Therapeutic Class Overview
Oral nonsteroidal anti-inflammatory drugs (NSAIDs)

INTRODUCTION

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are a large class of medications with analgesic, anti-inflammatory, and anti-pyretic properties used for a wide variety of conditions including pain, rheumatoid arthritis (RA), osteoarthritis (OA), primary dysmenorrhea, ankylosing spondylitis (AS), juvenile idiopathic arthritis (JIA), acute migraine, and acute gout *(Conaghan 2012).*
  - RA is an autoimmune inflammatory arthritis that can be treated with conventional or biologic disease-modifying antirheumatic drugs (DMARDs) such as Trexall (methotrexate) or Humira (adalimumab), systemic or intraarticular (IA) corticosteroids, and/or oral or topical analgesics including NSAIDs *(Singh et al 2015).*
  - OA is the most common form of arthritis, and is a degenerative inflammatory disease that can be treated with oral or topical analgesics including NSAIDs, IA corticosteroid or hyaluronate injections, Cymbalta (duloxetine), and physical therapy *(Hochberg et al 2012, Loeser 2018).*
  - Primary dysmenorrhea is menstrual pain in the absence of other pelvic pathology, and represents one of the most common causes of pelvic pain. It can be treated with oral NSAIDs, hormonal contraceptives, topical heat, and exercise *(Osayande et al 2013).*
  - AS is a chronic inflammatory arthritis characterized by sacro-iliac joint involvement that can be treated with oral or topical NSAIDs, tumor necrosis factor inhibitors, slow acting antirheumatic drugs including Plaquenil (hydroxychloroquine), locally administered parenteral glucocorticoids, physical therapy, or surgery *(Ward et al 2016).*
  - JIA is a chronic idiopathic inflammatory disorder that affects pediatric patients. JIA encompasses multiple forms of arthritis in childhood, including what was previously described as juvenile rheumatoid arthritis before being supplanted by the newer term. Treatment for JIA includes conventional or biologic DMARDs, intravenous immunoglobulin, calcineurin inhibitors, and NSAIDs *(Grom 2018, Ringold et al 2013).*
  - Migraine is a disorder associated with severe headaches worsened by activity, light, and/or sounds, and can be treated with oral analgesics including NSAIDs and opioids, ergot derivative medications, triptans, antiemetics, and antiepileptics *(Marmura et al 2015).*
  - Gout is the most common cause of inflammatory arthritis in adults, and typically presents acutely as synovitis due to tissue deposition of monosodium urate crystals. Acute gout can be treated with Colcrys (colchicine), systemic corticosteroids, and/or NSAIDs *(Khanna et al 2012).*
- Some NSAIDs including ibuprofen and naproxen are available at lower strengths as over-the-counter (OTC) formulations, which do not require a prescription. The same compounds are also available in higher strengths as a prescription-only product. Other NSAIDs are available only by prescription regardless of strength.
- Both prescription-strength and OTC NSAIDs are widely utilized, accounting for over 111 million prescriptions annually and 60% of the OTC analgesic market in the United States (U.S.). The use of NSAIDs has been increasing over time and utilization is highest in individuals over 60 years of age *(Conaghan 2012, Davis et al 2017).*
- The therapeutic effects of NSAIDs are primarily attributed to inhibition of cyclooxygenase (COX) enzymes, which participate in the formation of mediators associated with inflammation and pain. Most NSAIDs block both related isoforms of the COX enzyme: COX-1 and COX-2 *(Solomon 2017).*
  - COX-1 regulates normal cellular processes such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function. Inhibition of COX-1 is theorized to contribute to some adverse events associated with NSAID use *(Solomon 2017).*
  - COX-2 is usually undetectable in most tissues, but its expression is increased during states of inflammation *(Solomon 2017).*
- In 2005, the Food and Drug Administration (FDA) began requiring all prescription NSAIDs to carry a boxed warning highlighting the potential for increased risk of cardiovascular (CV) events such as myocardial infarction (MI) and stroke, as well as gastrointestinal (GI) bleeding. OTC NSAIDs were also required to have labeling providing more specific information about these risks *(FDA Drug Safety Communication).*
  - In 2015, following an advisory committee review of additional evidence, the FDA required revisions to existing warnings for both prescription and OTC NSAIDs to strengthen messaging regarding potential risks of use. Statements were included regarding the risk potentially increasing with duration of use *(FDA Drug Safety Communication).*

- Most NSAIDs on the market have been generic for some time. In fact, many of the originator brand products have been discontinued, leaving only generic versions on the market. The newer patented NSAIDs Cambia (diclofenac potassium), Durlaza (aspirin ER), Tivorbex (indomethacin), Vivlodex (meloxicam), and Zorvolex (diclofenac) are new formulations of previously approved molecular entities manufactured at a new strength, dosage form, and/or delivery system.
- This review includes an evaluation of orally-administered, single-agent, prescription NSAIDs. Products that are available OTC are included if they are also available in a prescription-only strength or formulation.
- Medispan class: Nonsteroidal Anti-inflammatory Drug (NSAID), Oral

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Anaprox (naproxen sodium)	✔
Anaprox DS (naproxen sodium)	✔
Cambia (diclofenac potassium)	-
Daypro (oxaprozin)	✔
diclofenac potassium	✔
diclofenac sodium DR	✔
diclofenac sodium ER	✔
diflunisal	✔
Durlaza (aspirin ER)	-
EC-Naprosyn (naproxen DR)	✔
etodolac	✔
etodolac ER	✔
Feldene (piroxicam)	✔
flurbiprofen	✔
ibuprofen	✔
Indocin (indomethacin)	✔ *
indomethacin ER	✔
ketoprofen	✔
ketoprofen ER	✔
ketorolac	✔
meclofenamate	✔ †
Mobic (meloxicam)	✔
nabumetone	✔
Nalfon (fenoprofen)	✔
Naprelan (naproxen sodium SR)	✔
Naprosyn (naproxen)	✔
Ponstel (mefenamic acid)	✔
ProFeno (fenoprofen)	✔
sulindac	✔
Tivorbex (indomethacin)	-
tolmetin	✔
Vivlodex (meloxicam)	-
Zipsor (diclofenac potassium)	✔
Zorvolex (diclofenac)	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)
*Only capsule formulation is available generically; the oral suspension and rectal suppository are branded products only.
†Available as a single-source generic product.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Mild to moderate pain	RA	OA	Primary dysmenorrhea	AS	Other indication(s)
Anaprox (naproxen sodium)	✔ *	✔	✔	✔ *	✔	• Juvenile RA • Tendonitis or bursitis* • Acute gout*
Anaprox DS (naproxen sodium)	✔ *	✔	✔	✔ *	✔	• Juvenile RA • Tendonitis or bursitis* • Acute gout*
Cambia (diclofenac potassium)						• Acute migraine
Daypro (oxaprozin)		✔	✔			• Juvenile RA
diclofenac potassium	✔	✔	✔	✔		
diclofenac sodium DR		✔	✔		✔	
diclofenac sodium ER		✔	✔			
diflunisal	✔	✔	✔			
Durlaza (aspirin ER)						• Reduce risk of death and MI • Reduce risk of death and recurrent stroke
EC-Naprosyn (naproxen DR)		✔	✔		✔	• Juvenile RA
etodolac	✔ †	✔	✔			
etodolac ER		✔	✔			• Juvenile RA
Feldene (piroxicam)		✔	✔			
flurbiprofen		✔	✔			
ibuprofen	✔	✔	✔	✔		
Indocin (indomethacin)		✔	✔		✔	• Acute painful shoulder • Acute gouty arthritis
indomethacin ER		✔	✔		✔	• Acute painful shoulder • Acute gouty arthritis
ketoprofen	✔	✔	✔	✔		
ketoprofen ER		✔	✔			
ketorolac	✔ ‡					
meclofenamate	✔	✔	✔	✔	✔	• Reduction of fever • Juvenile RA • Acute painful shoulder • Acute gouty arthritis
Mobic (meloxicam)		✔	✔			• Juvenile RA
nabumetone		✔	✔			
Nalfon (fenoprofen)	✔	✔	✔			

Drug	Mild to moderate pain	RA	OA	Primary dysmenorrhea	AS	Other indication(s)
Naprelan (naproxen sodium SR)	✔	✔	✔	✔	✔	• Tendonitis or bursitis • Acute gout
Naprosyn (naproxen)	✔ *	✔	✔	✔ *	✔	• Juvenile RA • Tendonitis or bursitis* • Acute gout*
Ponstel (mefenamic acid)	✔ §			✔		
Profeno (fenoprofen)	✔	✔	✔			
sulindac		✔	✔		✔	• Acute painful shoulder • Acute gouty arthritis
Tivorbex (indomethacin)	✔ †					
tolmetin		✔	✔			• Juvenile RA
Vivlodex (meloxicam)			✔			
Zipsor (diclofenac potassium)	✔					
Zorvolex (diclofenac)	✔ †		✔			

*Suspension formulation only
†Acute pain only
‡Acute pain only, treatment limited to 5 days of total therapy
§Acute pain only, when therapy will not exceed 7 days
(*Prescribing information: Anaprox/Anaprox DS, EC-Naprosyn, Naprosyn 2018, Cambia 2017, Daypro 2017, diclofenac potassium 2017, diclofenac sodium DR 2017, diclofenac sodium ER 2017, diflunisal 2017, Durlaza 2015, etodolac 2017, etodolac ER 2017, Feldene 2017, flurbiprofen 2017, ibuprofen 2014, Indocin 2018, indomethacin ER 2017, ketoprofen, ketoprofen ER 2015, ketorolac 2016, meclofenamate 2015, Mobic 2018, nabumetone 2016, Nalfon 2017, Naprelan 2017, Naprosyn 2018, Ponstel 2017, Profeno 2017, sulindac 2016, Tivorbex 2018, tolmetin 2015, Vivlodex 2015, Zipsor 2017, Zorvolex 2016*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Generally, the NSAID class has well-established efficacy as analgesic and anti-inflammatory medications. In addition to placebo-controlled pivotal trials for individual agents, several systematic reviews and meta-analyses have shown that NSAIDs compare favorably to placebo for pain reduction for various conditions. Most have also concluded that there is insufficient evidence that any one NSAID is more effective than any other *(Derry et al 2012, Enthoven et al 2016, Kroon et al 2015, Marjoribanks et al 2015, Wang et al 2016).*
  - A Cochrane review of NSAIDs for treatment of chronic low back pain evaluated 13 trials (N = 1354), and concluded that there is evidence that NSAIDs are more effective than placebo at reducing pain and disability. No difference in efficacy was seen between individual NSAIDs *(Enthoven et al 2016).*
  - A systematic review (N = 68 trials) of NSAID use in various types of chronic pain including OA, RA, soft-tissue pain, back pain, and AS found that there are no significant differences in pain relief between nonselective NSAIDs, partially selective NSAIDs (defined in the trial as meloxicam, nabumetone, and etodolac), and celecoxib. Comparisons between nonselective NSAIDs also found no clear differences in efficacy *(Peterson et al 2010).*
  - In a comparative effectiveness review, the Agency for Healthcare Research and Quality (AHRQ) assessed the efficacy of selective and non-selective NSAIDs, aspirin, acetaminophen, and topical NSAIDs and rubefacients for long-term improvements in OA symptoms. The review found that good evidence exists that nonselective and partially

selective NSAIDs do not differ significantly in efficacy for pain relief or symptom improvement as compared to each other or to COX-2 selective NSAIDs. However, the review concluded that no evidence exists comparing the efficacy of aspirin to NSAIDs for treatment of pain. Oral NSAIDs were found to have similar efficacy to topical NSAIDs for OA of the knee *(Chou et al 2006).*

- A Cochrane review including 80 trials (N = 5820) concluded that NSAIDs are a very effective treatment for primary dysmenorrhea. Insufficient evidence was found to determine if any individual NSAID is more effective than another NSAID, including comparisons between COX-2 selective and nonselective NSAIDs *(Marjoribanks et al 2015).*
- A network meta-analysis of 26 trials (N = 3410) for treatment of pain due to AS found that there were no significant differences in efficacy between NSAIDs. Etoricoxib (an NSAID not available in the U.S.) was found to be superior to celecoxib, ketoprofen, and tenoxicam (also not available in the U.S.). No other significant differences between NSAIDs were found. All 20 evaluated NSAIDs reduced pain as compared to placebo *(Wang et al 2016).*
- A systematic review of 39 studies (N = 4356) evaluating the use of NSAIDs for axial spondyloarthritis determined that there is high to moderate quality evidence that NSAIDs are efficacious for treatment of axial spondyloarthritis. NSAIDs were more beneficial than placebo and there was no difference in efficacy between the various evaluated NSAIDs, including COX-2 selective agents *(Kroon et al 2015).*
- A Cochrane review of NSAIDs for treatment of acute gout including 23 trials (N = 2200) determined that while data is insufficient to draw firm conclusions, they do not conflict with guideline recommendations for the use of NSAIDs as first-line treatment. Additionally, moderate-quality evidence was found to support the claim that COX-2 selective NSAIDs and nonselective NSAIDs are probably equally beneficial *(van Durme et al 2014).*

- Comparative reviews have also been conducted evaluating the efficacy of oral NSAIDs as compared to topical NSAIDs and other non-NSAID agents for the treatment of various types of pain.
  - A Cochrane review of 34 studies (N = 7688) evaluated oral NSAIDs and topical diclofenac for treatment of OA pain. The review found that while both were significantly more effective than placebo, there appeared to be no difference in efficacy between the two treatment modalities for knee or hand OA *(Derry et al 2012).*
  - A network meta-analysis of 137 studies (N = 33,243) comparing acetaminophen, oral NSAIDs, and IA injections of corticosteroids or hyaluronic acid concluded that IA treatments were clinically superior to oral NSAIDs after 3 months of treatment. Oral NSAIDs were in turn clinically superior to acetaminophen for treatment of OA pain after the same duration of treatment *(Bannuru et al 2015).*
  - For treatment of OA, AHRQ has stated that there is good evidence that acetaminophen is modestly inferior in efficacy compared to NSAIDs, although with a lower risk of GI complications *(Chou et al 2006).*
  - A network meta-analysis found that select NSAIDs (celecoxib, diclofenac, naproxen, and piroxicam) and opioids are similarly effective in reduction of pain for the treatment of knee OA *(Smith et al 2016).*
  - A network meta-analysis comparing ibuprofen, diclofenac potassium, aspirin, and multiple triptans (including a combination of naproxen and sumatriptan) for treatment of migraine found that ibuprofen and aspirin were inferior to eletriptan and rizatriptan with respect to pain relief, but that diclofenac potassium was more effective than any other intervention for pain relief at 2 hours. However, diclofenac did have the largest rate of migraine recurrence requiring rescue therapy. Addition of naproxen to sumatriptan significantly reduced the rate of migraine recurrence as compared to sumatriptan alone. Overall tolerability was similar between the NSAIDs, which as a class was superior to that of the triptans *(Xu et al 2016).*
  - A Cochrane review concluded that for primary dysmenorrhea, the NSAID class appears to be more effective than acetaminophen. However, this analysis was based on only 3 trials that compared NSAIDs with acetaminophen, and the quality of evidence was low *(Marjoribanks et al 2015).*
- Studies were conducted evaluating the efficacy of Tivorbex (indomethacin), Vivlodex (meloxicam), and Zorvolex (diclofenac) as compared to placebo. All 3 products were found to be superior to placebo for the treatment of pain in individual randomized controlled trials. Studies were not conducted comparing efficacy or safety of these products vs existing higher-dose generic formulations of indomethacin, meloxicam, or diclofenac. Systemic exposure of Tivorbex, Vivlodex, and Zorvolex has not been shown to be equivalent to other formulations of oral indomethacin, meloxicam, and diclofenac, respectively.
- Several large systematic reviews and meta-analyses have analyzed the risk of adverse events with use of NSAIDs, including comparisons between the nonselective NSAIDs and between nonselective and COX-2 selective NSAIDs.
  - A large meta-analysis of 280 trials (N = 124,513) evaluating the CV and GI risk of various NSAIDs concluded that the vascular risk of high-dose diclofenac (150 mg daily or greater) and possibly ibuprofen are comparable to that of COX-2 selective NSAIDs. By contrast, high-dose naproxen (100 mg daily or greater) is associated with less vascular risk than other NSAIDs. All NSAIDs increased risk of upper GI complications by a factor of 2 to 4, although the lowest

incidence was seen with COX-2 selective NSAIDs. None of the evaluated NSAIDs were found to increase risk of stroke *(Coxib and traditional NSAID Trialists' [CNT] Collaboration 2013).*
  - A Bayesian meta-analysis of MI risk with NSAID use in a cohort of 446,763 individuals found that all NSAIDs, including naproxen and celecoxib, were associated with an increased risk of acute MI. Risk was greatest with use of higher doses as well as during the first month of NSAID use. Risk did not appear to increase beyond the first 30 days of use *(Bally et al 2017).*
  - A comparative effectiveness review found that all NSAIDs can cause or aggravate hypertension, congestive heart failure, edema, and impaired renal function. Although no clear differences were seen between selective or nonselective NSAIDs in incidence of these adverse events, weak evidence was noted for a lower hypertensive effect with aspirin and sulindac than other NSAIDs. Overall tolerability was similar between the NSAIDs. Aspirin was less well tolerated than the oral NSAIDs *(Chou et al 2006).*

CLINICAL GUIDELINES

- **OA:** The American College of Rheumatology (ACR) conditionally recommends the use of oral NSAIDs as a class for the treatment of hand, hip, and knee OA. Within the NSAID class, no specific agents were identified as being more or less effective or safe as compared to other members of the class. Additional pharmacologic recommendations included acetaminophen, topical NSAIDs, and tramadol *(Hochberg et al 2012).*
  - A conditional recommendation was defined as one based on absence of high-quality evidence and/or evidence of only a small gradient of difference between desirable and undesirable effects of treatment.
  - For patients ≥ 75 years of age, an additional conditional recommendation was made for the use of topical rather than oral NSAIDs for treatment of hand OA. For patients < 75 years old, the technical expert panel expressed no preference for topical rather than oral NSAIDs.
- **Primary dysmenorrhea:** Based upon a Cochrane review of 73 randomized controlled trials, the American Academy of Family Physician recommends oral NSAIDs as first-line treatment for primary dysmenorrhea. Specifically, guidelines support the use of celecoxib, ibuprofen, mefenamic acid, and naproxen. Choice of NSAID should be based on individual patient characteristics as no NSAID has been shown to be more effective than any other *(Osayande et al 2014).*
  - Treatment initiation is recommended 1 to 2 days before expected onset of menses, with treatment duration of 2 to 3 days.
- **AS:** A joint guideline by the ACR, Spondylitis Association of America, and the Spondyloarthritis Research and Treatment Network strongly recommends treatment of active AS with oral NSAIDs. Additionally, a conditional recommendation was provided for continuous treatment with NSAIDs over on-demand treatment. As no formal comparative effectiveness studies of NSAIDs were available, the guideline recommended against designating any particular NSAID as the preferred treatment option. Instead, choice of NSAID should be determined by each patient's history, risk factors, and comorbidities *(Ward et al 2016).*
- **JIA:** ACR recommendations for JIA include initiation of NSAID monotherapy in patients without prior treatment for a maximum of 1 month. The guideline specifically states that continuation of NSAID monotherapy for longer than 2 months in patients with continued disease activity is inappropriate. Both recommendations were based on expert opinion *(Ringold et al 2013).*
- **Acute migraine:** The American Headache Society guidelines for acute treatment of migraine include various degrees of recommendations for use of oral NSAIDs depending on the specific agent. Aspirin, diclofenac, ibuprofen, and naproxen are recommended as having established efficacy. Additional NSAIDs including flurbiprofen and ketoprofen are recommended as probably effective, while celecoxib was deemed to have conflicting or inadequate evidence to support or refute use (*Marmura et al 2015).*
- **Gout:** Oral NSAIDs are recommended by the ACR as an appropriate first-line treatment option for acute gout, either as monotherapy or in combination with systemic corticosteroids and/or oral colchicine. However, the task force did not recommend any specific NSAID over the others *(Khanna et al 2012).*
  - The ACR also supports use of low-dose NSAID therapy as an appropriate first-line method of prophylaxis for acute gout attacks.
  - No consensus was reached on the use of intramuscular ketorolac or topical NSAIDs for the treatment of acute gout.

SAFETY SUMMARY

- **Boxed warnings:**
  - All oral NSAID products with the exception of Durlaza (aspirin ER) share the 2 boxed warnings below for CV and GI risk:
    - Serious CV thrombotic events: NSAIDs cause an increased risk of serious CV thrombotic events, including MI and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. NSAIDs are contraindicated in the setting of coronary artery bypass graft (CABG) surgery.
    - Serious GI bleeding, ulcerations and perforation: NSAIDs cause an increased risk of serious GI adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.
  - Ketorolac carries additional boxed warnings for the following:
    - Renal risk: Ketorolac is contraindicated in patients with advanced renal function impairment and in patients at risk for renal failure due to volume depletion.
    - Risk of bleeding: Ketorolac inhibits platelet function and is, therefore, contraindicated in patients with suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, or incomplete hemostasis, and in those at high risk of bleeding. Ketorolac is contraindicated as a prophylactic analgesic before any major surgery.
    - Risk during labor and delivery: The use of ketorolac tromethamine in labor and delivery is contraindicated because it may adversely affect fetal circulation and inhibit uterine contractions.
    - Concomitant use with NSAIDs: Ketorolac is contraindicated in patients currently receiving aspirin or NSAIDs because of the cumulative risks of inducing serious NSAID-related side effects.
    - Special populations: Dosage should be adjusted for patients 65 years or older, for patients under 50 kg (110 lbs) of body weight, and for patients with moderately elevated serum creatinine.
- **Contraindications:**
  - Most oral NSAID products share a contraindication for use in the setting of CABG surgery, as well as in patients with a history of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Additional contraindications specific to individual compounds are listed below.
  - Fenoprofen (Profeno only):
    - History of significantly impaired renal function
  - Ketorolac:
    - Active or history of peptic ulcer disease; recent or history of GI bleeding or perforation
    - Prophylactic analgesic before any major surgery
    - Advanced renal impairment or patients at risk for renal failure because of volume depletion
    - Labor and delivery
    - Suspected or confirmed cerebrovascular bleeding, hemorrhagic diathesis, incomplete hemostasis and those at high risk of bleeding
    - Patients currently receiving aspirin or NSAIDs
    - Concomitant use with probenecid or pentoxifylline.
- **Warnings and precautions:**
  - Most oral NSAID products share similar warnings and precautions for:
    - Increased risk of CV thrombotic events
    - New onset or worsening of hypertension
    - Increased risk of hospitalization due to heart failure and increased edema
    - Risk of GI effects including ulceration, bleeding, and perforation
    - Risk of renal injury and toxicity
    - Potential for skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis
    - Risk of premature closure of the ductus arteriosus when used in late pregnancy
    - Borderline elevations of one or more liver tests
    - Potential for anemia
    - Risk of severe bronchospasm in patients with preexisting aspirin-sensitive asthma
    - Risk of Reye's syndrome

- Ketorolac:
  - The total combined duration of use of ketorolac tromethamine tablets and IV or IM dosing of ketorolac tromethamine is not to exceed 5 days in adults. Ketorolac tromethamine tablets are not indicated for use in pediatric patients.

- **Adverse events:**
  - Adverse events were similar among products and commonly included GI complaints (abdominal pain, constipation, diarrhea, dyspepsia, flatulence, gross bleeding/perforation, heartburn, nausea, gastric/duodenal GI ulcers, and vomiting), abnormal renal function, anemia, dizziness, edema, elevated liver enzymes, headaches, increased bleeding time, pruritus, rashes, and tinnitus.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Anaprox (naproxen sodium)	Tablets	Oral	Twice daily
Anaprox DS (naproxen sodium)	Tablets	Oral	Twice daily
Cambia (diclofenac potassium)	Powder for oral solution	Oral	Once as needed
Daypro (oxaprozin)	Tablets	Oral	Once daily
diclofenac potassium	Tablets	Oral	Three times daily
diclofenac sodium DR	Tablets	Oral	Three times daily
diclofenac sodium ER	Tablets	Oral	Three times daily
diflunisal	Tablets	Oral	Twice daily
Durlaza (aspirin ER)	Capsules	Oral	Once daily
EC-Naprosyn (naproxen DR)	Tablets	Oral	Twice daily
etodolac	Capsules, Tablets	Oral	Two to four times daily
etodolac ER	Tablets	Oral	Once daily
Feldene (piroxicam)	Capsules	Oral	Once daily
flurbiprofen	Tablets	Oral	Two to four times daily
ibuprofen	Capsules, Tablets	Oral	Four to six times daily
Indocin (indomethacin)	Suspension, Tablets	Oral	Two to three times daily
indomethacin ER	Capsules	Oral	Once to twice daily
ketoprofen	Capsules	Oral	Three to four times daily
ketoprofen ER	Capsules	Oral	Once daily
ketorolac	Tablets	Oral	Four to six times daily
meclofenamate	Capsules	Oral	Three to four times daily
Mobic (meloxicam)	Capsules, Suspension, Tablets	Oral	Once daily
nabumetone	Tablets	Oral	Once to twice daily
Nalfon (fenoprofen)	Capsules, Tablets	Oral	Three to four times daily
Naprelan (naproxen sodium SR)	Tablets	Oral	Once daily
Naprosyn (naproxen)	Suspension, Tablets	Oral	Twice daily
Ponstel (mefenamic acid)	Capsules	Oral	Four times daily
ProFeno (fenoprofen)	Tablets	Oral	Three to four times daily
sulindac	Tablets	Oral	Twice daily
Tivorbex (indomethacin)	Capsules	Oral	Two to three times daily
tolmetin	Capsules, Tablets	Oral	Three times daily
Vivlodex (meloxicam)	Capsules	Oral	Once daily
Zipsor (diclofenac potassium)	Capsules	Oral	Four times daily
Zorvolex (diclofenac)	Capsules	Oral	Three times daily

See the current prescribing information for full details

CONCLUSION

- Oral NSAIDs are efficacious for the treatment of pain, RA, OA, primary dysmenorrhea, AS, acute migraine, and acute gout. Multiple systematic reviews and meta-analyses have shown that NSAIDs are superior to placebo for these indications. Furthermore, practice guidelines for these conditions recommend NSAIDs as a first-line treatment option.
- The totality of currently available evidence on relative efficacy between the available NSAIDs suggests that in general, there does not appear to be a significant difference in efficacy among the NSAIDs. Clinical practice guidelines for the aforementioned conditions support this finding and either recommend the use of NSAIDs as a class or recommend a list of NSAIDs for potential use without specifying a preference between listed agents.
- All NSAIDs carry some degree of risk for adverse events including CV thrombotic events and GI bleeding, ulceration, and perforation. Available evidence for the relative risk of these adverse events amongst NSAIDs is conflicting and inconclusive at this time. All reviewed NSAIDs with the exception of Durlaza (aspirin ER) carry the same boxed warnings for CV and GI risk. Contraindications, warnings/precautions, and adverse effects are similar among products.
- Differences between oral NSAIDs include FDA-labeled indications, available dosage formulations and strengths, and dosing frequency.

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