Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Therapeutic Class Review (TCR)

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Magellan Rx MANAGEMENT℠

FDA-APPROVED INDICATIONS

Oral NSAIDs

Drug	Mfg	OA	RA	JRA	AS	Pain	PD	Other
Single Ingredient Agents								
celecoxib (Celebrex®)[1]	Pfizer, generic	X	X	X	X	X	X	
diclofenac potassium[2]	generic	X	X			X	X	
diclofenac potassium (Zipsor®)[3]	Depo Med					X		
diclofenac sodium (Voltaren®/XR®)[4,5]	generic	X	X		X (IR)			
diclofenac submicronized (Zorvolex®)[6]	Iroko	X				X		
diflunisal[7]	generic	X	X			X		
etodolac (Lodine®)[8]	generic	X	X	X		X		
fenoprofen (Nalfon®)[9]	generic	X	X			X		
flurbiprofen[10]	generic	X	X					
ibuprofen (Motrin®)[11]	generic	X	X			X	X	
indomethacin (Indocin®)[12]	generic	X	X		X			Treatment of painful shoulder (tendonitis, bursitis) and acute gout
indomethacin (Tivorbex®)[13]	Iroko					X		
ketoprofen IR[14]	generic	X	X			X	X	
ketoprofen ER[15]	generic	X	X					

OA = Osteoarthritis, RA = Rheumatoid Arthritis, JRA = Juvenile Rheumatoid Arthritis (a.k.a Juvenile Idiopathic Arthritis [JIA]), AS = Ankylosing Spondylitis, PD = Primary Dysmenorrhea

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FDA-Approved Indications: Oral NSAIDs (continued)

Drug	Mfg	OA	RA	JRA	AS	Pain	PD	Other
Single Ingredient Agents *(continued)*								
ketorolac tromethamine[16]	generic					X		Short-term (≤ 5 days) management of moderately severe acute pain that requires analgesia at the opioid level, usually in a postoperative setting. Therapy should always be initiated with ketorolac tromethamine injectable formulation (IM/IV) and ketorolac tromethamine tablets are to be used only as continuation treatment, if necessary
meclofenamate[17]	generic	X	X			X	X	Treatment of idiopathic heavy menstrual blood loss
mefenamic acid (Ponstel®)[18]	Shionogi, generic					X < 1 week	X	
meloxicam (Mobic®)[19]	generic	X	X	X				
meloxicam submicronized (Vivlodex™)[20]	Iroko	X						
nabumetone[21]	generic	X	X					
naproxen (Anaprox® / DS, Naprelan®, EC- / Naprosyn®)[22,23]	generic	X	X	X	X	X	X	Treatment of tendonitis, bursitis, and acute gout
oxaprozin (Daypro®)[24]	generic	X	X	X				
piroxicam (Feldene®)[25]	generic	X	X					
sulindac[26]	generic	X	X		X			Treatment of acute painful shoulder and acute gouty arthritis
tolmetin[27]	generic	X	X	X				
Combination Agents								
celecoxib/ menthol/ capsaicin* (CapXib Kit)[28]	MAS	X	X	X	X	X	X	
celecoxib/ lidocaine/ menthol† (Lidoxib Kit)[29]	MAS	X	X	X	X	X	X	

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* Oral celecoxib co-packaged with topical menthol and capsaicin patch. The patch is indicated for temporary relief of minor aches and pains of the muscles and joints.

† Oral celecoxib co-packaged with topical lidocaine 4%/menthol 1% patch. The patch is indicated for the temporary relief of pain associated with minor cuts, scrapes and skin irritations.

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FDA-Approved Indications: Oral NSAIDs (continued)

Drug	Mfg	OA	RA	JRA	AS	Pain	PD	Other
Combination Agents *(continued)*								
diclofenac/ misoprostol (Arthrotec®)[30]	Pfizer, generic	X	X					Indicated for patients who are at high risk for NSAID-induced GI ulcers
esomeprazole/ naproxen (Vimovo®)[31]	Horizon	X	X		X			Indicated for the relief of signs and symptoms of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis and the reduction of risk of stomach (gastric) ulcers in patients at risk of developing stomach ulcers due to treatment with NSAIDs
ibuprofen/ famotidine (Duexis®)[32]	Horizon	X	X					Indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper gastrointestinal ulcers
naproxen/ capsaicin/ menthol/ methyl salicylate‡ (Sallus Pain Relief Collection)[33]	Sallus	X	X	X	X	X	X	Treatment of tendonitis, bursitis, and acute gout

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‡ Oral naproxen co-packaged with topical Comfort Gel containing capsaicin, menthol, and methyl salicylate for topical pain relief.

Nasal NSAIDs

Drug	Mfg	OA	RA	JRA	AS	Pain	PD	Other
ketorolac tromethamine (Sprix®)[34]	American Regent					X		Short-term (up to 5 days) management of moderate to moderately severe pain that requires analgesia at the opioid level

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Topical NSAIDs

Drug	Mfg	OA	RA	JRA	AS	Pain	PD	Other
diclofenac epolamine (Flector®)[35]	Pfizer, generic					X		Topical treatment of acute pain due to minor strains, sprains, and contusions
diclofenac sodium (Pennsaid® 1.5%, Pennsaid® 2% pump, Vopac MDS, Xrylix™)[36,37,38,39]	Mallinckrodt; Sircle Labs; PureTek	X						Treatment of signs and symptoms of osteoarthritis of the knee(s)
diclofenac sodium (Voltaren® Gel, DS Prep Pak)[40,41]	Endo, generic; Alvix	X						Relief of pain of osteoarthritis of joints amenable to topical treatment, such as the knees and those of the hands
diclofenac sodium/ capsaicin (DermacinRx® Lexitral™ PharmaPak, Sure Result DSS Premium Pak)[42,43]	PureTek; International Brand Management	X						Treatment of signs and symptoms of osteoarthritis of the knee(s)
diclofenac sodium/ camphor/menthol/ methyl salicylate (Inflamma-K Kit)[44]	Solutech	X						Treatment of signs and symptoms of osteoarthritis of the knee(s)

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OVERVIEW

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat rheumatoid arthritis (RA), osteoarthritis (OA), and pain from various etiologies. NSAIDs are the most widely used drugs in the United States, with approximately 80 million prescriptions being filled yearly, which account for roughly 4.5% of all prescriptions.[45] It is estimated that over-the-counter (OTC) NSAIDs are used 5 to 7 times more often than prescription NSAIDs.[46,47] Most oral NSAIDs are now available as generics and are generally considered to be safe and effective with some exceptions that will be discussed.

NSAIDs are associated with adverse effects including gastrointestinal (GI) bleeding, peptic ulcer disease, hypertension, edema, and renal disease. In addition, NSAIDs have been linked with an increased risk of myocardial infarction which is reflected in the black box warning for all NSAIDs. In July 2015, the Food and Drug Administration (FDA) issued a Safety Alert strengthening the existing warning on the increased risk of heart attack and stroke risk associated with NSAIDs.[48]

GI adverse effects induced by NSAIDs lead to significant morbidity and mortality. Ulcers are found by endoscopy in 15 to 30% of patients who are using NSAIDs regularly, and the incidence of upper GI clinical events due to NSAIDs is 2.5 to 4.5%. In the United States, GI side effects due to NSAIDs in patients with arthritis account for approximately 107,000 hospitalizations and result in 16,500 deaths each year.[49] Products designed to lessen NSAID GI adverse reactions (Arthrotec, Vimovo, and Duexis) are available.

Celecoxib (Celebrex, CapXib, Lidoxib), which selectively inhibits the cyclooxygenase-2 (COX-2) enzyme, has equal efficacy to many of the other NSAIDs, but the issue of a better safety profile is unclear. Rofecoxib (September 2004) and valdecoxib (April 2005) have been removed from the market due to safety concerns. Celecoxib and all nonselective NSAIDs have come under greater scrutiny due to concerns over their cardiovascular safety.

Drug delivery technology overcomes the disadvantages of oral drug administration. First pass metabolism may impact oral administration and has the potential for systemic adverse effects.[50] 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.

NSAIDs reduce swelling and ease inflammation that can cause pain. NSAIDs are commonly used to treat osteoarthritis and pain from different etiologies. Oral and topical NSAIDs are among pharmacologic therapies recommended for OA by the 2012 American College of Rheumatology (ACR) OA of the hand, knee, and hip.[51] The 2013 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.[52] If the risk of GI adverse events is increased, the topical route is preferred among other treatment strategies.

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PHARMACOLOGY

Both oral and topical NSAIDs inhibit the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes that catalyze the synthesis of prostaglandins from arachidonic acid. These prostaglandins are partially responsible for the development of pain and inflammation associated with various medical conditions. COX-1 plays a role in maintaining normal gastric mucosa and influences kidney function. COX-2 activity is rapidly upregulated during inflammatory pain conditions and may be involved in the pathogenesis of some malignancies.[53,54,55,56,57] Selective COX-2 inhibitors provide anti-inflammatory effects and analgesia while theoretically resulting in fewer adverse effects than the nonselective NSAIDs. However, other prostaglandins may be affected that alter platelet aggregation, affecting the cardiovascular risk with some of the NSAIDs.

Zorvolex capsules contain diclofenac free acid, whereas other diclofenac products contain a salt of diclofenac (e.g., diclofenac potassium or sodium). The reduction in Zorvolex particle size increases surface area, leading to faster dissolution and absorption of the drug.

Vivlodex capsules contain submicronized meloxicam particles which allow a faster dissolution, resulting in an earlier time to maximum peak concentration compared to the tablet (approximately 2 hours versus 4 hours, respectively).[58]

The inhibition of platelet aggregation seen with NSAIDs is due to the inhibition of COX-1 in platelets, causing decreased levels of platelet thromboxane A2 and increased bleeding time. The inhibition of platelet aggregation is reversible.

Esomeprazole, a component of Vimovo, works by inhibiting H+/K+-ATPase in gastric parietal cells, resulting in suppression of gastric acid secretions. This activity is dose-dependent.[59]

Misoprostol, a component of Arthrotec, is a synthetic prostaglandin E1 analog. This agent counteracts the inhibition of prostaglandin synthesis noted with NSAIDs, increasing bicarbonate and mucus production. At doses of 200 mcg or greater, misoprostol is also noted to have significant anti-secretory properties, making the exact nature of its gastroprotective properties unclear.[60]

Famotidine, a component of Duexis, is a competitive inhibitor of histamine-2 receptors, which thereby suppresses both the acid concentration and volume of gastric secretion.[61] Changes in pepsin secretion are proportional to volume output.

In peripheral sensory neurons, topical capsaicin depletes and limits reaccumulation of substance P, which is thought to be a primary mediator of pain impulses to the central nervous system (CNS). Thus, it limits local pain sensations as these sensations cannot be transmitted to the brain. Topical menthol also has a local effect, including mild analgesia, a cooling sensation, and an irritant/counter-irritant effect. Menthol also causes vasodilation. There are multiple mechanisms of menthol theorized on a cellular level; however, the exact mechanism of its effects is not well defined.[62] Methyl salicylate acts similarly to menthol and functions as a counterirritant.[63]

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The following chart indicates the location of COX-1 and COX-2 enzymes in the body:[64,65,66]

Location	Brain	Breast Cancer	Colorectal Adenomas, Carcinomas	Endothelial Cells	GI Tract	Head and Neck Cancer	Liver	Lung	Platelets	Renal Cortex, Medullary Interstitial Cells	Renal Medullary Collecting Ducts, Interstitium	Site of Inflammation	Spleen	Synovial Tissue
COX-1				X	X		X	X	X		X		X	
COX-2	X	X	X			X				X		X		X

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PHARMACOKINETICS[67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111]

Oral NSAIDs: Drug	Bioavailability (%)	Time to Peak (hr)	Half-Life (hr)	Excretion (%)
Single Ingredient Agents				
celecoxib (Celebrex)	nr	3	11	Renal: 27 Feces: 57
diclofenac submicronized (Zorvolex)	50	1	1–2	Renal: 65 Bile: 35
diclofenac potassium	50	1	1–2	Renal: 65 Bile: 35
diclofenac potassium (Zipsor)		0.47		
diclofenac sodium (Voltaren)	55	2.3	2	
diclofenac sodium XR/DR (Voltaren XR)	55	5.3	2	
diflunisal	100	2–3	8–12	90-urine
etodolac (Lodine)	≥ 80	1.4–6.7	6.4–8.4	Renal: 72 Feces: 16
fenoprofen (Nalfon)	nr	2	3	Renal: 90
flurbiprofen	96	1.9	7.5	Renal: 70
ibuprofen (Motrin)	< 80	1-2	1.8–2	Renal: 45–79
indomethacin (Indocin)	98	2	4.5	Renal: 60 Feces: 33
indomethacin (Tivorbex)	~ 100	1.67	7.6	Renal: 60 Feces: 33
ketoprofen	90	0.5–7	2–5.4	Renal: 80
ketorolac	100	0.75	2.5–5	Renal: 92 Feces: 6
meclofenamate	~ 100	0.5–2	0.8-5.3	Renal: 70 Feces: 30
mefenamic acid (Ponstel)	nr	2–4	2	Renal: 52 Feces: 20
meloxicam (Mobic)	89	5	15–20	Renal: 50 Feces: 50
meloxicam submicronized (Vivlodex)	nr	2	22	Renal: 50 Feces: 50
nabumetone	> 80	2.5–4	24	Renal: 80 Feces: 9
naproxen (Anaprox / DS, Naprelan, EC/ Naprosyn)	95	1-6	12–17	Renal: 95

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Pharmacokinetics (continued)

Oral NSAIDs: Drug	Bioavailability (%)	Time to Peak (hr)	Half-Life (hr)	Excretion (%)
Single Ingredient Agents *(continued)*				
oxaprozin (Daypro)	95	2.5–3	41–55	Renal: 65 Feces: 35
piroxicam (Feldene)	nr	3–5	50	Renal: 95 Feces: 5
sulindac	90	3–4	7.8	Renal: 50 Feces: 25
tolmetin	99	0.5–1	5	Renal: 99
Combination Agents				
celecoxib/ menthol/ capsaicin (CapXib Kit)	nr	3	11	Renal: 27 Feces: 57
	nr	nr	~ 3–6	nr
	nr	1	nr	nr
celecoxib/ lidocaine/ menthol (Lidoxib Kit)	nr	3	11	Renal: 27 Feces: 57
	nr	nr	nr	nr
	nr	nr	nr	nr
diclofenac/ misoprostol (Arthrotec)	50	2	2	Renal: 65 Feces: 35
	nr	0.33	0.5	Renal: 70
esomeprazole/ naproxen (Vimovo)	nr	0.43–1.2	1	Renal: 80
	95	3	15	Renal: 95 Feces: 3
ibuprofen/ famotidine (Duexis)	< 80	1.9	2	Renal: 45–79
	nr	2	4	Renal: 65–70 Metabolic: 30–35
naproxen/ capsaicin/ menthol/ methyl salicylate (Sallus Pain Relief Collection)	95	1–6	12–17	Renal: 95
	nr	nr	nr	nr
	nr	nr	nr	nr
	nr	nr	nr	nr

nr = not reported

Nasal NSAIDs: Drug	Bioavailability (%)	Time to Peak (hr)	Half-Life (hr)	Excretion (%)
ketorolac nasal spray (Sprix)	60	0.75	2.5–6	Renal: 92 Feces: 6

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Topical NSAIDs

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% protein bound. Diclofenac sodium (Voltaren Gel, diclofenac gel component of co-packaged products) has 17 times less systemic exposure than the orally administered diclofenac. The amount of diclofenac sodium that is absorbed is on average 6% 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.

CONTRAINDICATIONS/WARNINGS[112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154]

Oral NSAIDs

NSAIDs (non-selective and selective) should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin, other NSAIDs, or sulfonamides. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

Ibuprofen/famotidine (Duexis) is contraindicated in patients in late stages of pregnancy. This agent should not be used in patients with a known hypersensitivity to a histamine 2 receptor antagonist (H_2RA).

Diclofenac/misoprostol (Arthrotec) is contraindicated in patients who are pregnant because misoprostol can cause abortion, premature birth, or birth defects. This agent should also not be used in women of childbearing potential unless the benefits clearly outweigh the risks of therapy.

Borderline elevations (less than 3 times the upper limit of the normal [ULN] range) or greater elevations of transaminases occurred in about 15% of diclofenac-treated patients in clinical trials of indications other than acute pain. Alanine transaminase (ALT) should be monitored to detect liver injury.

Long-term PPI therapy is associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine.[155] The risk of fracture was increased in patients who received multiple daily doses for a year or longer. Esomeprazole/naproxen (Vimovo) is approved for use twice a day and does not allow for administration of a lower daily dose of the PPI.

Hypomagnesemia has been reported rarely in patients treated with PPIs for at least 3 months, in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures.[156]

In addition, PPI use may be associated with an increased risk of C*lostridium difficile*–associated diarrhea (CDAD).[157] It is unknown if patients using a H_2RA, such as famotidine, are at increased risk of CDAD.

Acute interstitial nephritis may occur at any time during PPI therapy and has been observed in patients taking PPIs. Esomeprazole/naproxen should be discontinued if interstitial nephritis occurs.

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Malabsorption of cyanocobalamin (Vitamin B-12) due to hypo-achlorhydria may occur for patients taking medications that suppress acid (PPIs) for longer than 3 months. Although rare, a diagnosis of cyanocobalamin deficiency should be considered if clinical symptoms present.

Cardiovascular Concerns

NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. In April 2005, the FDA asked the manufacturers of all marketed prescription NSAIDs (non-selective and COX-2 selective), to revise the labeling for the products to include a black box warning stating that NSAIDs may cause an increased risk of potentially fatal cardiovascular thrombotic events, myocardial infarction, and stroke. All NSAIDs may have a similar risk, which increases with longer duration of use.[158] Patients with cardiovascular disease or cardiovascular risk factors may be at greater risk. All NSAIDs are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. NSAIDs cause an increased risk of potentially fatal bleeding, ulceration, and perforation of the stomach or intestines, occurring at any time during use and without warning. Elderly patients are at greater risk for serious GI events. In July 2015, the FDA issued a Safety Alert strengthening the existing warning on the increased risk of heart attack and stroke risk associated with NSAIDs.[159]

In an August 2001 review of the COX-2 inhibitors and risk of cardiovascular events, the authors concluded that a prospective trial may be necessary to evaluate the potential risk of cardiovascular events with these agents. CLASS and VIGOR were designed to examine the GI effects of these medications, not the cardiovascular safety.[160,161,162] However, the VIGOR data were particularly concerning, since it showed a higher incidence of MI in rofecoxib (Vioxx®) patients compared to naproxen patients. The implications of these data were unclear because it was unknown if naproxen had a cardioprotective effect or if rofecoxib had adverse effects on the cardiovascular system. Data became available that brought the COX-2 inhibitors under more scrutiny; several retrospective studies and meta-analyses questioned the safety of these products.[163,164,165,166] Newer studies evaluating these agents for use for other indications had more stringent monitoring in place for cardiovascular problems, which proved to be a critical step in evaluating their true effects.[167]

Rofecoxib was withdrawn from the market after the discovery of higher cardiovascular risk with the agent in the APPROVe study. Not long after the withdrawal of rofecoxib, the cardiovascular effects of the other COX-2 inhibitors were called into question. Valdecoxib (Bextra®) was withdrawn from the market in February 2005 following extensive study of available clinical trials by the FDA. Celecoxib was allowed to remain on the market, but the advisement was given to use celecoxib at the lowest effective dose.[168,169]

The American Heart Association recommended soon afterward that any COX-2 inhibitors be reserved in patients with a history or risk of GI bleeding unless potential benefits of treatment are felt to outweigh the potential cardiovascular risks or nonselective NSAID therapy is insufficient.[170] The 2007 update to the American Heart Association Scientific Statement on the use of NSAIDs reiterates the reservation of COX-2 inhibitor use in patients with history of or at risk of CV disease and strengthens the point by suggesting COX-2 selective agents be used as a last resort with the prior steps being non-pharmacologic treatments (physical therapy, weight loss, exercise, etc.) followed by a stepped

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pharmacologic approach.[171] The first-line agents recommended are acetaminophen, aspirin, or a short-term narcotic analgesic. If therapeutic alternatives are needed, physicians should consider the nonselective NSAIDs prior to the selective COX-2 inhibitor. This stepped approach focuses on the reported risk of cardiovascular events with the need for assessment of risk/benefit ratio at each step.

NSAIDs can lead to the onset of hypertension or worsening of existing hypertension. In addition, fluid retention and edema have been observed in some patients taking NSAIDS. Also, patients taking NSAIDs may have a decreased response to thiazide or loop diuretics. Therefore, monitoring patients with hypertension and patients at risk for the development of edema is recommended with all NSAIDs.

GI Toxicity

NSAIDs can cause an increased risk of serious GI adverse effects including bleeding, ulceration, and perforation of the stomach or intestine, which can be fatal. Serious GI toxicity can occur with or without warning with all NSAIDs. Patients at higher risk for the development of GI toxicity include patients on corticosteroids, anticoagulants, or long duration of NSAID therapy, as well as those with the following risk factors: smoking, alcoholism, poor health status, and older age. NSAIDs can exacerbate inflammatory bowel disease and should therefore be given with caution to patients with a history of this condition.

Renal Toxicity

Long-term use of NSAIDs can lead to renal papillary necrosis, renal insufficiency, acute renal failure, and other renal injuries. Patients with impaired renal function, heart failure, liver dysfunction, the elderly, and those taking diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers are at greatest risk for this reaction. The FDA notes that discontinuation of NSAID therapy usually is followed by recovery to the pretreatment state.

CNS adverse effects, including seizures, delirium, and coma, have been reported with famotidine in patients with moderate (creatinine clearance < 50 mL/min) and severe (creatinine clearance < 10 mL/min) renal impairment. Since the dosage of the famotidine component in Duexis is fixed, this product is not recommended in patients with moderate to severe renal insufficiency.

Naproxen/esomeprazole (Vimovo) is not recommended in patients with moderate or severe renal impairment.

Safety and efficacy of submicronized meloxicam (Vivlodex) has not been established in patients with severe renal impairment; use is not recommended. The maximum dose in patients on hemodialysis is 5 mg.

Hepatic Impairment

Elevations of 1 or more liver tests may occur in up to 15% of patients taking NSAIDs. Elevations of up to 3 times the upper limit of normal of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have been reported in about 1% 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.

Naproxen/esomeprazole (Vimovo) is not recommended in patients with severe hepatic impairment because esomeprazole doses should not exceed 20 mg daily in these patients.

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Skin Reactions

NSAIDs can cause serious skin adverse events, such as exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrosis, which can be fatal. These conditions can occur without warning. NSAID therapy should be stopped at the first appearance of skin rash or other sign of hypersensitivity.

Hematological

NSAID therapy should be stopped if active and clinically significant bleeding from any source occurs. Anemia is sometimes seen in patients taking NSAIDs. This may be due to fluid retention, occult or gross GI blood loss, or an effect upon erythropoiesis. Patients with initial hemoglobin values of 10 g/dL or less who are to receive long-term therapy with NSAIDs/NSAID combinations should have hemoglobin values assessed periodically.

Pre-existing Asthma

The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe and possibly fatal bronchospasm. Since cross-reactivity between aspirin and the various NSAIDs has been reported in such aspirin-sensitive patients, oral and topical NSAIDs should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Visual Disturbances

Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported with ibuprofen/famotidine (Duexis). If a patient develops such complaints while on therapy, the drug should be discontinued, and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Nasal NSAIDs

Ketorolac tromethamine nasal spray (Sprix) is contraindicated in patients with a known hypersensitivity to ethylenediamine tetraacetic acid. Ketorolac nasal spray is contraindicated for use as a prophylactic analgesic before any major surgery. Probenecid decreases the clearance of ketorolac nasal spray; concomitant use is contraindicated. Similarly, the combination of pentoxifylline with ketorolac nasal spray is contraindicated due to increased bleeding risk.

Topical NSAIDs

Diclofenac formulations (Flector, Pennsaid, Voltaren Gel, diclofenac components of co-packaged products) carry a black box warning for cardiovascular (CV) and gastrointestinal risk. These agents may cause an increased risk of serious CV thrombotic events, myocardial infarction, and stroke, which can be fatal. Formulations are also contraindicated for the treatment of perioperative 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,

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congestive heart failure, and edema). Diclofenac formulations should be used cautiously in patients with these conditions.

NSAIDS, including diclofenac formulations, can cause serious GI adverse events, including inflammation, ulceration, and bleeding and perforation of the stomach, small intestine, or large intestine, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious GI events.

Diclofenac formulations 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).

Capsaicin, copackaged with DermacinRx Lexitral PharmaPak, Sure Result DSS Premium Pak, and Sallus Pain Relief Collection, is an irritant and should be used with caution to avoid irritation to mucous membranes or the eyes. Menthol/capsaicin patch (co-packaged with celecoxib in CapXib kit) should not be used on wounds or damaged skin. It should also not be used in combination with any bandage, wrap, or other similar garment. Camphor/menthol/methyl salicylate patches (co-packaged in Inflamma-K kit) should not be used on wounds or damaged skin; contact with eyes, mucous membranes, or rashes should also be avoided. Likewise, Sallus Pain Relief Collection also should not be used on wounds or damaged skin and the patient should avoid contact with eyes, mucous membranes, or rashes.

Medication Guide/Risk Evaluation and Mitigation Strategy (REMS)

A Medication Guide must accompany every prescription NSAID, except for diclofenac potassium 25 mg capsules (Zipsor), at the time of dispensing to better inform patients of possible adverse effects. In June 2005, the FDA requested that the manufacturers of OTC NSAIDs revise their labeling to include more specific information about the potential GI and CV risks. In July 2015, the FDA issued a Safety Alert strengthening the existing warning on the increased risk of heart attack and stroke associated with NSAIDs.[172] As a result, the FDA is requiring updates to all prescription labels and requesting updates to over-the-counter (OTC) Drug Facts labels.

DRUG INTERACTIONS[173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216]

Oral NSAIDs

ACE inhibitors/ARBs, or beta-blockers

NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta blockers (including propranolol). Deterioration of renal function, including possible acute renal failure may occur with the coadministration of an NSAID with an ACE or ARB in elderly patients, those volume depleted or in those with renal impairment. These effects are usually reversible.

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aspirin

Concomitant use of aspirin and NSAIDs is not generally recommended because of the potential for GI ulceration. NSAID therapy is not a substitute for aspirin for cardiovascular prophylaxis.

bisphosphonates

The risk of GI ulceration is increased with concurrent use of NSAIDs and bisphosphonates.

cyclosporine

NSAIDs may affect renal prostaglandins and increase the nephrotoxic effect of cyclosporine.

diuretics

Due to the inhibition of renal prostaglandin synthesis, NSAIDs may reduce the natriuretic effect of furosemide and thiazide diuretics.

fluconazole

Concomitant use of fluconazole and celecoxib has been noted to increase the celecoxib plasma concentration as much as two-fold.

voriconazole

Concomitant use of voriconazole increases the systemic exposure to diclofenac. When concomitant voriconazole use is necessary, the total daily dose of diclofenac should not exceed the lowest recommended dose of diclofenac/misoprostol (Arthrotec) 50 twice daily.

lithium

NSAIDs may produce an elevation of plasma lithium levels and a reduction in renal lithium clearance. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Patients should be monitored for signs of lithium toxicity when lithium and NSAIDs are given concurrently.

selective serotonin receptor inhibitors (SSRIs)

There is an increased risk of GI bleeding when SSRIs and NSAIDs are given concurrently.

warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, thereby increasing the risk of serious GI bleeding when used together.

methotrexate

Concomitant use of NSAIDs with methotrexate may increase the toxicity of methotrexate. Concomitant use of esomeprazole, a proton pump inhibitor, with methotrexate may increase and prolong serum levels of methotrexate and its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the esomeprazole/naproxen (Vimovo) may be considered in some patients.

St John's Wort

Avoid concomitant use of esomeprazole/naproxen (Vimovo) with St John's Wort due to the potential reduction in esomeprazole levels.

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rifampin

Avoid concomitant use of esomeprazole/naproxen (Vimovo) with rifampin due to the potential reduction in esomeprazole levels.

tacrolimus

Concomitant administration of esomeprazole/naproxen and tacrolimus may increase the serum levels of tacrolimus.

gastric pH

Esomeprazole inhibits gastric acid secretion and may interfere with the absorption of drugs where gastric pH is an important determinant of bioavailability (e.g., ketoconazole, iron salts, and digoxin).

sodium polystyrene

Intestinal necrosis, possibly fatal has been reported with the concomitant use of sorbitol with sodium polystyrene sulfonate (Kayexalate®). Due to the presence of sorbitol in meloxicam (Mobic) oral suspension, use with Kayexalate is not recommended.

Ketorolac nasal spray is contraindicated in combination with probenecid and pentoxifylline.

Nasal NSAIDs

ACE inhibitors and angiotensin receptor antagonists

NSAIDs may diminish the antihypertensive effect of these agents.

antiepileptic drugs (phenytoin, carbamazepine)

Cases of seizures have been reported with patients taking concomitant ketorolac.

aspirin

Concomitant use of aspirin and NSAIDs is not generally recommended because of the potential for GI ulceration. NSAID therapy is not a substitute for aspirin for cardiovascular prophylaxis.

diuretics

Due to the inhibition of renal prostaglandin synthesis, NSAIDs may reduce the natriuretic effect of furosemide and thiazide diuretics.

lithium

NSAIDs may produce an elevation of plasma lithium levels and a reduction in renal lithium clearance. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Patients should be monitored for signs of lithium toxicity when lithium and NSAIDs are given concurrently.

methotrexate

Concomitant use of NSAIDs with methotrexate may increase the toxicity of methotrexate.

psychoactive drugs

hallucinations have been reported in patients taking psychoactive drugs and ketorolac.

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selective serotonin receptor inhibitors (SSRIs)

There is an increased risk of GI bleeding when SSRIs and NSAIDs are given concurrently.

warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, thereby increasing the risk of serious GI bleeding when used together.

Topical NSAIDs

All topical diclofenac formulations, including products co-packaged as a kit, have a similar profile to other NSAIDs and may interact with ACE inhibitors, aspirin, diuretics, lithium, methotrexate, and warfarin.

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ADVERSE EFFECTS[217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262]

Oral NSAIDs

Drug	Abdominal Pain (%)	Diarrhea (%)	Dyspepsia (%)	Nausea (%)	Headache (%)	Rash (%)	Edema (%)
Single Ingredient Agents							
celecoxib (Celebrex)	4.1 (2.8)	5.6 (3.8)	8.8 (6.2)	3.5 (4.2)	15.8 (20.2)	2.2 (2.1)	2.1 (1.1)
diclofenac potassium	1–10	1–10	1–10	1–10	1–10	1–10	1–10
diclofenac potassium (Zipsor)	7 (3.4)	2.3 (2.8)	1.2 (2.4)	16.5 (20.2)	12.5 (17.1)	nr	nr
diclofenac sodium (Voltaren, Voltaren XR)	1–10	1–10	1–10	1–10	1–10	1–10	1–10
diclofenac submicronized (Zorvolex)	1–10	1–10	2 (1)	27 (37)	13 (15)	1–10	33 (32)
diflunisal	3–9	3–9	3–9	3–9	3–9	3–9	< 1
etodolac (Lodine)	1–10	1–10	1–10	1–10	1–10	1–10	1–10
fenoprofen (Nalfon)	2 (1.1)	1.8 (4.1)	10.3 (2.3)	7.7 (7.1)	8.7 (7.5)	3.7 (0.4)	5 (0.4)
flurbiprofen	≥ 1	≥ 1	≥ 1	≥ 1	≥ 1	≥ 1	≥ 1
ibuprofen (Motrin)	3–9	3–9	reported	3–9	1–3	3–9	1–3
indomethacin (Indocin)	> 1	> 1	> 1	> 1	11.7	< 1	< 1
indomethacin (Tivorbex)	1–2 (1)	2–3 (1)	1–3 (1)	33–34 (36)	11–16 (11)	1–2 (0)	24–26 (32)
ketoprofen (Orudis)	3–9	3–9	11	3–9	3–9	> 1	2
ketorolac	> 10	1–10	> 10	> 10	> 10	1–10	1–10
ketorolac nasal spray (Sprix)	1–10	1–10	1–10	> 10	> 10	1–10	1–10
meclofenamate	nr	10–33	nr	11	3–9	3–9	1–3
mefenamic acid (Ponstel)	1–10	1–10	1–10	1–10	1–10	1–10	1–10
meloxicam (Mobic)	1.3–2.9 (0.6–2.5)	3.2–9.2 (3.8–5.1)	4–6.5 (3.8–4.5)	3.3–7.2 (2.6–3.2)	5.5–8.3 (6.4–10.2)	0.6–2.6 (1.7–2.5)	1.9–4.5 (2.5)
meloxicam submicronized (Vivlodex)	≥ 2	≥ 2 (1)	nr	≥ 2	nr	nr	nr
nabumetone	12	14	13	3–9	3–9	3–9	3–9

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Adverse Effects (continued)

Drug	Abdominal Pain (%)	Diarrhea (%)	Dyspepsia (%)	Nausea (%)	Headache (%)	Rash (%)	Edema (%)
Single Ingredient Agents *(continued)*							
naproxen (Anaprox / DS, Naprelan, EC/ Naprosyn)	3–9	< 3	< 3	< 3	3–9	1–10	3–9
oxaprozin (Daypro)	>1	>1	>1	>1	> 1	>1	>1
piroxicam (Feldene)	1–10	1–10	1–10	1–10	1–10	1–10	1–10
sulindac	10	3–9	3–9	3–9	3–9	3–9	1–3
tolmetin	3–9	3–9	3–9	11	3–9	reported	3–9
Combination Agents							
celecoxib/menthol/ capsaicin (CapXib Kit)*	4.1 (2.8)	5.6 (3.8)	8.8 (6.2)	3.5 (4.2)	15.8 (20.2)	2.2 (2.1)	2.1 (1.1)
celecoxib/lidocaine/ menthol (Lidoxib Kit)*	4.1 (2.8)	5.6 (3.8)	8.8 (6.2)	3.5 (4.2)	15.8 (20.2)	2.2 (2.1)	2.1 (1.1)
diclofenac/ misoprostol (Arthrotec)	21	19	14	11	reported	reported	nr
esomeprazole/ naproxen (Vimovo)	4 (3)	6 (4)	8 (12)	4 (4)	3 (5)	reported	3 (1)
ibuprofen/famotidine (Duexis)	2	4–5	5–8	5–6	3	nr	2
naproxen/ capsaicin/ menthol/ methyl salicylate (Sallus Pain Relief Collection)*	3–9	< 3	< 3	< 3	3–9	1–10	3–9

Adverse effects data are obtained from prescribing information and therefore, should not be considered comparative or all inclusive. Incidences for the placebo group indicated in parentheses. nr = not reported

*Adverse effects reported are based on the NSAID component.

Nasal NSAIDs

The most commonly reported adverse effects of ketorolac nasal spray (Sprix) (incidence > 2%) and occurring at a rate at least twice that of placebo are: nasal discomfort, rhinalgia, increased lacrimation, throat irritation, oliguria, rash, bradycardia, decreased urine output, increased ALT and/or AST, hypertension, and rhinitis.

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Topical NSAIDs

Drug	Pruritus (%)	Dermatitis (%)	Burning (%)	Nausea (%)	Dysgeusia (%)	Headache (%)
diclofenac epolamine (Flector)	5	2	< 1	3	2	1
diclofenac sodium (Pennsaid 1.5%, Pennsaid 2% pump, Vopac MDS, Xrylix)	4 (2)	9 (2)	nr	4 (1)	nr	reported
diclofenac sodium (Voltaren Gel, DS Prep Pak)	< 1	4	nr	nr	nr	nr
diclofenac sodium/ capsaicin (DermacinRx Lexitral PharmaPak, Sure Result DSS Premium Pak)	4 (2)	9 (2)	nr	4 (1)	nr	reported
diclofenac sodium/ camphor/menthol/ methyl salicylate (Inflamma-K Kit)	4 (2)	9 (2)	nr	4 (1)	nr	reported

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. Safety information for Pennsaid 2% pump was based on the safety studies done for the Pennsaid 1.5% solution.

SPECIAL POPULATIONS[263,264,265,266,267,268,269,270271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307]

Oral NSAIDs

Pediatrics

NSAIDs should be used with caution in patients with systemic onset juvenile rheumatoid arthritis (JRA), also known as juvenile idiopathic arthritis (JIA), due to the risk of disseminated intravascular coagulation. Patients with systemic onset JRA should be monitored for the development of abnormal coagulation tests.

Celecoxib (Celebrex, CapXib, Lidoxib) is indicated for the relief of the signs and symptoms of JRA in patients 2 years and older. The use of celecoxib in patients 2 years to 17 years of age with pauciarticular, polyarticular course JRA or in patients with systemic onset JRA was studied in a 12-week, double-blind, active-controlled, pharmacokinetic, safety, and efficacy study, with a 12-week open-label extension. Safety and efficacy have not been studied beyond 6 months in children. Celecoxib has not been studied in patients under the age of 2 years, in patients with body weight less than 10 kg (22 lbs), and in patients with active systemic features. In some patients with systemic onset JRA, both celecoxib and naproxen were associated with mild prolongation of activated partial thromboplastin time (aPTT) but not prothrombin time (PT). NSAIDs, including celecoxib, should be used only with caution in patients with systemic onset JRA due to the risk of disseminated intravascular coagulation. Patients with systemic onset JRA should be monitored for the development of abnormal coagulation tests. Data on the menthol/capsaicin and lidocaine/menthol patch (co-packaged with celecoxib capsules in CapXib kit, Lidoxib) are limited; a physician should be consulted prior to use in patients < 12 years old.

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Safety and efficacy of etodolac extended-release tablets for the relief of signs and symptoms of JRA in patients 6 to 16 years of age are supported by extrapolating data from adequate and well-controlled studies in adult rheumatoid arthritis patients and also by safety, efficacy, and pharmacokinetic data from an open-label clinical trial in JRA patients 6 to 16 years of age. However, safety and effectiveness of etodolac immediate-release in pediatric patients less than the age of 18 years have not been established.

Ibuprofen (Motrin) has been tested in children 6months of age and older. It has not been shown to cause different adverse effects or problems than it does in adults. Over-the-counter strengths of ibuprofen are available for use in children.

Meloxicam (Mobic) is indicated in patients who weigh ≥ 60 kg. Safety and efficacy of indomethacin (Indocin) and mefenamic acid (Ponstel) in children 14 years of age and younger have not been established.

Safety and efficacy of diflunisal in children younger than 12 years of age have not been established.

Safety and efficacy of oxaprozin for the relief of signs and symptoms of JRA in patients 6 to 16 years of age are supported by extrapolating from adequate and well-controlled studies in adult rheumatoid arthritis patients. Safety and efficacy of oxaprozin in pediatric patients less than 6 years of age have not been established.

Safety and efficacy of tolmetin sodium have not been established in children less than 2 years of age.

Safety and efficacy of naproxen (EC-Naprosyn, Naprosyn, Anaprox, Anaprox DS, and Sallus Pain Relief Collection) in patients less than 2 years of age have not been established. The use of naproxen suspension (Naprosyn Suspension) is recommended for JRA in children 2 years or older because it allows for more flexible dose titration based on the child's weight. Single doses of 2.5 to 5 mg/kg, with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Per the pharmacokinetic section of the manufacturer prescribing information, naproxen delayed-release (EC-Naprosyn) has not been studied in patients under 18 years of age. Naproxen controlled-release (Naprelan) has not been studied in patients under 18 years of age.

Safety and efficacy have not been established in patients less than 18 years of age for the following agents: diclofenac (Zorvolex), diclofenac potassium (Zipsor), diclofenac sodium (Voltaren, Voltaren XR), diclofenac/misoprostol (Arthrotec), fenoprofen (Nalfon), flurbiprofen, prescription strength ibuprofen (Motrin), ibuprofen/famotidine (Duexis), indomethacin (Tivorbex), ketoprofen, meclofenamate, meloxicam submicronized (Vivlodex), nabumetone, piroxicam (Feldene), and sulindac.

NSAIDs combined with proton pump inhibitors have no data supporting pediatric use; however, esomeprazole (Nexium®) is indicated for use in patients older than 1 year of age, and naproxen has been proven safe and effective in patients 2 years and older.

Pregnancy

All oral NSAIDs are in Pregnancy Category C prior to 30 weeks gestation, as is ibuprofen/famotidine and naproxen/esomeprazole. Diclofenac/misoprostol (Arthrotec) is Category X and has a black box warning because misoprostol may cause abortions in pregnant women. All other NSAIDs are Category D in late pregnancy since they can cause premature closure of the ductus arteriosus and should therefore be avoided. Also, meclofenamate may be associated with miscarriage and minor skeletal malformations.

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NSAIDs, including meloxicam (Mobic), may be associated with a reversible delay in ovulation. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, use of meloxicam is not recommended.

Renal Insufficiency

Please see Warnings section of this review.

The maximum meloxicam submicronized (Vivlodex) dose for patients on hemodialysis is 5 mg per day.

Hepatic Insufficiency

The daily dose of celecoxib in patients with moderate hepatic impairment should be decreased by 50%; celecoxib use in patients with severe hepatic impairment is not recommended.

Patients who are known or suspected to be poor CYP2C9 metabolizers based on previous history and/or experience with other CYP2C9 substrates (such as warfarin, phenytoin) should be administered celecoxib with caution. Consider starting treatment at half the lowest recommended dose in poor metabolizers. Consider using alternative management in JRA patients who are poor metabolizers.

Elderly

NSAIDs should be used with caution in elderly patients (65 years of age and older) since advancing age appears to increase the possibility of adverse effects. Elderly patients may be less tolerant of GI ulceration or bleeding than other individuals, and fatal GI reactions have been reported in this population. Indomethacin may cause confusion or, on rare occasions, psychosis.

NSAIDs and famotidine are known to be substantially excreted by the kidney, and the risk of toxic effects to NSAIDs may be greater in patients with renal function impairment. Because elderly patients are more likely to have decreased renal function, take care in dose selection, and it may be useful to monitor renal function.

For patients > 65 years, the dosage of ketorolac nasal spray (Sprix) is reduced to 15.75 mg (1 spray in only 1 nostril) every 6 to 8 hours for a daily maximum dose of 63 mg.

Nasal NSAIDs

Pediatrics

Safety and efficacy of ketorolac and ketorolac nasal spray (Sprix) in patients less than 17 years of age have not been established.

Pregnancy

Ketorolac nasal spray (Sprix) is Pregnancy Category C prior to 30 weeks gestation; thereafter, it is Category D in late pregnancy since it can cause premature closure of the ductus arteriosus and should therefore be avoided.

Renal Impairment

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

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Hepatic Impairment

Elevations of 1 or more liver tests may occur in up to 15% of patients taking NSAIDs including diclofenac formulations. Notable elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (approximately 3 times the upper limit of normal) have been reported in about 1% 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

Exercise caution when using ketorolac nasal spray (Sprix) in elderly patients.

Topical NSAIDs

Pediatrics

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

Pregnancy

Diclofenac containing formulations 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 1 or more liver tests may occur in up to 15% of patients taking NSAIDs including diclofenac formulations. Notable elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (approximately 3 times the upper limit of normal) have been reported in about 1% 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.

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DOSAGES[308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354]

Oral NSAIDs

Drug	Recommended Dosages	Maximum Daily Dose (MDD)	Availability
Single Ingredient Agents			
celecoxib (Celebrex)	**OA:** 200 mg daily or 100 mg twice daily **RA:** 100–200 mg twice daily **JRA:** 50 mg twice daily (patients ≥ 10 kg to ≤ 25 kg); 100 mg twice daily (patients > 25 kg) **AS:** 200 mg daily or 100 mg twice daily; may increase to 400 mg/day after 6 weeks **Dysmenorrhea or acute pain:** 400 mg once with an additional 200 mg on day 1, then 200 mg twice daily, as needed	**OA:** 200 mg **RA:** 400 mg **JRA:** 100 mg in patients ≥ 10 kg; 200 mg in patients > 25 kg **AS:** 400 mg **Dysmenorrhea/Acute Pain:** 400 mg	**Capsules:** 50, 100, 200, 400 mg
diclofenac potassium	**OA:** 50 mg 2 to 3 times daily **RA:** 50 mg 3 to 4 times daily **Pain & Primary Dysmenorrhea (PD):** 50 mg 3 times daily OR initial dose of 100 mg, followed by 50 mg 3 times daily	**OA:** 200 mg **RA:** 225 mg **Pain & PD:** 200 mg on initial day, followed by 150 mg	**Tablets:** 50 mg
diclofenac potassium (Zipsor)	**Pain:** 25 mg 4 times daily	**Pain (mild to moderate acute):** 100 mg	**Capsules:** 25 mg
diclofenac sodium (Voltaren)	**OA:** 50 mg 2 to 3 times daily, or 75 mg twice daily **RA:** 50 mg 3 to 4 times daily, or 75 mg twice daily **AS:** 25 mg 4 times daily. May repeat 25 mg dose at bedtime, if necessary **PD:** Initial dose of 50 mg to 100 mg daily; may titrate up to a maximum of 200 mg/day	**OA:** 150 mg **RA:** 200 mg **AS:** 125 mg **PD:** 200 mg	**Tablets, delayed-release:** 25 mg, 50 mg, 75 mg
diclofenac sodium XR/DR (Voltaren XR)	**OA:** 100 mg once daily **RA:** 100 mg once daily; may be increased to 100 mg twice daily	**OA:** 100 mg **RA:** 200 mg	**Tablets, extended-release:** 100 mg
diclofenac submicronized (Zorvolex)	**Pain:** 18 to 35 mg 3 times daily **OA:** 35 mg 3 times daily	**Pain (mild to moderate acute) & OA:** 105 mg	**Capsules:** 18, 35mg Take on an empty stomach
diflunisal	**OA & RA:** 250 mg once daily to 500 mg twice daily **Pain:** An initial dose of 1,000 mg followed by 500 mg every 12 hours; Following the initial dose, some patients may require 500 mg every 8 hours; A lower dosage may be appropriate depending on factors such as pain severity, patient response, weight, or advanced age (e.g., 500 mg initially, followed by 250 mg every 8 to 12 hours)	**OA & RA:** 1,500 mg **Pain maintenance:** 1,500 mg	**Tablets:** 500 mg Tablets should be swallowed whole, not crushed or chewed

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Dosages: Oral NSAIDs (continued)

Drug	Recommended Dosages	MDD	Availability
Single Ingredient Agents *(continued)*			
etodolac (Lodine)	**OA & RA:** 300 mg 2 to 3 times daily, 400 mg twice daily, or 500 mg twice daily for immediate-release; 400 to 1,000 mg daily for extended-release **Pain:** 200 to 400 mg every 6 to 8 hours, up to 1000 mg/day for immediate-release **JRA (**extended-release only)**:** Daily, based on body weight: ▪ 20 to 30 kg: 400 mg ▪ 31 to 45 kg: 600 mg ▪ 46 to 60 kg: 800 mg ▪ > 60 kg: 1,000 mg	**OA & RA:** 1,000 mg **Pain:** 1,000 mg **JRA:** 1,000 mg	**Capsules:** 200, 300 mg **Tablets:** 400, 500 mg **Tablets, extended-release:** 400, 500, 600 mg
fenoprofen (Nalfon)	**OA & RA:** 300 to 600 mg 3 to 4 times daily **Pain:** 200 mg every 4 to 6 hours, as needed	**OA & RA:** 3,200 mg **Pain:** 1,200 mg	**Capsules:** 400 mg **Tablets:** 600 mg
flurbiprofen	**OA & RA:** 200 to 300 mg per day administered in divided doses 2 to 4 times a day; the largest recommended single dose in a multiple-dose daily regimen is 100 mg	**OA & RA:** 300 mg	**Tablets:** 50, 100 mg
ibuprofen (Motrin)	**OA & RA:** 300 mg 4 times daily; 400, 600, or 800 mg 3 or 4 times daily **Pain:** 400 mg every 4 to 6 hours, as needed **PD:** 400 mg every 4 hours, as needed	**OA & RA:** 3,200 mg **Pain:** 2,400 mg **PD:** 2,400 mg	**Tablets:** 400, 600, 800 mg **Suspension:** 100 mg/ 5 mL
indomethacin (Indocin)	**OA, RA & AS:** 25 mg 2 to 3 times daily for immediate release; 75 mg once daily for extended release (a large portion of total daily dose may be administered in the evening rectally with suppository retained for at least 60 minutes) **Acute painful shoulder:** 75 to 150 mg daily in 3 or 4 divided doses immediate release; 75 mg twice daily for ER capsules; when 150 mg is prescribed, give as 1 capsule twice daily; Continue therapy until the signs and symptoms of inflammation have been controlled for several days; the usual course of therapy is 7 to 14 days **Acute gouty arthritis** (immediate-release)**:** 50 mg 3 times daily until pain is tolerable; rapidly reduce dose to complete cessation of the drug	**OA, RA & AS:** 200 mg **ER capsules:** 75 mg twice daily **Acute painful shoulder:** 150 mg **Acute gouty arthritis:** 150 mg	**Capsules, oral:** 25, 50 mg **Capsules, sustained-release:** 75 mg **Suppository:** 50 mg **Suspension:** 25 mg/ 5 mL ER capsules can be administered once a day and can be substituted for indomethacin 25 mg capsules 3 times a day
indomethacin (Tivorbex)	20 mg 3 times daily or 40 mg 2 to 3 times daily	120 mg	**Capsules, oral:** 20, 40 mg
ketoprofen	**OA & RA:** 75 mg 3 times daily or 50 mg 4 times daily for immediate-release; 200 mg once daily for extended-release **Pain & PD:** 25 to 50 mg every 6 to 8 hours, as necessary for immediate-release	**OA & RA:** 200–300 mg **Pain & PD:** 300 mg	**Capsules:** 50, 75 mg **Capsules, extended-release:** 200 mg

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Dosages: Oral NSAIDs (continued)

Drug	Recommended Dosages	MDD	Availability
Single Ingredient Agents *(continued)*			
ketorolac tromethamine	**Short-term (≤ 5 days) for acute pain:** Adult patients younger than 65 years of age: Following conversion from injectable formulation, first dose may be 1 or 2 tablets followed by 1 tablet every 4 to 6 hours, not to exceed 40 mg in 24 hours Patients 65 years of age and older, renally impaired, or less than 50 kg (110 lbs) of body weight**:** Following conversion from injectable formulation, 1 tablet every 4 to 6 hours, not to exceed 40 mg in 24 hours	**Short-term (≤ 5 days) for acute pain:** Adult patients younger than 65 years of age: 40 mg Patients 65 years of age and older, renally impaired, or less than 50 kg (110 lbs) of body weight**:** 40 mg	**Tablet:** 10 mg Oral formulation should not be given as initial dose
meclofenamate sodium	**OA & RA:** 200 to 400 mg per day, administered in 3 to 4 equal doses **Excessive menstrual blood loss & PD**: 100 mg 3 times a day, for up to 6 days, starting at the onset of menstrual flow **Pain:** 50 mg to 100 mg every 4 to 6 hours	**OA & RA:** 400 mg **Excessive menstrual blood loss & PD:** 300 mg **Pain:** 400 mg	**Capsules:** 50, 100 mg
mefenamic acid (Ponstel)	**Pain in patients ≥ 14 years of age :** 500 mg as an initial dose followed by 250 mg every 6 hours, as needed, usually not to exceed 1 week **PD:** 500 mg as an initial dose followed by 250 mg every 6 hours, starting with the onset of bleeding and associated symptoms; treatment should not be necessary for more than 2 to 3 days	**Pain:** 1,000 mg **PD:** 1,000 mg	**Capsules:** 250 mg
meloxicam (Mobic)	**OA & RA:** 7.5 mg once daily **JRA:** 7.5mg once daily for children who weigh ≥ 60	**OA & RA:** 15 mg once daily **JRA:** 7.5 mg once daily	**Tablets:** 7.5, 15 mg **Suspension:** 7.5 mg/5 mL*
meloxicam submicronized (Vivlodex)	**OA:** 5 mg once daily, initially; may increase dose to 10 mg once daily for those requiring additional analgesia	**OA:** 10 mg once daily	**Capsules:** 5, 10 mg
nabumetone	**OA & RA:** 1,000 mg once or twice daily; some patients may obtain more relief from 1,500 to 2,000 mg/day which can be given as a single or twice daily dose	**OA & RA:** 2,000 mg	**Tablets:** 500, 750 mg

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Dosages: Oral NSAIDs (continued)

Drug	Recommended Dosages	MDD	Availability
Single Ingredient Agents *(continued)*			
naproxen (Naprosyn)	**OA, RA & AS:** 750–1,000 mg once daily or 250–500 mg twice daily **JRA:** 5 mg/kg given twice daily; suspension is recommended for patients 2 years of age and older to allow for more accurate titration of the dose **Pain, PD & acute tendonitis/bursitis:** 1,000 mg to 1,500 mg once daily for a limited period; thereafter, the total daily dose should not exceed 1,000 mg Alternatively, a 500–550 mg first dose, followed by 500-550 mg every 12 hours or 250–275 mg every 6 to 8 hours **Acute gout:** The starting dose is 1,000–1,500 mg once daily, then 1,000 mg once daily Alternatively, 750–825 mg to start, followed by 250–275 mg every 8 hours until the attack subsides	**OA, RA & AS:** 550–1,500 mg **JRA:** 10 mg/kg **Pain, PD & acute tendonitis/bursitis:** The initial total daily dose should not exceed 1,250–1,500 mg; thereafter, the total daily dose should not exceed 750–1,100 mg **Acute gout:** The initial total daily dose should not exceed 1,250–1,500 mg; thereafter, the total daily dose should not exceed 750–1,000 mg	**Tablets:** 250, 275, 375, 500, 550 mg **Tablet, delayed-release:** 375, 500 mg **Tablets, controlled-release:** 375, 500, 750 mg **Suspension:** 125 mg/5 mL
oxaprozin (Daypro)	**OA & RA:** 1,200 mg once daily **JRA**: For patients 22–31 kg, give 600 mg; for 32-54 kg, give 900 mg; for ≥ 55 kg, give 1,200 mg	**OA & RA:** 1,800 mg **JRA:** 26 mg/kg	**Tablet:** 600 mg
piroxicam (Feldene)	**OA & RA:** 10 mg twice daily or 20 mg once daily	**OA & RA:** 20 mg	**Capsules:** 10, 20 mg
sulindac	**OA, RA & AS:** 150 mg twice daily with food **Acute shoulder pain:** 200 mg twice daily with food **Acute gouty arthritis:** 200 mg twice daily with food	**OA & RA:** 400 mg **Acute shoulder pain:** 400 mg **Acute gouty arthritis:** 400 mg	**Tablets:** 150, 200 mg
tolmetin	**OA & RA:** 400 mg 3 times daily **JRA:** Starting dosage is 20 mg/kg/day in 3 to 4 divided doses; the usual dose is 15 to 30 mg/kg/day once control is achieved	**OA & RA:** 1,800 mg **JRA:** 30 mg/kg/day	**Tablets:** 200, 600 mg **Capsules:** 400 mg
Combination Agents			
celecoxib/ menthol/ capsaicin (CapXib Kit)	**Celecoxib:** dosing based on celecoxib component (described above) with the intent of the kit providing 200 mg/day celecoxib; use lowest effective dose for the shortest duration consistent with treatment goals **Menthol/capsaicin patch:** apply over affected area; change patch 1 to 2 times daily	**Celecoxib: 2**00 mg/day **Menthol/capsaicin patch:** twice daily use	Kit containing fifteen 200 mg celecoxib oral capsules co-packaged with 30 capsaicin 0.0375%/menthol 5% (Trans-D) topical patches

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Dosages: Oral NSAIDs (continued)

Drug	Recommended Dosages	MDD	Availability
Combination Agents *(continued)*			
celecoxib/lidocaine/ menthol (Lidoxib Kit)	**Celecoxib:** dosing based on celecoxib component (see above); the lowest effective dose and treatment duration should be used to achieve the treatment goal for each patient **Lidocaine/menthol patch:** apply to affected area not more than 3 to 4 times daily	**celecoxib:** 200 mg/day **Lidocaine/menthol patch:** 4 times daily	Kit containing fifteen 200 mg celecoxib oral capsules co-packaged with 15 lidocaine 4%/menthol 1% topical patches (AvaLin Analgesic Patch)
diclofenac/ misoprostol (Arthrotec)	**OA:** 50 mg/200 mcg 2 to 3 times daily; or 75 mg/200 mcg twice daily **RA:** 50 mg/200 mcg 2 to 4 times daily; or 75 mg/200 mcg twice daily	**OA:** 150 mg of diclofenac **RA:** 225 mg of diclofenac **Note:** Limit misoprostol to 200 mcg at any 1 time.	**Tablets:** 50 mg/200 mcg, 75 mg/200 mcg
esomeprazole/ naproxen (Vimovo)	**OA, RA, AS:** 375 mg or 500 mg of naproxen with 20 mg of esomeprazole twice daily	**OA, RA, AS:** 1,000 mg of naproxen	**Tablets:** 375 mg/20 mg, 500 mg/20 mg Do not split, crush or dissolve; take at least 30 minutes before meals
ibuprofen/ famotidine (Duexis)	**OA, RA:** 1 tablet 3 times daily	3 tablets	**Tablets:** 800 mg/26.6 mg Do not chew, divide, or crush tablets
naproxen/capsaicin/ menthol/methyl salicylate (Sallus Pain Relief Collection)	**Naproxen:** dosing based on naproxen component (see above); the lowest effective dose and treatment duration should be used to achieve the treatment goal for each patient **Comfort Gel:** As directed	**Naproxen:** see above for individually packaged naproxen **Comfort Gel:** As directed	**Tablets:** 500 mg **Comfort Gel:** 60 mL (capsaicin 0.014%/menthol 10%/methyl salicylate 23%)

MDD = Maximum Daily Dose.

*Mobic Suspension is no longer being marketed as of July 2016. Mobic suspension or its authorized generic (Roxane) will remain available until the product is depleted.

Different formulations of oral diclofenac (e.g., diclofenac sodium enteric-coated tablets, diclofenac sodium extended-release tablets, or diclofenac potassium immediate-release tablets) may not be bioequivalent even if the milligram strength is the same. Diclofenac capsules are not interchangeable with other oral diclofenac formulations.

Meloxicam submicronized (Vivlodex) capsules are not interchangeable with other formulations of oral meloxicam, even if the mg strength is the same.

Zorvolex can be taken with or without food, but food can decrease its effectiveness.

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Nasal NSAIDs

Drug	Recommended Dosages	Maximum Daily Dose (MDD)	Availability
ketorolac nasal spray (Sprix)	**Short-term (≤ 5 days) for acute pain:** Adult patients younger than 65 years of age: 31.5 mg (1 spray [15.75mg] in each nostril) every 6 to 8 hours Patients 65 years of age and older, renally impaired, or less than 50 kg (110 lbs) of body weight**:** 15.75 mg (1 spray [15.75 mg] in only 1 nostril) every 6 to 8 hours; maximum daily dose is 63 mg (4 doses)	**Short-term (≤ 5 days) for acute pain:** Adult patients younger than 65 years of age: 126 mg (4 doses per 24 hours) Patients 65 years of age and older, renally impaired, or less than 50 kg (110 lbs) of body weight**:** 63 mg (4 doses per 24 hours)	**Nasal spray:** 8 sprays per bottle. Bottle must be discarded 24 hours after priming

Topical NSAIDs

Drug	Adult Dosage	Special Handling and Disposal	Availability
diclofenac epolamine (Flector)	Apply 1 patch to the most painful area twice daily	Hand washing is recommended after applying, handling, or removing this patch Do not wear patch during bathing/showering Place only on intact skin If patch begins to "peel back" it may be taped down or use a non occlusive mesh netting sleeve Storage envelope should remain sealed at all times when not in use	1.3% patch
diclofenac sodium (Pennsaid, Xrylix)	40 drops per knee (applying 10 drops at a time), 4 times daily and spread evenly around knee	Wash and dry hands after use	1.5% topical solution Xrylix: kit containing 1.5% topical solution co-packaged with 30 Xrylix sheets (kinesiology tape/cross tape)
diclofenac sodium (Vopac MDS kit)	6 sprays per knee (equivalent to 40 drops), every 6 to 8 hours	Clean area with alcohol prep pads (in kit), allow area to dry prior to application; wash and dry hands after use	1.5% topical solution (150 mL) co-packaged with 100 alcohol prep pads, 1 pair sterile gloves, and a metered dose spray bottle
diclofenac sodium (Pennsaid 2% pump)	2 pump actuations per knee 2 times per day and spread evenly around knee	Wash and dry hands after use	2% topical solution

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Dosages: Topical NSAIDs (continued)

Drug	Adult Dosage	Special Handling and Disposal	Availability
diclofenac sodium (Voltaren Gel, DS Prep Pak)	Lower extremities: Apply 4 g to the affected area 4 times daily Upper extremities: Apply 2 g to the affected area 4 times daily	Do not apply more than 16 g daily to any 1 of the affected joints of the lower extremities Do not apply more than 8 g daily to any 1 of the affected joints of the upper extremities Total dose should not exceed 32 g per day over all affected joints Patient should wash hands after use, unless the hands are the treated joint; in which case wait at least 1 hour after the application before washing Showering/bathing should be avoided for at least 1 hour after the application The gel should be measured using the dosing card supplied and can be used to apply the gel; card should be rinsed and dried after use	1% gel (Voltaren, generic) DS Prep Pak: kit containing 1% gel co-packaged with 20 gloves and 20 antiseptic wipes
diclofenac sodium/ capsaicin (DermacinRx Lexitral PharmaPak, Sure Result DSS Premium Pak)	40 drops diclofenac sodium per knee (applying 10 drops at a time), 4 times daily and spread evenly around knee; Co-packaged capsaicin cream may be applied up to 4 times daily	Wash and dry hands after use	DermacinRx Lexitral PharmaPak: Package containing 2 agents (1) 1.5% diclofenac sodium topical solution and (2) DermacinRx Penetral™ cream, containing a time released 0.025% capsaicin with acai berry oil and omega 3, 6, and 9 oils Sure Result DSS Premium Pak: Package containing 2 agents (1) 1.5% diclofenac sodium topical solution and (2) Sure Result SR Relief Cream, containing 0.025% capsaicin
diclofenac sodium/ camphor/ menthol/ methyl salicylate (Inflamma-K Kit)	40 drops diclofenac sodium per knee (applying 10 drops at a time), 4 times daily and spread evenly around knee; Co-packaged patch should be applied over affected area following diclofenac application and may be used up to 4 times daily; remove patch after 8 hours	Wash and dry hands after use	Package containing 2 agents (1) 1.5% diclofenac sodium topical solution and (2) Salonpas patch, containing camphor 3.1%, menthol 6%, and methyl salicylate 10%

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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 review. 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% 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 and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Oral NSAIDs

Comparative Efficacy of Non-selective NSAIDs

A number of studies have attempted to define relative efficacy of non-selective NSAIDs.[355,356,357,358,359] These efforts have consistently found that there is generally no significant difference in the efficacy among the non-selective NSAIDS. It was found that there was no statistically significant difference in efficacy, either between non-selective NSAIDs or between a non-selective NSAID and celecoxib. Additionally, no particular non-selective NSAID was associated with increased GI risk when compared to any other non-selective NSAID.

celecoxib (Celebrex) and diclofenac SR

In an Asian population, a 7-day, multicenter, double-blind, parallel-group trial randomized 370 patients with first- or second-degree ankle sprain occurring at or less than 48 hours prior to the first dose of study medication.[360] Patients received celecoxib 200 mg twice daily after a 400 mg loading dose or diclofenac SR 75 mg twice daily. Patients were required to demonstrate moderate to severe ankle pain on weight bearing by visual analogue scale (VAS) at baseline. The primary efficacy endpoint was the patient's assessment of ankle pain by VAS on day 4. Celecoxib was as effective as diclofenac SR in improving the signs and symptoms of ankle sprain; treatment differences were not statistically significant. The incidence of upper gastrointestinal adverse events was low in both treatment groups.

celecoxib (Celebrex) and diclofenac/omeprazole

Patients who used NSAIDs for arthritis and who presented with ulcer bleeding were screened for study inclusion in a randomized, double-blind trial. Once ulcers healed as determined by endoscopy, patients were randomized to receive either 200 mg of celecoxib twice daily plus daily placebo or 75 mg of diclofenac twice daily plus 20 mg of omeprazole daily for 6 months.[361] Patients were negative for *Helicobacter pylori*. Approximately 85% of each group had osteoarthritis. In the intention-to-treat analysis, which included 287 patients, the probability of recurrent bleeding during the 6month period was 4.9% for celecoxib patients and 6.4% for diclofenac/omeprazole patients (difference, -1.5 percentage points; 95% confidence interval (CI) for the difference, -6.8 to 3.8). The difference between

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the groups was not significant (p=0.60). A separate analysis of this group performed by the same investigators showed that the probability of recurrent ulcers in 6 months was 18.7% in the celecoxib group and 25.6% in the diclofenac/omeprazole group (p=0.21).[362]

celecoxib (Celebrex), ibuprofen, and diclofenac

A total of 8,059 patients with OA and RA were enrolled in the double-blind, randomized, controlled study of Celecoxib Long-Term Arthritis Safety Study (CLASS).[363] A total of 4,573 patients received treatment for 6 months. Patients were randomly assigned to receive celecoxib 400 mg twice daily, ibuprofen 800 mg 3 times daily, or diclofenac 75 mg twice daily. Aspirin use (≤ 325 mg daily) for cardiovascular prophylaxis was permitted and was used by 20% of patients. Patients with active GI disease or renal, hepatic, or coagulation disorders were excluded. GI toxicity was defined as upper GI ulcers and ulcer complications including bleeding, perforation, and obstruction. For the entire patient population, the yearly incidence of upper GI complications was 0.76% and 1.45% for celecoxib and NSAIDs, respectively. The overall incidence of upper GI ulcer complications was not statistically different among the groups. When the upper GI complications data were combined with symptomatic gastroduodenal ulcers, celecoxib was found to have a lower annual incidence compared to the NSAIDs (2.08 versus 3.54%, respectively; p=0.02). For patients not taking aspirin, the yearly incidence of upper GI ulcer complications was significantly lower in the celecoxib group (0.44%) versus NSAIDs group (1.27%; p=0.04). Combining the multiple endpoints of the annualized incidence of upper GI ulcer complications and symptomatic ulcers for the patients not receiving aspirin, celecoxib group (1.4%, p=0.02) had significantly fewer events than the NSAIDs group (2.91%). In the patients taking aspirin, the annualized rate of upper GI ulcer complications for the 2 groups was similar (celecoxib, 2.01%; diclofenac, 2.12%; p=0.92). The yearly incidence of upper GI complications for patients taking aspirin was higher in both treatment groups than patients not taking aspirin. Chronic GI blood loss, GI intolerance, and renal or hepatic toxicity occurred less frequently in the celecoxib group. No difference in cardiovascular events was noted between celecoxib and NSAIDs, despite aspirin use.

celecoxib (Celebrex) and ketoprofen

In a 6 week, randomized, double-blind, placebo-controlled trial, celecoxib 100 mg twice daily and ketoprofen 100 mg twice daily were compared in 246 patients who had active ankylosing spondylitis without peripheral synovitis.[364] Decrease in pain and functional impairment was greater in the active treatment groups than in the placebo group, with a trend in favor of celecoxib when the 2 active treatments were compared. During treatment, epigastric pain was reported in 8, 14, and 13% of patients in the placebo, ketoprofen, and celecoxib groups, respectively.

celecoxib (Celebrex) and naproxen

The objective of the multicenter, randomized, double-blind, placebo-controlled study was to compare the efficacy and safety of celecoxib and naproxen for the treatment of OA of the hip.[365] In the trial, 1,061 patients were randomized to receive celecoxib 100, 200, or 400 mg/day, naproxen 1,000 mg/day, or placebo for 12 weeks. Patients were evaluated at baseline, 2 to 4 days after discontinuing previous NSAID or analgesic therapy, and after 2, 6, and 12 weeks of treatment. All doses of celecoxib and naproxen significantly improved the symptoms of OA at all time points compared with placebo. In terms of pain relief and improvement in functional capacity, celecoxib 200 mg/day and 400 mg/day were similarly efficacious and were as efficacious as naproxen. Both drugs were generally well tolerated.

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In a similarly designed trial, 1,003 patients with OA of the knee received celecoxib 50, 100, or 200 mg twice daily, naproxen 500 mg twice daily, or placebo for 12 weeks.[366] All celecoxib doses were efficacious compared with placebo, although celecoxib 50 mg twice daily dosage regimen was minimally effective. Improvement observed with the higher dosing regimens of celecoxib was comparable to that seen with naproxen. All doses of celecoxib and naproxen were well tolerated.

In another double-blind, parallel-group, multicenter study, 537 patients with OA or RA were randomized to treatment with celecoxib 200 mg or naproxen 500 mg twice daily for 12 weeks.[367] The 2 agents produced similar improvements in Patient's and Physician's Global Assessments of arthritis efficacy. Incidence of adverse events and withdrawal rates did not differ significantly between treatments. Celecoxib produced a significantly lower incidence rate of both gastric ($p<0.001$) and duodenal ($p<0.030$) ulcers.

celecoxib (Celebrex), naproxen (Naprosyn), and diclofenac (Voltaren)

A total of 13,274 OA patients were randomly assigned to treatment with celecoxib 100 mg, celecoxib 200 mg, or nonselective NSAID therapy (diclofenac 50 mg or naproxen 500 mg) twice daily for 12 weeks.[368] In the double-blind trial, results from all primary efficacy assessments showed that both dosages of celecoxib were as effective as NSAIDs in treating OA. Significantly more ulcer complications (adjudication based on lesion) occurred within the nonselective NSAID group (0.8/100 patient-years) compared with the celecoxib group (0.1/100 patient-years; OR 7.02; 95% CI, 1.46 to 33.80, $p=0.008$). The number of cardiovascular thromboembolic events was low and not statistically different between the groups.

celecoxib (Celebrex) and diclofenac (Zorvolex) in acute pain

A randomized, double-blind, placebo-controlled, parallel-arm, single center study in 428 patients with moderate-to-severe pain following bunionectomy evaluated patients randomized to diclofenac 18 mg or 35 mg 3 times daily, celecoxib 200 mg twice daily after a 400-mg loading dose, or placebo.[369] At 12 hours, pain intensity with diclofenac 18 and 35 mg was reduced from baseline by 48% and 51%, respectively, compared to 24% in the placebo group. At 24 hours, pain intensity was reduced by 69%, 73%, versus 52%, in diclofenac 18 and 35 mg versus placebo. All of these differences from placebo were statistically significant. Compared with celecoxib, overall reductions in pain intensity were greater with diclofenac 35 mg and similar with diclofenac 18 mg.

diclofenac (Zorvolex) and placebo in OA

A randomized, double-blind, parallel-group, placebo-controlled, 12-week, multicenter trial evaluated 305 patients with osteoarthritis of the hip or knee.[370] Patients were randomized to diclofenac 35 mg 3 times daily, 35 mg twice daily, or placebo. Efficacy parameters included mean change from baseline in Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale score at week 12 (primary efficacy parameter) and in average total WOMAC score over 12 weeks. Submicron diclofenac 35 mg 3 times daily for 12 weeks significantly improved (WOMAC) pain subscale scores from baseline at 12 weeks (-44.1; $p=0.0024$) compared with placebo (-32.5). The twice-daily regimen was not significantly better (-39; $p=0.0795$) than placebo. Submicron diclofenac 35 mg 3 times daily (-35.9; $p=0.0002$) and 35 mg twice daily (-30.3; $p=0.0363$) improved the average total WOMAC score in patients over 12 weeks compared with placebo (-23.2). Diarrhea, headache, nausea, and constipation were the most common adverse events in the submicron diclofenac groups.

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celecoxib (Celebrex) and other NSAIDs in acute pain

Celecoxib has been studied in numerous head-to-head trials with other NSAIDs, such as ibuprofen, ketoprofen, and naproxen, in the treatment of various acute injuries, such as shoulder tendonitis/bursitis, ankle sprain, and tonsillectomy.[371,372,373,374,375] Efficacy between celecoxib and the NSAIDs was generally found to be comparable, with no clinical difference in the incidence of adverse effects.

diclofenac/misoprostol (Arthrotec) and diclofenac

Diclofenac was compared to the combination of diclofenac and misoprostol for efficacy, safety, and incidence of endoscopic upper GI ulcers in a 6 week, double-blind trial enrolling 572 patients with OA and a history of ulcers or erosions.[376] Patients were randomized to diclofenac 75 mg twice daily, diclofenac 50 mg/misoprostol 200 mcg 3 times daily, diclofenac 75 mg/misoprostol 200 mg twice daily, or placebo. All active treatment groups were more effective than placebo in relieving arthritis symptoms. Following the 6 week course of treatment, endoscopic ulcer rates (both gastric and duodenal ulcers) were as follows: diclofenac monotherapy (17%), diclofenac 50 mg with misoprostol (8%), diclofenac 75 mg with misoprostol (7%), and placebo (4%). A higher incidence of flatulence was observed in the diclofenac 75 mg with misoprostol group, whereas diclofenac 50 mg with misoprostol had a higher incidence of diarrhea.

A double-blind, randomized, parallel-group study was conducted to compare the safety and efficacy of a fixed combination of diclofenac 50 mg and misoprostol 200 mcg with a combination of diclofenac 50 mg and placebo in 361 patients with osteoarthritis.[377] Patients with no significant gastroduodenal lesions were enrolled and received study medication 2 or 3 times daily for 4 weeks. Post-treatment endoscopic examination of the gastroduodenal mucosa revealed ulcers in 4% of patients in the diclofenac/placebo group compared with none in the diclofenac/misoprostol group (p=0.015). There were no clinically or statistically significant differences between the 2 treatment groups in formal assessments of OA after either 2 or 4 weeks. Discontinuation of study drug due to adverse events was similar in each group (diclofenac/misoprostol group n=11, diclofenac/placebo group n=10). Eight patients in each group discontinued due to GI adverse events.

Similarly, another double-blind, randomized, parallel-group study compared the efficacy of diclofenac 50 mg/misoprostol 200 mcg or diclofenac 50 mg/placebo in treating the signs and symptoms of RA.[378] A total of 346 patients with RA who had been stabilized on diclofenac for at least 30 days were randomly assigned to receive either combination for 12 weeks. Diclofenac 50 mg/misoprostol 200 mcg demonstrated no statistically significant difference in efficacy in the treatment of the signs and symptoms of RA compared with diclofenac 50 mg/placebo.

diclofenac/misoprostol (Arthrotec) and nabumetone

In a 6 week trial, diclofenac sodium 75 mg with misoprostol 200 mcg twice daily was compared to nabumetone 1,500 mg once daily or placebo for ulcer rates in 1,203 patients with symptomatic OA of the hip or knee.[379] All patients enrolled had a history of endoscopically proven ulcers or erosions. Patients were evaluated by endoscopy at baseline, at withdrawal, or at the end of the 6 week time period. The incidence of duodenal and gastric ulcers confirmed with endoscopy was significantly lower in diclofenac/misoprostol group (4%) compared to nabumetone (11%). Duodenal ulcers were similar between the 2 active treatments. Gastric ulcers were significantly less with diclofenac/misoprostol (1%) compared to nabumetone (9%). Types of adverse events were similar for all treatment groups,

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with GI adverse events predominating. Diclofenac sodium 75 mg with misoprostol 200 mcg was well tolerated by the majority of patients. Withdrawals due to adverse effects were reported as 13% of patients in the diclofenac/misoprostol group, 10% in the nabumetone group, and 9% in the placebo group.

ibuprofen/famotidine (Duexis) and ibuprofen

Ibuprofen/famotidine was compared to ibuprofen in 2 multicenter, double-blind, active-controlled, randomized studies in patients who were expected to require daily administration of an NSAID for at least 6 months for conditions such as the following: OA, RA, chronic low back pain, chronic regional pain syndrome, and chronic soft tissue pain.[380] Duexis is FDA approved only for the treatment of OA and RA. The studies compared the incidence of upper GI (gastric and/or duodenal) ulcer formation in a total 1,533 patients, either as a primary or secondary endpoint. Patients were assigned in a 2:1 ratio to ibuprofen/famotidine
(800 mg/26.6 mg) or ibuprofen (800 mg) 3 times a day for 24 consecutive weeks. Patient age ranged from 39 to 80 years (median age 55 years). Approximately 15% of the patients in both studies were taking concurrent low-dose aspirin (less than or equal to 325 mg daily) and 6% had a history of previous upper gastrointestinal ulcer. *Helicobacter pylori* status was negative at baseline; however, *H. pylori* status was not reassessed during the trials. In both trials ibuprofen/famotidine was associated with a statistically significant reduction in the risk of developing upper GI ulcers compared with ibuprofen alone. Each endpoint was analyzed in 2 fashions. In 1 analysis patients who terminated early, without an endoscopic evaluation within 14 days of their last dose of study drug, were classified as not having an ulcer. This analysis reported GI ulcer in 17.4 to 18.6% of patients in the ibuprofen/famotidine group, compared to 31 to 34.3% of patients in the ibuprofen group ($p<0.0001$). In the second analysis, those patients were classified as having an ulcer, which reported GI ulcer in 8.7 to 10.1% of patients in the ibuprofen/famotidine group, compared to 17.6 to 21.3% of patients in the ibuprofen group ($p\leq0.0004$). The results of the patients that used low-dose aspirin were consistent with the overall findings of the study. In these clinical studies, 23% of patients 65 years of age and older who were treated with ibuprofen/famotidine developed an upper GI ulcer compared to 27% of those patients who received only ibuprofen. In addition, 25% of patients with a prior history of GI ulcer who were treated with ibuprofen/famotidine developed an upper GI ulcer compared to 24% of those patients who received ibuprofen only.

indomethacin (Tivorbex) and placebo

Efficacy of indomethacin (Tivorbex) was demonstrated for treatment of acute pain based on 2 phase 3 randomized, double-blind, placebo-controlled, parallel-arm, multicenter, studies that compared 20 mg of the drug 3 times daily, 40 mg 2 times daily, 40 mg 3 times daily, and placebo taken by patients with pain following bunionectomy.[381] There were a total of 835 patients, randomized equally across the treatment groups, enrolled in the 2 studies. The patients were a mean age of 40 years, ranging from 18 to 68 years, with at least a pain intensity rating of 40 mm on a 100 mm visual analog scale (VAS) during the 9 hour period after anesthetic block was discontinued following the surgery. Mean pain intensity in both studies ranged from 71 to 74 mm. One tablet of 10 mg/325 mg hydrocodone/acetaminophen was allowed every 4 to 6 hours as rescue medication. The use of rescue medication was greater in placebo-treated patients than in Tivorbex-treated patients. In both studies, all 3 Tivorbex dosages demonstrated efficacy in reduction of pain intensity compared to placebo, as measured by the sum of pain intensity difference over zero to 48 hours after the first dose.

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meloxicam submicronized (Vivlodex) and placebo

A multicenter, randomized, double-blind, parallel-arm, placebo-controlled trial evaluated the safety and efficacy of meloxicam (Vivlodex) for the treatment of osteoarthritis pain of the hip or knee in adult patients (n=402).[382,383] Adult patients were assigned meloxicam 5 mg, meloxicam 10 mg, or placebo orally once daily. The primary efficacy endpoint was the change in the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) Pain Subscale score from baseline to 12 weeks. Both meloxicam doses (5 mg and 10 mg) significantly reduced pain compared to placebo at 12 weeks.

naproxen/esomeprazole (Vimovo) and naproxen enteric coated (EC)

The manufacturer performed 2 randomized, multicenter, double-blind studies comparing the incidence of gastric ulcer formation in patients with medical conditions expected to require daily NSAID therapy for at least 6 months.[384,385] If patients (n=854) were less than 50 years old, they required documented history of gastric or duodenal ulcer within the past 5 years. Patients received naproxen/esomeprazole 500 mg/20 mg twice daily or enteric-coated naproxen 500 mg twice daily. About one quarter of the patients were taking low-dose aspirin also. Naproxen/esomeprazole patients showed statistically significant reductions in the 6 month cumulative incidence of gastric ulcers compared to naproxen EC (4.1–7.1% of patients with gastric ulcer versus 23.1–24.3%, respectively; $p<0.001$).

The manufacturer performed two, 12-week, randomized, double-blind, placebo-controlled studies to determine effectiveness of naproxen/esomeprazole in treating the signs and symptoms of OA of the knee.[386] Patients receiving naproxen/esomeprazole 500 mg/20 mg twice daily had significantly better results compared to placebo as measured by Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain subscale and WOMAC physical function subscale, as well as a Patient Global Assessment score.

lansoprazole (Prevacid) and misoprostol (Cytotec)

A prospective, double-blind, multicenter, active- and placebo-controlled study evaluated 537 patients without *H. pylori* who were long-term users of NSAIDs and who had a history of gastric ulcer documented by endoscopy.[387] Patients were randomized to receive placebo, misoprostol 200 mcg 4 times a day, or lansoprazole 15 or 30 mg once daily for 12 weeks. Patients receiving lansoprazole (15 or 30 mg) remained free from gastric ulcer longer than those who received placebo ($p<0.001$), but for a shorter time than those who received misoprostol. By week 12, the percentages of gastric ulcer-free patients were as follows: placebo, 51%; misoprostol, 93%; lansoprazole 15 mg, 80%; and lansoprazole 30 mg, 82%. A significantly higher proportion of patients in the misoprostol group reported treatment-related adverse events and early withdrawal from the study. Therapy was successful for 69% of each active treatment group and 35% for the placebo group. Lansoprazole was superior to placebo for the prevention of NSAID-induced gastric ulcers but was not superior to misoprostol 800 mcg per day. When the poor compliance and potential adverse effects associated with misoprostol are considered, however, proton pump inhibitors (PPIs) and full-dose misoprostol are clinically equivalent.[388,389]

Nasal NSAIDs

ketorolac nasal spray (Sprix) and placebo

Ketorolac nasal spray was studied in a phase 3, randomized, multicenter, double-blind, placebo-controlled trial of 300 adults who had elective abdominal or orthopedic surgery.[390] Post-operatively,

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patients were treated with morphine dosed via patient controlled analgesia (PCA) on an as-needed basis. They were then randomized to the addition of ketorolac nasal spray or placebo, administered every 8 hours for 48 hours. Patients in the ketorolac nasal spray arm had a significantly reduced summed pain intensity difference over 48 hours compared to those in the placebo group. Patients in the ketorolac nasal spray arm required 36% less morphine over 48 hours than those treated with placebo.

A second phase 3, multicenter, double-blind, placebo-controlled study randomized 321 patients who had elective abdominal surgery to treatment with ketorolac nasal spray or placebo.[391] Post-operatively, patients were treated using morphine PCA on an as-needed basis. In addition, ketorolac nasal spray or placebo was administered every 6 hours for 48 hours. Patients in the ketorolac nasal spray group had a significantly greater reduction in summed pain intensity difference over 48 hours compared to those in the placebo group. Patients treated with ketorolac nasal spray required 26% less morphine over 48 hours compared to those in the placebo group.

Topical NSAIDs

diclofenac patch (Flector)

A randomized, double-blind, multicenter, placebo-controlled trial was conducted in 120 patients with traumatic soft tissue injury within 3 hours post-injury.[392] Patients were randomized to twice daily treatment with either diclofenac patch or placebo over a period of 7 days. The primary efficacy endpoint was the area under the curve (AUC) for tenderness over the first 3 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.[393] Either a diclofenac or placebo topical patch was applied directly to the skin overlying the injured site twice daily for 2 weeks. Measures of pain intensity were performed in a daily diary and at clinic visits on days 3, 7, and 14. Diclofenac patch was superior to placebo patch in relieving pain. Statistical significance was seen on clinic days 3 ($p=0.036$) and 14 ($p=0.048$), as well as the daily diary pain ratings at days 3, 7, and 14 ($p\leq0.044$). 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 1 solution to their painful knee for 4 weeks: diclofenac solution 1.5%, vehicle solution, or placebo solution.[394] 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 (-

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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% of patients. In a similarly designed 6-week study, diclofenac solution was again found to be superior to vehicle in 216 patients with osteoarthritis of the knee.[395] A 12-week trial in 216 patients with osteoarthritis of the knee came to the same conclusions.[396]

A 12-week, double-blind, double-dummy, randomized controlled trial was performed in 775 subjects with symptomatic primary osteoarthritis of the knee.[397] 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 4 times daily and took 1 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 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 4 times daily for 8 weeks.[398] 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 4 and 6 weeks. Diclofenac gel decreased pain intensity scores by 42 to 45%, total AUSCAN scores by 35 to 40%, and global rating of disease by 36 to 40%. Significant differences favoring diclofenac gel over vehicle were observed at week 4 for pain intensity and AUSCAN. At week 6, 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 4 times daily for 12 weeks.[399] 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 1. Application site reactions occurred in 5.1 and 2.5% of patients in the diclofenac gel and vehicle groups, respectively.

SUMMARY

The available clinical data do not suggest that any one NSAID offers a clear advantage compared to the others in terms of safety or efficacy, given the complex tradeoffs between the many benefits (e.g., pain relief, improved function, and improved tolerability) and harms (e.g., cardiovascular, renal, and gastrointestinal [GI]) involved. Adequate pain relief at the expense of an increase in cardiovascular risk

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could be an acceptable tradeoff for some patients. Others may consider even a marginal increase in cardiovascular risk unacceptable. When weighing the potential effects of any of these agents, the following patient factors should be considered prior to initiation of therapy: age, comorbid conditions, and concomitant medications. NSAIDs should be used in the lowest effective dose. Zorvolex, a low-dose diclofenac formulation, lacks comparison to other diclofenac formulations or other traditional NSAIDs.

The addition of misoprostol to diclofenac (Arthrotec) in an attempt to reduce GI ulcers is efficacious, but many patients have difficulty tolerating the GI adverse effects, including diarrhea, associated with misoprostol. Esomeprazole/naproxen (Vimovo) has been approved to relieve the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), and ankylosing spondylitis (AS) and to decrease the risk of stomach (gastric) ulcers in patients at risk of developing stomach ulcers from treatment with NSAIDs. Data are available that support use of any proton pump inhibitor with concurrent NSAID administration. Ibuprofen/famotidine (Duexis) is the newest combination agent in this class and is indicated for the relief of signs and symptoms of OA and RA and to decrease the risk of developing upper GI ulcers.

Ketorolac nasal spray (Sprix) offers an alternative method of drug delivery.

The topical NSAIDs are indicated for treatment of acute pain conditions, including strains and sprains, as well as chronic pain conditions like osteoarthritis. For patients at risk for GI or cardiovascular events, topical administration of diclofenac (Flector, Pennsaid, Voltaren gel, and diclofenac-containing kits) provides an alternative method of drug delivery.

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