TEXAS Health and Human Services

Medicaid Drug Use Criteria

Oral/Rectal Nonsteroidal Anti-Inflammatory Drugs

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

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

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1 Dosage

Nonselective oral and rectal NSAIDs are FDA-approved for use in rheumatoid arthritis/juvenile rheumatoid arthritis (JRA), osteoarthritis, ankylosing spondylitis, pain management, dysmenorrhea, fever, migraines, and cluster headaches. JRA is

now also known as juvenile idiopathic arthritis (JIA) or juvenile arthritis (JA). Diclofenac, ibuprofen, and naproxen are also available as combination therapy with gastric acid suppressants to minimize the risk of NSAID-associated gastric ulcer development.[1-3]

1.1 Adults

Adult maximum daily NSAID dosages as monotherapy and combination therapy are summarized in Tables 1 and 2 and should not exceed these recommended maximum values.

Table 1. NSAID Maximum Recommended Daily Dosages for Adults: Monotherapy

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Daily Dosage
acute ischemic stroke	aspirin extended-release (ER) (Durlaza®)	162.5 mg ER capsule	162.5 mg once daily
stroke prevention in patients with TIA or other stroke risk factors	aspirin ER		162.5 mg once daily
arterial thromboembolism prophylaxis	aspirin (generics)	81 mg chewable/EC tablets; 325 mg regular/EC tablets	325 mg once daily
fever, pain (mild to moderate including dysmenorrhea)	aspirin (generics)	81 mg chewable/ enteric-coated (EC) tablets; 325 mg, 500 mg regular/EC tablets; 300 mg, 600 mg rectal suppositories	4000 mg/day in divided doses
myocardial infarction	aspirin (generics)	81 mg chewable/EC tablets; 325 mg regular/EC tablets	325 mg x1 dose, chewed
myocardial infarction prevention	aspirin (generics)	81 mg chewable/EC tablets	162 mg once daily
osteoarthritis	aspirin (generics)	325 mg, 500 mg, regular/EC tablets	3000 mg/day in divided doses

rheumatoid arthritis	aspirin (generics)	325 mg, 500 mg, regular/EC tablets	titrate to a plasma salicylate level between 150- 300 mcg/ mL
stroke prevention in patients with TIA or other stroke risk factors	aspirin (generics)	81 mg chewable/EC tablets; 325 mg regular/EC tablets	325 mg once daily
fever, mild/ moderate pain	choline magnesium trisalicylate	500 mg, 750 mg, 1000 mg tablets; 500 mg/5 mL solution	3000 mg/day in divided doses
osteoarthritis	diclofenac (Zorvolex®)	18 mg, 35 mg capsules	105 mg/day in divided doses
	diclofenac potassium immediate-release (IR) (generics)	50 mg IR tablets	150 mg/day in divided doses
	diclofenac sodium delayed-release (DR) (generics)	25 mg, 50 mg, 75 mg DR tablets	150 mg/day in divided doses
	diclofenac sodium extended-release (ER) (generics)	100 mg ER tablets	100 mg once daily
rheumatoid arthritis	diclofenac potassium (generics)		200 mg/day in divided doses
	diclofenac sodium DR (generics)		200 mg/day in divided doses
	diclofenac sodium ER (generics)		200 mg/day in divided doses
migraine	diclofenac potassium (Cambia®)	50 mg oral powder for solution	50 mg (1 packet) as single dose
ankylosing spondylitis	diclofenac sodium DR		125 mg/day in divided doses
primary dysmenorrhea	diclofenac potassium IR		150 mg/day in divided doses

pain (mild to moderate)	diclofenac (Zorvolex®)		105 mg/day in divided doses
	diclofenac potassium (Zipsor®)	25 mg capsule	100 mg/day in divided doses
	diclofenac potassium		150 mg/day in divided doses
osteoarthritis	diflunisal	500 mg tablets	1500 mg/day in divided doses
pain (mild to moderate)	diflunisal		1500 mg/day in divided doses
rheumatoid arthritis	diflunisal		1500 mg/day in divided doses
acute pain	etodolac IR (generics)	200 mg, 300 mg IR capsule; 400 mg, 500 mg IR tablet	1200 mg/day in divided doses
osteoarthritis	etodolac IR	300 mg IR capsules; 400 mg, 500 mg IR tablets	1200 mg/day in divided doses
	etodolac ER (generics)	400 mg, 500 mg, 600 mg ER tablets	1200 mg once daily
rheumatoid arthritis	etodolac IR		1200 mg/day in divided doses
	etodolac ER		1200 mg once daily
osteoarthritis	fenoprofen capsules (Nalfon®, generics); tablets (generics)	200 mg, 400 mg capsules; 600 mg tablets	3200 mg/day in divided doses
pain (mild to moderate)	fenoprofen		3200 mg/ day in divided doses
rheumatoid arthritis	fenoprofen		3200 mg/day in divided doses
osteoarthritis	flurbiprofen (generics)	50 mg, 100 mg tablets	300 mg/day in divided doses
rheumatoid arthritis	flurbiprofen		300 mg/day in divided doses

dysmenorrhea	ibuprofen (Advil®, Motrin®, generics)	100 mg chewable tablets; 200 mg, 400 mg, 600 mg, 800 mg tablets; 200 mg capsule; 100 mg/5 mL suspension	3200 mg/day in divided doses
fever	ibuprofen		3200 mg/day in divided doses
headache	ibuprofen		3200 mg/day in divided doses
migraine	ibuprofen		3200 mg/day in divided doses
osteoarthritis	ibuprofen		3200 mg/day in divided doses
pain (mild to moderate)	ibuprofen		3200 mg/day in divided doses
rheumatoid arthritis	ibuprofen		3200 mg/day in divided doses
acute bursitis or tendinitis	indomethacin IR (generics)	25 mg, 50 mg capsules; 25 mg/5 mL suspension	200 mg/day in divided doses
	indomethacin ER (generics)	75 mg ER capsules	150 mg/day in divided doses
	indomethacin rectal (generics)	50 mg rectal suppository	200 mg/day in divided doses; no more than 100 mg per dose
acute gouty arthritis	indomethacin IR (generics)		200 mg/day in divided doses
	indomethacin rectal (generics)		200 mg/day in divided doses; no more than 100 mg per dose
acute pain (mild to moderate)	indomethacin (Tivorbex®)	20 mg, 40 mg capsules	120 mg/day in divided doses
ankylosing spondylitis	indomethacin IR (generics)		200 mg/day in divided doses
	indomethacin ER (generics)		150 mg/day in divided doses
	indomethacin rectal (generics)		200 mg/day in divided doses; no more than 100 mg per dose

osteoarthritis	indomethacin IR (generics)		200 mg/day in divided doses
	indomethacin ER (generics)		150 mg/day in divided doses
	indomethacin rectal (generics)		200 mg/day in divided doses; no more than 100 mg per dose
rheumatoid arthritis	indomethacin IR (generics)		200 mg/day in divided doses
	indomethacin ER (generics)		150 mg/day in divided doses
	indomethacin rectal (generics)		200 mg/day in divided doses; no more than 100 mg per dose
osteoarthritis	ketoprofen IR (generics)	25 mg, 50 mg, 75 mg IR capsules	300 mg/day in divided doses
	ketoprofen ER (generics)	200 mg ER capsule	200 mg once daily
pain (mild/moderate, including acute dysmenorrhea)	ketoprofen IR (generics)		300 mg/day in divided doses
rheumatoid arthritis	ketoprofen IR (generics)		300 mg/day in divided doses
	ketoprofen ER (generics)		200 mg once daily
pain (mild/moderate)	magnesium salicylate (Doans®, generics)	580 mg extended-release caplets	4640 mg/day (8 tablets) in divided doses
dysmenorrhea	meclofenamate (generics)	50 mg, 100 mg capsules	300 mg/day in divided doses
osteoarthritis	meclofenamate		400 mg/day in divided doses
pain (mild/ moderate)	meclofenamate		400 mg/day in divided doses
rheumatoid arthritis	meclofenamate		400 mg/day in divided doses
pain (mild/ moderate including dysmenorrhea)	mefenamic acid (generics)	250 mg capsules	1250 mg in divided doses on day 1; 1000 mg/day in divided doses on days 2-7

osteoarthritis	meloxicam (Mobic®, generics)	7.5 mg, 15 mg tablets, 7.5 mg/ 5 mL suspension	15 mg/day once daily
	meloxicam (Vivlodex®)	5 mg, 10 mg capsules	10 mg/day once daily
	meloxicam (Qmiiz® ODT)	7.5 mg, 15 mg oral disintegrating tablets (ODT)	15 mg/ day once daily
rheumatoid arthritis	meloxicam (Mobic®, generics)		15 mg/day once daily
	meloxicam (Qmiiz® ODT)		15 mg/ day once daily
osteoarthritis	nabumetone (generics)	500 mg, 750 mg tablets	2000 mg/day in single or divided doses
rheumatoid arthritis	nabumetone		2000 mg/day in single or divided doses
acute gout	naproxen IR (Aleve®, Naprosyn®, generics)	220 mg IR capsule; 220 mg, 250 mg, 275 mg, 375 mg, 500 mg IR tablets; 125 mg/5 mL IR suspension	1500 mg/day in divided doses
ankylosing spondylitis	naproxen IR		1500 mg/day in divided doses
bursitis/tendinitis	naproxen IR		1500 mg/day in divided doses
osteoarthritis	naproxen IR		1500 mg/day in divided doses
pain (mild/moderate including dysmenorrhea)	naproxen IR**		1500 mg/day in divided doses
rheumatoid arthritis	naproxen IR		1500 mg/day in divided doses
acute gout	naproxen sodium (Anaprox DS®, generics)	220 mg, 275 mg, 550 mg IR tablets	1650 mg/day in divided doses
ankylosing spondylitis	naproxen sodium		1650 mg/day in divided doses
bursitis/tendinitis	naproxen sodium		1650 mg/day in divided doses

osteoarthritis	naproxen sodium		1650 mg/day in divided doses
pain (mild/moderate including dysmenorrhea)	naproxen sodium		1650 mg/day in divided doses
rheumatoid arthritis	naproxen sodium		1650 mg/day in divided doses
ankylosing spondylitis	naproxen DR (EC-Naprosyn®, generics)	375 mg, 500 mg DR tablets	1500 mg/day in divided doses
osteoarthritis	naproxen DR		1500 mg/day in divided doses
rheumatoid arthritis	naproxen DR		1500 mg/day in divided doses
acute gout	naproxen ER (Naprelan®, generics	375 mg, 500 mg, 750 mg ER tablets	1500 mg/day in divided doses
ankylosing spondylitis	naproxen ER		1500 mg/day in divided doses
bursitis/tendinitis	naproxen ER		1500 mg/day in divided doses
osteoarthritis	naproxen ER		1500 mg/day in divided doses
pain (mild/moderate including dysmenorrhea)	naproxen ER		1500 mg/day in divided doses
rheumatoid arthritis	naproxen ER		1500 mg/day in divided doses
osteoarthritis	oxaprozin (Daypro®, generics)	600 mg tablets	1800 mg/day (not to exceed 26 mg/kg/day) in divided doses
rheumatoid arthritis	oxaprozin		1800 mg/day (not to exceed 26 mg/kg/day) in divided doses
osteoarthritis	piroxicam (Feldene®, generics)	10 mg, 20 mg capsules	20 mg once daily
rheumatoid arthritis	piroxicam		20 mg once daily
osteoarthritis	salsalate (Disalcid®, generics)	500 mg, 750 mg tablets	3000 mg/day in divided doses

rheumatoid arthritis	salsalate		3000 mg/day in divided doses
acute gouty arthritis	sulindac (generics)	150 mg, 200 mg tablets	400 mg/day in divided doses
ankylosing spondylitis	sulindac		400 mg/day in divided doses
bursitis/ tendinitis of shoulder	sulindac		400 mg/day in divided doses
osteoarthritis	sulindac		400 mg/day in divided doses
rheumatoid arthritis	sulindac		400 mg/day in divided doses
osteoarthritis	tolmetin (generics)	200 mg, 600 mg tablets; 400 mg capsules	1800 mg/day in divided doses
rheumatoid arthritis	tolmetin		1800 mg/day in divided doses

Table 2. NSAID Maximum Recommended Daily Dosages for Adults: Non-Opioid Combination Therapy

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Daily Dosage
migraine headache	acetaminophen/ aspirin/ caffeine (Excedrin® Migraine, generics)	250 mg/ 250 mg/65 mg tablets	2 tablets/24 hours
pain, including headache	acetaminophen/ aspirin/ caffeine (Excedrin®, generics)		8 tablets/24 hours in divided doses
	acetaminophen/ aspirin/ caffeine (Goody's®)	260 mg/ 520 mg/ 32.5 mg powders	4 powders/24 hours in divided doses
tension or muscle contraction headache	aspirin/butalbital/ caffeine (Fiorinal®, generics)	325 mg/50 mg/40 mg capsules, tablets	6 capsules/24 hours in divided doses (1 or 2 every 4 hours)
osteoarthritis	diclofenac/ misoprostol (Arthrotec®, generics)	50 mg/200 mcg, 75 mg/200 mcg delayed-release tablet	150 mg/600 mcg/day in divided doses
rheumatoid arthritis	diclofenac/ misoprostol		200 mg/800 mcg/day in divided doses

osteoarthritis	ibuprofen/famotidine (Duexis®)	800 mg/26.6 mg tablet	2400 mg/79.8 mg/day in divided doses
rheumatoid arthritis	ibuprofen/ famotidine		2400 mg/79.8 mg/day in divided doses
ankylosing spondylitis in patients at risk of developing NSAID-associated ulcers	naproxen/ esomeprazole (Vimovo®)	375 mg/20 mg, 500 mg/20 mg delayed-release tablet	1000 mg/40 mg/day in divided doses
osteoarthritis in patients at risk of developing NSAID-associated ulcers	naproxen/ esomeprazole		1000 mg/40 mg/day in divided doses
rheumatoid arthritis in patients at risk of developing NSAID-associated ulcers	naproxen/ esomeprazole		1000 mg/40 mg/day in divided doses

1.2 Pediatrics

NSAID safety and efficacy in children have not been established for all available agents. Ibuprofen is FDA-approved for short-term management of fever and mild to moderate pain and long-term management of JRA/JIA/JA in pediatric patients; meloxicam, naproxen, and tolmetin are FDA-approved for use in children as young as 2 years of age. Indomethacin is not FDA-approved in those less than 15 years of age, but JRA/JIA/JA patients between 2 and 14 years of age who have experienced toxicity/lack of benefit from other medications, may receive indomethacin up to a maximum dose of 3 mg/kg/day (no more than 200 mg/day orally). Aspirin, while FDA-approved for use in fever and pain for adolescents, should not be given for fever and muscle aches seen in viral illness due to the potential for Reye's syndrome. Aspirin in combination with acetaminophen and caffeine is FDA-approved for use in adolescent patients for mild to moderate pain, while naproxen/esomeprazole (Vimovo®) is approved for use in adolescents weighing at least 38 kg diagnosed with juvenile rheumatoid arthritis/juvenile idiopathic arthritis at increased risk for NSAID associated gastric ulcers. NSAID dosages for pediatric indications are summarized in Tables 3 and 4. Dosages exceeding these recommendations will be reviewed.

Table 3. NSAID Recommended Maximum Daily Dosages for Pediatric Patients

Treatment Indication	Drug Name	Dosage Form / Strength	Maximum Recommended Daily Dosage
fever/pain	aspirin*	81 mg chewable/EC tablets; 325 mg, 500 mg regular/EC tablets; 300 mg, 600 mg rectal suppositories	Greater than or equal to 12 years of age: 4000 mg/day in divided doses
juvenile rheumatoid arthritis (JRA)/ juvenile idiopathic arthritis (JIA)	choline magnesium trisalicylate	500 mg, 750 mg, 1000 mg tablets; 500 mg/5 mL solution	Less than 37 kg: 50 mg/kg/day Greater than 37 kg: 2250 mg/day adolescents: 3000 mg/day
osteoarthritis	diflunisal (generics)	500 mg tablets	Greater than or equal to 12 years of age: 1500 mg/day in divided doses
pain (mild/ moderate)	diflunisal (generics)		Greater than 12 years of age: 1500 mg/day in divided doses
rheumatoid arthritis	diflunisal (generics)		Greater than 12 years of age: 1500 mg/day in divided doses
JIA/JRA	etodolac extended-release (ER) (generics)	400 mg, 500 mg, 600 mg ER tablets	Greater than or equal to 6 years of age: 20-30 kg: 400 mg/day 31-45 kg: 600 mg/day 46-60 kg: 800 mg/day Greater than 60 kg: 1000 mg/day
fever, pain (mild to moderate)	ibuprofen (Motrin®, generics)	50 mg/1.25 ml oral drops	6 months to 11 months: 200 mg/day in divided doses 12 to 23 months: 300 mg/day in divided doses

fever, pain (mild to moderate)	ibuprofen (Advil®, Motrin®, generics)	100 mg/5 ml suspension	6 months to 2 years: 40 mg/kg/day in divided doses 24-35 lbs (2-3 yrs): 400 mg/day in divided doses 36-47 lbs (4-5 yrs): 600 mg/day in divided doses 48-59 lbs (6-8 yrs): 800 mg/day in divided doses 60-71 lbs (9-10 yrs): 1000 mg/day in divided doses 72-95 lbs (11 yrs): 1200 mg/day in divided doses
fever, pain (mild to moderate)	ibuprofen (Advil®, generics)	100 mg chewable tablets	24-35 lbs (2-3 yrs): 400 mg/day in divided doses 36-47 lbs (4-5 yrs): 600 mg/day in divided doses 48-59 lbs (6-8 yrs): 800 mg/day in divided doses 60-71 lbs (9-10 yrs): 1000 mg/day in divided doses 72-95 lbs (11 yrs): 1200 mg/day in divided doses
fever, pain (mild to moderate)	ibuprofen (Advil®, generics)	200 mg caplets, capsules, or tablets	12 years to 17 years: 1200 mg/day in divided doses
JIA/JRA	ibuprofen (Advil®, Motrin®, generics)	chewable tablets, suspension, tablets	1 to less than 16 years of age: 50 mg/kg/day in divided doses up to 2400 mg/day

arthritic disorders	indomethacin IR+ (generics)	25 mg, 50 mg IR capsules; 25 mg/5 mL suspension	15 to 17 years of age: 200 mg/day in divided doses
	indomethacin ER+ (generics)	75 mg ER capsules	15 to 17 years of age: 150 mg/day in divided doses
	indomethacin+ (generics)	50 mg rectal suppository	15 to 17 years of age: 200 mg/day in divided doses; no more than 100 mg per dose
pain (mild to moderate)	magnesium salicylate (Doans®, generics)	580 mg extended-release caplets	Greater than 12 years of age: 4640 mg/day (8 tablets) in divided doses
dysmenorrhea	meclofenamate (generics)	50 mg, 100 mg capsules	Greater than or equal to 14 years of age: 300 mg/day in divided doses
JIA/JRA	meclofenamate		Greater than or equal to 14 years of age: 400 mg/day in divided doses
pain (mild/ moderate)	meclofenamate		Greater than or equal to 14 years of age: 400 mg/day in divided doses
pain (mild/ moderate, including dysmenorrhea)	mefenamic acid (generics)	250 mg capsules	Greater than or equal to 14 years of age: 1250 mg/day on day 1 500 mg x1 followed by 250 mg every 6 hours); 1000 mg/day on days 2-7
JIA/JRA	meloxicam (Mobic®, generics)	7.5 mg tablets; 7.5 mg orally disintegrating tablets (ODT)	Greater than or equal to 60 kg: 7.5 mg once daily
	meloxicam	7.5 mg/5 mL suspension	Greater than or equal to 2 years of age: 7.5 mg once daily
JIA/JRA	naproxen (Aleve®, Naprosyn®, generics)	220 mg IR capsule; 220 mg, 250 mg, 275 mg, 375 mg, 500 mg IR tablets; 125 mg/5 mL IR suspension	Greater than or equal to 2 years of age: 15 mg/kg/day in divided doses up to 1,000 mg/ day

pain (mild to moderate including dysmenorrhea)	naproxen		Greater than 12 years of age: 1000 mg/day in divided doses
JIA/JRA	oxaprozin (Daypro®, generics)	600 mg tablets	Greater than 6 years to 16 years of age: 22-31 kg: 600 mg/day 32-54 kg: 900 mg/day Greater than 55 kg: 1200 mg/day
JIA/JRA	tolmetin sodium		Greater than or equal to 2 years of age: 30 mg/kg/day, not exceeding 1800 mg daily

- *Do not use in children less than 12 years of age with flu-like symptoms or chickenpox due to risk of Reye syndrome
- +indomethacin not recommended in pediatric patients 2-14 years of age unless adverse effects/lack of efficacy with other NSAIDs justifies risk; maximum dose is 4 mg/kg/day or 200 mg/day, whichever is less

Table 4. NSAID Maximum Recommended Daily Dosages for Pediatrics: Non-Opioid Combination Therapy

Treatment Indication	Drug Name	Dosage Form/ Strength	Maximum Recommended Daily Dosage
pain, including headache	acetaminophen/ aspirin/ caffeine (Excedrin®, generics)	250 mg/ 250 mg/65 mg tablets	12-17 years of age: 8 tablets/24 hours in divided doses
	acetaminophen/ aspirin/ caffeine (Goody's®)	260 mg/ 520 mg/ 32.5 mg powders	12-17 years of age: 4 powders/24 hours in divided doses
juvenile rheumatoid arthritis/ juvenile idiopathic arthritis in patients at risk of developing NSAID-associated ulcers	naproxen/ esomeprazole (Vimovo®)	375 mg/20 mg, 500 mg/20 mg delayed-release tablet	12-17 years of age and Greater than or equal to 50 kg:1000 mg/40 mg/day in two divided doses 12-17 years of age and 38 to 49 kg: 750 mg/40 mg/day in two divided doses

2 Duration of Therapy

2.1 Therapy Limits

The duration of therapy derived for NSAIDs may be long-term and indefinite when prescribed for chronic indications; however, the lowest effective dosages for the shortest possible time period should be utilized. NSAIDs should be prescribed cautiously, if at all, to patients at high risk for gastrointestinal complications and patients with known cardiovascular disease. High-risk patients include those with a history of peptic ulcer disease or gastrointestinal bleeding, those with concurrent prescriptions for anticoagulants or corticosteroids, those prescribed high NSAID doses, those with a history of alcohol use and/or smoking, and the elderly. High-risk patients unable to discontinue or reduce NSAID use may benefit from adjunctive therapy with gastroprotective agents such as misoprostol, a histamine-2 receptor antagonist, or proton pump inhibitors.

Treatment duration is limited for mefenamic acid to minimize the occurrence of adverse events. Mefenamic acid should be prescribed for no longer than seven days for pain management and no longer than three days for dysmenorrhea to reduce the incidence of diarrhea associated with the use of this drug.

Diclofenac powder for oral solution is indicated as a single 50 mg dose to treat acute migraine headaches. The safety and efficacy of a second dose for an attack have not been established.

2.2 NSAID Use in Elderly Patients

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

should be considered in some individuals to reduce GI complications. Medication profiles of elderly patients greater than 60 years of age prescribed NSAIDs with increased risk factors for adverse events or drug-drug interactions will be reviewed.

2.3 NSAID Use and Cardiovascular Risk

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

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

NSAIDs may cause fluid retention or edema in some patients and

should be used cautiously in patients with a history of fluid retention or heart failure.

2.4 NSAID Use and Gastrointestinal Risk

All NSAIDs may be associated with an increased risk of serious gastrointestinal (GI) adverse events, including potentially fatal GI bleeding, ulceration, or gastric/intestinal perforation. The risk of NSAID-associated severe GI adverse events increases in patients with a history of peptic ulcer disease, GI bleeding, smoking, alcohol use, concurrent use of anticoagulants or oral corticosteroids, advanced age, poor health and prolonged NSAID use. However, COX-2 inhibitors like celecoxib may be associated with fewer GI adverse events due to selective COX-2 inhibition. Some trials have shown reduced ulcer complications and lower GI

bleeding rates with celecoxib compared to nonselective NSAIDs. Further long-term studies are necessary to substantiate the perceived lower GI risk associated with COX-2 inhibitors.

3 Duplicative Therapy

The combination of two or more NSAIDs is not recommended except the use of less than 325 mg daily of aspirin plus another NSAID. (Unfortunately, aspirin use is not usually included in a Medicaid database.)

Concurrent administration of an NSAID and ketorolac, another NSAID utilized primarily for pain management with limited treatment duration, is contraindicated due to the potential for increased gastrointestinal adverse events.

The combined use of specific COX-2 inhibitors like celecoxib and nonspecific COX-1/COX-2 inhibitors does not provide additional therapeutic benefit and may result in additive adverse effects, including gastrointestinal toxicity. Concurrent therapy with specific COX-2 inhibitors and nonspecific COX-1/COX-2 inhibitors is not recommended and will be reviewed.

4 Drug-Drug Interactions

Patient profiles will be assessed to identify those drug regimens which may result in clinically significant drug-drug interactions. Drug-drug interactions considered clinically significant for NSAIDs are summarized in Table 5. Only those drug-drug interactions classified as clinical significance level 1 or those considered life-threatening which have not yet been classified will be reviewed.

Table 5. NSAID Drug-Drug Interactions

Target Drug	Interacting Drug	Interaction	Recommendation	Clinical Significance Level[#]

NSAIDs	antihypertensive agents (e.g., ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics)	potential for decreased antihypertensive effects, increased renal impairment risk (especially in patents dependent on renal prostaglandins for perfusion), with combined therapy; increased hyperkalemia risk with potassium-sparing diuretics; NSAIDs may block production of vasodilator and natriuretic prostaglandins	monitor blood pressure, renal function; observe for hyperkalemia with potassium-sparing diuretics; modify therapy as necessary; use combination cautiously in elderly; sulindac, nonacetylated salicylates may be alternative NSAIDS – have less inhibitory effect on prostaglandin synthesis	moderate (DrugReax) 3-moderate (CP)
NSAIDs	antiplatelet drugs (e.g., clopidogrel, prasugrel)	potential for increased bleeding risk due to additive inhibitory effects on platelet aggregation	administer cautiously together; monitor for increased bleeding, especially gastrointestinal (GI) bleeding	clopidogrel – major; prasugrel - moderate (DrugReax) 3-moderate (CP)
NSAIDs	aspirin (ASA)	combined therapy may result in reduced ASA antiplatelet/ cardioprotective effects due to competitive inhibition of COX-1 binding site	ASA should be administered at least 30 minutes before or 8 hours after NSAID; NSAID should be given at least 1 hour after enteric-coated ASA	moderate (DrugReax)
NSAIDs	bisphosphonates	combined therapy may result in additive GI, renal toxicity; NSAIDs also decrease bone mineral density, may attenuate bone mineral stabilizing effects by bisphosphonates	administer combination cautiously; monitor for increased GI/renal adverse effects, reduced bone mineral density	2-major (CP)
NSAIDs	corticosteroids	potential for increased GI adverse effects with combined therapy	monitor for adverse effects; avoid prolonged concurrent administration	3-moderate (CP)

NSAIDs	cyclosporine	increased risk for additive renal dysfunction with concurrent administration; potential for reduced cyclosporine elimination/ increased pharmacologic and adverse effects due to NSAID effects on renal prostaglandins; NSAIDs may mask signs of infection (e.g., fever, swelling)	use cautiously together; monitor clinical status, renal function, serum potassium concentrations	3-moderate (CP)
NSAIDs	fluoroquinolones	increased risk for CNS stimulation and seizures	administer cautiously together; consider alternative therapy in patients with predisposition to seizures	moderate (DrugReax) 3-moderate (CP)
NSAIDs	lithium	NSAIDs may decrease lithium clearance most likely by blocking renal tubular prostaglandins; may result in increased lithium levels and potential for adverse effects	avoid combination, if possible; if concurrent therapy necessary, monitor lithium levels and signs/symptoms of lithium toxicity; sulindac, aspirin do not affect lithium clearance -may be alternative NSAIDS	moderate (DrugReax) 3-moderate (CP)
NSAIDs	low molecular weight heparins	potential for additive bleeding adverse effects; NSAIDs inhibit platelet aggregation and have increased GI bleeding risk, prolonged bleeding time	avoid concurrent therapy, if possible; if drug combination necessary, use cautiously, monitor for signs/symptoms of bleeding	major (DrugReax) 2-major (CP)
NSAIDs	methotrexate (MTX)	potential for increased MTX serum levels, risk of enhanced pharmacologic/toxic effects as NSAIDs can reduce MTX clearance	avoid concurrent NSAIDs within 10 days of high-dose MTX; otherwise, use cautiously together; monitor for increased myelopsuppressive, GI adverse effects; may consider using longer leucovorin rescue	major (DrugReax) 1-severe (CP)

NSAIDs	phenytoin	NSAIDs may inhibit phenytoin metabolism, with increased risk for enhanced phenytoin pharmacologic/toxic effects (e.g., ataxia, nystagmus, hyperreflexia)	monitor for signs/symptoms of phenytoin toxicity, especially in patients with renal impairment; adjust doses as necessary	moderate (DrugReax)
NSAIDs	select azole antifungals (e.g., fluconazole, voriconazole)	for NSAIDs metabolized by CYP2C9, increased risk of elevated NSAID plasma levels and potential for enhanced pharmacologic/adverse effects; select antifungals inhibit CYP2C9	administer cautiously together; monitor for increased NSAID pharmacologic/adverse effects (e.g., bleeding, renal dysfunction); consider reduced NSAID doses, if necessary, or alternate NSAID/antifungal that does not affect metabolism	moderate (DrugReax) 3-moderate (CP)
NSAIDs	SSRIs/SNRIs (e.g., milnacipran)	increased bleeding risk with combined therapy, especially GI bleeding; SSRIs/SNRIs deplete platelet serotonin, which may impair platelet aggregation	monitor for signs/symptoms of bleeding; may consider lower NSAID doses, shorter treatment durations, adding proton pump inhibitor, or substituting tricyclic antidepressant for SSRI/SNRI	SSRIs –major; SNRIs-moderate (DrugReax) 3-moderate (CP)
NSAIDs	sulfonylureas	increased risk for additive hypoglycemia	monitor serum glucose concentrations; adjust doses as necessary	moderate (DrugReax) 4-minor (CP)
NSAIDs	tacrolimus	potential for additive nephrotoxicity with combined therapy due to NSAID inhibitory effects on renal prostaglandins	avoid combination, if possible; if concurrent therapy necessary, closely monitor renal function	major (DrugReax) 3-moderate (CP)
NSAIDs	warfarin	combined therapy may result in increased INR and increased risk of GI adverse effects, especially in elderly; mechanism unknown	monitor anticoagulant activity, especially in first several days of combination therapy; adjust warfarin doses as necessary	major (DrugReax) 2-major (CP)

- #CP = Clinical Pharmacology

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