

Texas Vendor Drug Program

Drug Use Criteria: Oral Ketorolac/Intranasal Ketorolac (Sprix®)

Publication History

1. Developed February 1995.
2. Revised May 2019; May 2016; December 2014; March 2013; May 2011; January 2009; October 2003; October 2002; September 2001; October 2000; September 1999; September 1998; September 1997; October 1996; October 1995.

Notes: Information on indications for use or diagnosis is assumed to be unavailable. All criteria may be applied retrospectively; prospective application is indicated with an asterisk [*]. The information contained is for the convenience of the public. The Texas Health and Human Services Commission is not responsible for any errors in transmission or any errors or omissions in the document.

Medications listed in the tables and non-FDA approved indications included in these retrospective criteria are not indicative of Vendor Drug Program formulary coverage.

Prepared by:

- Drug Information Service, UT Health San Antonio.
- The College of Pharmacy, the University of Texas at Austin.



TEXAS
Health and Human
Services

*Medical and
Social Services*

1 Dosage

1.1 Adults

Intranasal or oral ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), is FDA-approved for short-term (no more than 5 days) management of acute moderate to severe pain, usually in the postoperative setting, that requires pain management at the opioid level.

Oral ketorolac is only approved for use after therapy initiation with intravenous or intramuscular ketorolac. Therefore, a prescription for a parenteral form of ketorolac should precede treatment with oral ketorolac to satisfy manufacturer and FDA recommendations.

The maximum recommended dosage for oral ketorolac is 40 mg/24 hours given in divided doses every 4 to 6 hours. Dosages exceeding this recommendation will be reviewed.

Intranasal ketorolac is dosed as one spray (15.75 mg) in each nostril every 6 to 8 hours for a maximum total of 8 sprays (126 mg) in a 24-hour period for patients less than 65 years of age. In patients with renal impairment, age greater than or equal to 65 years, or those weighing less than 50 kg, intranasal ketorolac should be dosed as one spray (15.75 mg) in one nostril every 6 to 8 hours for a total of 4 doses (63 mg) per 24-hour period. Discard the intranasal ketorolac bottle after 24 hours, even if liquid is still present in the bottle, as the delivery system is not designed to deliver the intended dose after 24 hours.

1.2 Pediatrics

Oral ketorolac is not FDA-approved for pediatric patients younger than 17 years of age as safety and efficacy in this age group have not been established. In adolescents 17 years of age and older, the maximum oral daily ketorolac dose is 40 mg in divided doses as continuation from parenteral ketorolac therapy. The maximum intranasal dose in pediatric patients 17 years of age and older is 126 mg per 24 hours in divided doses [one spray (15.75 mg) in each nostril (31.5 mg total) every 6 to 8 hours]. Discard the intranasal ketorolac bottle after 24 hours, even if liquid is still present in the bottle, as the delivery system is not designed to deliver the intended dose after 24 hours.

2 Duration of Therapy

2.1 Therapy Limits

The maximum treatment duration for oral and parenteral ketorolac, combined, is 5 days due to increased frequency and severity of adverse effects associated with extended use. The maximum treatment period for nasal ketorolac when used as monotherapy or sequentially with other ketorolac dosage forms is also 5 days. Treatment regimens exceeding these requirements will be reviewed.

2.2 NSAID Use and Elderly Patients

Elderly patients frequently utilize prescription and nonprescription NSAIDs to manage acute and chronic pain. Several issues surface with NSAID use in elderly patients, including potential adverse effects and drug interactions. NSAID-induced gastrointestinal and renal toxicity as well as adverse central nervous system effects are more prevalent in elderly patients due to changes in metabolism, underlying disease states, and concurrent drug therapy. Most fatal gastrointestinal events associated with ketorolac use have been seen in elderly or debilitated patients. The potential for increased cardiovascular risk with NSAID use is also a factor when evaluating NSAID therapy in elderly patients. Elderly patients prescribed NSAIDs, especially those at higher risk, should be evaluated for appropriateness of therapy as well as potential for drug-drug interactions. Appropriate ketorolac therapy duration as well as appropriate dosages should also be evaluated.

2.3 NSAID Use and Cardiovascular Risk

Some clinical trials have shown that patients prescribed selective and nonselective NSAIDs may be at increased risk for serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke, all of which can be fatal. Patients at greater risk are those with known CV disease or risk factors for CV disease. Due to the lack of long-term clinical trial data, CV risks associated with NSAID use remains controversial, especially in high-risk patients. Risk also varies between nonselective NSAIDs and cyclooxygenase-2 (COX-2) inhibitors, as well as between individual NSAIDs. The Center for Drug Evaluation and Research has determined that the increased risk of CV events associated with NSAID use should be considered a class effect for both selective and nonselective NSAIDs until more results are available. Patients should be prescribed the lowest effective NSAID dose

for the shortest possible treatment duration to minimize the potential for cardiovascular adverse events.

NSAIDs may induce new onset hypertension or worsen pre-existing hypertension in some patients, which may contribute to the development of cardiovascular adverse events. Blood pressure should be routinely monitored in patients prescribed NSAIDs.

NSAIDs may cause fluid retention or edema in some patients and should be used cautiously in patients with a history of fluid retention or heart failure.

2.4 NSAID use and Gastrointestinal Risk

All NSAIDs may be associated with an increased risk of serious gastrointestinal (GI) adverse events, including potentially fatal GI bleeding, ulceration, or gastric/intestinal perforation. The risk of NSAID-associated severe GI adverse events increases in patients with a history of peptic ulcer disease, GI bleeding, smoking, alcohol use, concurrent use of anticoagulants or oral corticosteroids, advanced age, poor health and prolonged NSAID use. Ketorolac has a greater incidence of gastritis, gastric ulceration with or without perforation and gastric bleeding compared to other NSAIDs and is contraindicated for use in patients with a history of or active peptic ulcer disease, GI bleeding, or perforation, and should be used cautiously in patients with other types of GI disease (e.g., inflammatory bowel disease). Additionally, total systemic use for ketorolac is limited to 5 days due to increased incidence of severe adverse events, including GI events, with prolonged use.

3 Duplicative Therapy

Adjunctive use of ketorolac with other ketorolac dosage forms, aspirin or other NSAIDs is contraindicated as combined therapy may result in an increased risk of gastrointestinal (GI) adverse effects and may also increase serum ketorolac levels. Therefore, concurrent ketorolac use with these agents will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically significant for ketorolac are summarized in Table 1. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 1: Ketorolac Drug-Drug Interactions

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
Ketorolac	Pentoxifylline	adjunctive administration may increase bleeding risk, due to unknown mechanism	combined therapy contraindicated	contraindicated (DrugReax) 1-severe (CP)
Ketorolac	Phenytoin	concurrent administration increases seizure risk due to unknown mechanism; ketorolac may displace phenytoin from binding sites	monitor for seizures, signs/symptoms of phenytoin toxicity; adjust phenytoin doses as necessary	major (DrugReax) 3-moderate (CP)
Ketorolac	Probenecid	combined administration may increase ketorolac serum concentrations and potential for enhanced pharmacologic/adverse effects due to decreased ketorolac clearance	adjunctive administration contraindicated	contraindicated (DrugReax) 1-severe (CP)
NSAIDs	antihypertensive agents (e.g., angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta blockers, diuretics)	potential for decreased antihypertensive effects, increased renal impairment risk (especially in patients dependent on renal prostaglandins for perfusion), with combined therapy; increased hyperkalemia risk with potassium-sparing diuretics; NSAIDs may block production of vasodilator and natriuretic prostaglandins	monitor blood pressure, renal function; observe for hyperkalemia with potassium-sparing diuretics; modify therapy as necessary; use combination cautiously in elderly; sulindac, nonacetylated salicylates may be alternative NSAIDs – have less inhibitory effect on prostaglandin synthesis	moderate (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
NSAIDs	antiplatelet drugs (e.g., clopidogrel, prasugrel)	potential for increased bleeding risk due to additive inhibitory effects on platelet aggregation	administer cautiously together; monitor for increased bleeding, especially gastrointestinal (GI) bleeding	clopidogrel – major; prasugrel - moderate (DrugReax) 3-moderate (CP)
NSAIDs	bisphosphonates	combined therapy may result in additive GI, renal toxicity; NSAIDs also decrease bone mineral density, may attenuate bone mineral stabilizing effects by bisphosphonates	administer combination cautiously; monitor for increased GI/renal adverse effects, reduced bone mineral density	2-major (CP)
NSAIDs	corticosteroids	potential for increased GI adverse effects with combined therapy	monitor for adverse effects; avoid prolonged concurrent administration	3-moderate (CP)
NSAIDs	Cyclosporine	increased risk for additive renal dysfunction with concurrent administration; potential for reduced cyclosporine elimination/ increased pharmacologic and adverse effects due to NSAID effects on renal prostaglandins; NSAIDs may mask signs of infection (e.g., fever, swelling)	use cautiously together; monitor clinical status and signs/symptoms of cyclosporine toxicity (e.g., renal dysfunction, cholestasis, paresthesias)	moderate (DrugReax) 3-moderate (CP)
NSAIDs	fluoroquinolones	increased risk for seizures, potentially due to inhibition of gamma aminobutyric acid (GABA) which results in CNS stimulation	administer cautiously together; consider alternative therapy in patients with predisposition to seizures	moderate (DrugReax) 3-moderate (CP)
NSAIDs	lithium	NSAIDs like ketorolac decreases lithium clearance by blocking renal tubular prostaglandins; may result in increased lithium levels and potential for adverse effects	avoid combination, if possible; if concurrent therapy necessary, monitor lithium levels and signs/symptoms of lithium toxicity when ketorolac therapy initiated or discontinued	moderate (DrugReax) 3-moderate (CP)

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level [#]
NSAIDs	low molecular weight heparins	potential for additive bleeding adverse effects; NSAIDs inhibit platelet aggregation and have increased GI bleeding risk, prolonged bleeding time	avoid concurrent therapy, if possible; if drug combination necessary, use cautiously, monitor for signs/symptoms of bleeding	major (DrugReax) 2-major (CP)
NSAIDs	methotrexate (MTX)	potential for increased MTX serum levels, risk of enhanced pharmacologic/toxic effects as NSAIDs like ketorolac can reduce MTX clearance	avoid concurrent NSAIDs prior to, concurrently or following intermediate or high-dose MTX; use cautiously together with low-dose MTX; monitor for increased myelosuppressive, GI adverse effects; may consider using longer leucovorin rescue	major (DrugReax) 1-severe (CP)
NSAIDs	SSRIs/SNRIs (e.g., milnacipran)	increased bleeding risk with combined therapy, especially GI bleeding; SSRIs/SNRIs deplete platelet serotonin, which may impair platelet aggregation	monitor for signs/symptoms of bleeding; may consider shorter treatment duration, adding proton pump inhibitor, or substituting tricyclic antidepressant for SSRI/SNRI or acetaminophen for NSAID	major, moderate (DrugReax) 3-moderate (CP)
NSAIDs	sulfonylureas	increased risk for additive hypoglycemia due to inhibition of sulfonylurea metabolism	monitor serum glucose concentrations; adjust doses as necessary	moderate (DrugReax)
NSAIDs	tacrolimus	potential for additive nephrotoxicity with combined therapy due to NSAID inhibitory effects on renal prostaglandins	avoid combination, if possible; if concurrent therapy necessary, closely monitor renal function	major (DrugReax) 3-moderate (CP)
NSAIDs	warfarin	combined therapy may increase risk of GI bleeding as NSAIDs, including ketorolac, inhibit platelet aggregation and may cause gastric erosion	monitor anticoagulant activity and signs of bleeding, especially in first several days of combination therapy; adjust warfarin doses as necessary	moderate (DrugReax) 2-major (CP)

- * Clinical Pharmacology
- NSAIDs = nonsteroidal anti-inflammatory drugs
- SNRIs = serotonin-norepinephrine reuptake inhibitors
- SSRIs = selective serotonin reuptake inhibitors

5 References

1. IBM Micromedex® DRUGDEX® (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at micromedexsolutions.com.libproxy.uthscsa.edu/ (cited: May 17, 2019).
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2019. Available at clinicalpharmacology-ip.com.ezproxy.lib.utexas.edu/. Accessed May 17, 2019.
3. Facts and Comparisons eAnswers [database online]. Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2019; May 17, 2019.
4. AHFS Drug Information 2019. Jackson, WY: Teton Data Systems, Version 8.10.1, 2019. Stat!Ref Electronic Medical Library. Available at online-statref-com.libproxy.uthscsa.edu/. Accessed May 17, 2019.
5. Ketorolac tromethamine nasal spray (Sprix®) package insert. Egalet US Inc., January 2018.
6. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. *JAMA*. 2006;1633-44.
7. Garnock-Jones K. Intranasal ketorolac for short-term pain management. *Clin Drug Investig*. 2012;32(6):361-71.
8. United States Food and Drug Administration. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. (July 9, 2015). Available at fda.gov/Drugs/DrugSafety/ucm451800.htm. Accessed May 17, 2019.
9. Joshi GP, Gertler R, Fricker R. Cardiovascular thromboembolic adverse effects associated with cyclooxygenase-2 selective inhibitors and nonselective antiinflammatory drugs. *Anesth Analg*. 2007; 105: 1793–804.