groups. However, one patient receiving IV diclofenac did experience acute renal failure/renal insufficiency. This patient was 81 years old and had a history of renal insufficiency, anemia, pulmonary hypertension and congestive heart failure. Serum creatinine increased from 1.5-2.6. Patient was hydrated and received blood with discontinuation of diclofenac along with other offending agents and the renal insufficiency resolved in one day.

Table 2. Summary of Common Adverse Events³

Adverse Events	Injectable diclofenac (n=145)	Ketorolac (n=60)	Placebo
Nausea	36 (24.8%)	18 (30.0%)	26 (36.1%)
Vomiting	11 (7.6%)	6 (10.0%)	14 (19.4%)
Constipation	19 (13.1%)	6 (10.0%)	11 (15.3%)
Anemia	16 (11.0%)	9 (15.0%)	11 (15.3%)
Epistaxis	2 (1.4%)	0 (0.0%)	0 (0.0%)
Contusion	1 (0.7%)	2 (3.3%)	1 (1.4%)
Dizziness	16 (11.0%)	5 (8.3%)	5 (6.9%)
Fever/Increase in body temp	6 (4.1%)	5 (8.3%)	14 (19.4%)

Table 3. Total Adverse Events by System³

Total Events	Injectable diclofenac (n=145)	Ketorolac (n=60)	Placebo (n=62)

Total GI-related events	48 (33.1%)	24 (40.0%)	40 (57.1%)
Total renal-related events	5 (3.5%)	1 (1.7%)	1 (1.4%)
Total bleeding-related events	23 (15.9%)	13 (21.7%)	12 (16.7%)

Adverse Reactions

Common adverse reactions	Incidence >5%: nausea, constipation, headache, infusion site pain, dizziness, flatulence, vomiting, and insomnia
Death/Serious adverse reactions	None noted in clinical trials but potential for serious adverse events similar to NSAID class.
Discontinuations due to adverse reactions	Discontinuation due to adverse events was found to be minimal and non-significant between groups.
Adverse reactions of special interest	In the manufacturer's labeling, there is a paragraph regarding an analysis of pooled data from multi-dose, controlled trials in post operative patients which showed a higher incidence of adverse reactions related to wound healing (7.5%) vs. placebo (4%)

Drug-Drug Interactions

- Diclofenac and aspirin: concomitant use is not recommended due to the potential for increased adverse effects, including increased GI bleeding.
- Diclofenac and anticoagulants: concomitant use has a higher risk of serious GI bleeding compared to users of either drug alone.
- ACE inhibitors: NSAIDs may reduce the antihypertensive effect of ACE inhibitors.
- Cyclosporin: NSAIDs may increase cyclosporine's nephrotoxicity. Use caution when IV diclofenac is administered with cyclosporine.
- CYP2C9 inhibitors and Inducers: diclofenac is metabolized primarily by CYP2C9. Co-administration of diclofenac with CYP2C9 inhibitors (e.g. voriconazole) may increase the exposure and toxicity of diclofenac. Co-administration of diclofenac with CYP2C9 inducers (e.g. rifampin) may lead to reduced efficacy of diclofenac. Use caution when dosing IV diclofenac with CYP2C9 inhibitors or inducers; a dosage adjustment may be indicated.
- Diuretics: IV diclofenac can reduce the diuretic effect of furosemide and thiazides in some patients. This effect has been attributed to inhibition of renal prostaglandin synthesis by NSAIDs. During concomitant therapy with NSAIDs, observe patients closely for signs of renal impairment and continued effect of the diuretic.
- Lithium: NSAIDs have produced elevations of plasma lithium levels and a reduction in renal lithium clearance. When NSAIDs and lithium are administered together, observe patients for signs of lithium toxicity.
- Methotrexate: NSAIDs may increase the toxicity of methotrexate. Use caution when NSAIDs are administered with methotrexate.

Risk Evaluation

As of 10/28/15

	Comments				
Sentinel event advisories	• None				
Look-alike/Sound alike (LA/SA) Error Risk Potential	NME Drug Name	Lexi-Comp	First DataBnk	ISMP	Clinical Judgment

	Diclofenac sodium injection	Diflucan	None	None	Diclofenac (topical, oral) Darifenacin Bromfenac Nepafenac
	Dyloject	None	None	None	Caverject Dynacirc

Other Considerations

- Store at Controlled Room Temperature 20-25° C (68-77° F)
- Do not freeze
- Protect from light
- Pharmacokinetics of diclofenac following injection appear to be dependent on body weight, yet the full effect of body weight on clinical efficacy and safety has not been fully elucidated. Therefore, adjusting dose based on body weight is not recommended.

Dosing and Administration

- Use IV diclofenac for the shortest duration possible based on individual patient treatment goals.
- Dyloject is for intravenous use only.
 - Manufacturer labeling recommends IV administration only. In pharmacokinetic studies, IM exposure was similar to IV exposure and subcutaneous exposure was similar to IM exposure. Safety and efficacy of IM and subcutaneous administration have not been established.^{6,7}
 - Different formulations of diclofenac are not bio-equivalent, even if milligram strength is the same; do not interchange.
- For the treatment of acute pain, the recommended dose of IV diclofenac is 37.5mg administered by intravenous bolus injection over 15 seconds every 6 hours as needed, not to exceed 150mg/day.
- Patients must be well hydrated prior to administration to prevent adverse renal outcomes.
- Visually inspect solution for particulate matter and discoloration prior to administration. If any of the former is observed, the solution should not be administered.

Special Populations (Adults)

	Comments
Elderly	<ul style="list-style-type: none"> • Use caution in elderly patients since these patients generally have a greater frequency of impaired hepatic, renal, or cardiac function, and of co-morbid conditions and/or other drug therapy.
Pregnancy	<ul style="list-style-type: none"> • Teratogenic effects – Pregnancy category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation • Starting at 30 weeks gestation, diclofenac and other NSAIDs should be avoided by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. There are no adequate and well-controlled studies in pregnant women. Prior to 30 weeks gestation, diclofenac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Lactation	<ul style="list-style-type: none"> • Based on available data, diclofenac may be present in human milk. Reports of diclofenac in the breast milk are conflicting. Use caution when IV diclofenac is administered to a nursing woman.
Renal Impairment	<ul style="list-style-type: none"> • IV diclofenac is not recommended in patients with moderate to severe renal insufficiency. AND, it is contraindicated in patients with moderate to severe renal insufficiency in the perioperative

	period and who are at risk for volume depletion.
Hepatic Impairment	<ul style="list-style-type: none">• Dosing adjustments in patients with mild hepatic impairment is not necessary. The pharmacokinetics of IV diclofenac were not studied in patients with moderate to severe hepatic impairment and use in this population is not recommended.
Pharmacogenetics/genomics	<ul style="list-style-type: none">• No data identified

Projected Place in Therapy

- The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. An estimated 25 million Americans will experience some form of acute pain each year either caused by trauma, surgery, or a variety of other factors. Left untreated, acute pain can cause medical complications, impair recovery, and progress into chronic pain. One of the most common forms of acute pain is post-operative pain.
- Post-operative pain results from tissue inflammation or nerve damage caused by various forms of trauma during surgery. Treatment of post-operative pain is primarily based on each specific patient’s report of the degree and severity of their pain. Goals of treatment often include decreased suffering and length of hospital stay, as well as early patient mobilization and satisfaction. Treatment of post-operative pain can be either pharmacologic or non-pharmacologic, with pharmacologic therapy being the mainstay of treatment. Both non-opioid and opioid analgesics are frequently used in the treatment of post-operative pain, with non-opioid agents being the “first-line” agents.
- Postoperative opioid use is associated with a number of unwanted adverse events including nausea, constipation, altered mental status, respiratory depression and therefore may complicate and prolong hospital stay. Besides a variety of oral non-opioid analgesics that are available, other injectable non-opioid analgesics are available for use in postoperative patients and include ketorolac (IV/IM), IV acetaminophen and IV ibuprofen (nonformulary).
- In the three clinical trials evaluating the safety and efficacy of IV diclofenac compared to IV ketorolac and placebo, no consistent advantages or disadvantages were observed between active treatments. However, both active treatments were significantly better at improving measures of acute pain vs. placebo. There are currently no studies comparing IV diclofenac to IV acetaminophen or IV ibuprofen. Because of the lack of substantive differences between IV diclofenac and IV ketorolac, the use of IV diclofenac will be limited in VA.

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Appendix A: GRADEing the Evidence

Designations of Quality

<u>Quality of evidence designation</u>	<u>Description</u>
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. *Ann Intern Med* 2010;153:194-199.