ANTI-INFLAMMATORY DRUGS, NONSTEROIDAL (Systemic)

Introduction

Revised: 08/15/2000

Interim revision:

This monograph includes information on the following:1) Diclofenac ; 2) Diflunisal ; 3) Etodolac b; 4) Fenoprofen ; 5) Floctafenine a; 6) Flurbiprofen ; 7) Ibuprofen ; 8) Indomethacin ; 9) Ketoprofen ; 10) Meclofenamate b; 11) **Mefenamic Acid;** 12) Meloxicam; 13) Nabumetone ; 14) Naproxen ; 15) Oxaprozin ; 16) Phenylbutazone ; 17) Piroxicam ; 18) Sulindac ; 19) Tenoxicam a; 20) Tiaprofenic Acid a; 21) Tolmetin .

Note: See also individual Ketorolac (Systemic) monograph.
See also individual Meloxicam (Systemic) monograph.
See also Indomethacin¾For Patent Ductus Arteriosus (Systemic) monograph.
See also Anti-inflammatory Agents, Nonsteroidal (Ophthalmic) monograph for information on ophthalmic use of diclofenac, flurbiprofen, and indomethacin.
See also Salicylates (Systemic) monograph for information on aspirin and other salicylates.
INN:

Etodolac b¾Etodolic acid.
Indomethacin¾Indometacin.
Meclofenamate b¾Meclofenamic acid.
BAN:

Meclofenamate b¾Meclofenamic acid.
JAN:

Indomethacin¾Indometacin.
VA CLASSIFICATION (Primary/Secondary)
Diclofenac¾MS102/CN104; MS400; CN105
Diflunisal¾MS102/; MS400; CN105
Etodolac¾MS102/; MS400; CN105
Fenoprofen¾MS102/; MS400; CN105
Floctafenine¾CN104/; MS400
Flurbiprofen¾MS102
Ibuprofen¾MS102/; CN850; MS400 ; CN105
Indomethacin¾MS102/; CN850; CN105; CV900
Ketoprofen¾MS102/; MS400; CN105
Meclofenamate¾MS102/; CN105
Mefenamic Acid¾CN104/
Meloxicam¾MS102
Nabumetone¾MS102
Naproxen¾MS102/; CN850; MS400 ; CN105
Oxaprozin¾MS102
Phenylbutazone¾MS102/

Piroxicam¾MS102/
Sulindac¾MS102/
Tenoxicam¾MS102
Tiaprofenic Acid¾MS102
Tolmetin¾MS102
Commonly used brand name(s):Actiprofen Caplets7; Actron9; Advil7; Advil Caplets7; Advil, Children's7; Albert Tiafen20; Aleve14; Alka Butazolidin16; Anaprox14; Anaprox DS14; Ansaid6; Apo-Diclo1; Apo-Diflunisal2; Apo-Flurbiprofen6; Apo-Ibuprofen7; Apo-Indomethacin8; Apo-Keto9; Apo-Keto-E9; Apo-Napro-Na14; Apo-Napro-Na DS14; Apo-Naproxen14; Apo-Phenylbutazone16; Apo-Piroxicam17; Apo-Sulin18; Apo-Tenoxicam19; Bayer Select Ibuprofen Pain Relief Formula Caplets7; Butazolidin16; Cataflam1; Clinoril18; Cotylbutazone16; Cramp End7; Daypro15; Dolgesic7; Dolobid2; EC-Naprosyn14; Excedrin IB7; Excedrin IB Caplets7; Feldene17; Froben6; Froben SR6; Genpril7; Genpril Caplets7; Haltran7; Ibifon 600 Caplets7; Ibren7; Ibu7; Ibu-2007; Ibu-47; Ibu-67; Ibu-87; Ibu-Tab7; Ibuprin7; Ibuprohm7; Ibuprohm Caplets7; Idarac5; Indocid8; Indocid SR8; Indocin8; Indocin SR8; Lodine3; Lodine XL3; Meclomen10; Medipren7; Medipren Caplets7; Midol IB7; Mobic12; Motrin7; Motrin Chewables7; Motrin, Children's7; Motrin, Children's Oral Drops7; Motrin, Junior Strength Caplets7; Motrin-IB7; Motrin-IB Caplets7; Nalfon4; Nalfon 2004; Naprelan14; Naprosyn14; Naprosyn-E14; Naprosyn-SR14; Naxen14; Novo-Difenac1; Novo-Difenac SR1; Novo-Diflunisal2; Novo-Flurprofen6; Novo-Keto-EC9; Novo-Methacin8; Novo-Naprox14; Novo-Naprox Sodium14; Novo-Naprox Sodium DS14; Novo-Pirocam17; Novo-Profen7; Novo-Sundac18; Novo-Tenoxicam19; Novo-Tolmetin21; Nu-Diclo1; Nu-Flurbiprofen6; Nu-Ibuprofen7; Nu-Indo8; Nu-Naprox14; Nu-Pirox17; Nuprin7; Nuprin Caplets7; Orudis9; Orudis KT9; Orudis-E9; Orudis-SR9; Oruvail9; PMS-Piroxicam17; Pamprin-IB7; Ponstan11; Ponstel11; Q-Profen7; Relafen13; Rhodis9; Rhodis-EC9; Rufen7; Surgam20; Surgam SR20; Synflex14; Synflex DS14; Tolectin 20021; Tolectin 40021; Tolectin 60021; Tolectin DS21; Trendar7; Voltaren1; Voltaren Rapide1; Voltaren SR1.
Other commonly used names are Etodolic acid Etodolac b.

, Indometacin Indomethacin.

, Meclofenamic acid Meclofenamate b.

Note: For a listing of dosage forms and brand names by country availability, see Dosage Forms section(s).

a Not commercially available in the U.S.

b Not commercially available in Canada.

Category

Note: All of these medications have analgesic, antipyretic, and anti-inflammatory actions; however, indications for specific agents may vary because of lack of specific testing and/or clinical-use data as well as the toxicity of the individual nonsteroidal anti-inflammatory drug (NSAID). Clinically, most of these agents are used to treat a variety of painful and/or inflammatory conditions, both rheumatic and nonrheumatic, even though the specific uses are not listed in U.S. or Canadian product labeling. 225Antirheumatic (nonsteroidal anti-inflammatory)¾Diclofenac; Diflunisal; Etodolac b; Fenoprofen; Flurbiprofen; Ibuprofen; Indomethacin; Ketoprofen; Meclofenamate b; Meloxicam; Nabumetone; Naproxen; Oxaprozin; Phenylbutazone; Piroxicam; Sulindac; Tenoxicam; Tiaprofenic Acid; Tolmetin.

Analgesic¾Diclofenac; Diflunisal; Etodolac b; Fenoprofen; Floctafenine; Ibuprofen; Ketoprofen; Meclofenamate b; Mefenamic Acid; Naproxen.

Antigout agent¾Diclofenac; Diflunisal; Etodolac b; Fenoprofen; Floctafenine; Ibuprofen; Indomethacin; Ketoprofen; Naproxen; Phenylbutazone; Piroxicam; Sulindac.

Anti-inflammatory (nonsteroidal)¾Flurbiprofen; Indomethacin; Naproxen; Sulindac; Tenoxicam.

Antipyretic¾Ibuprofen; Indomethacin; Naproxen.

Antidysmenorrheal¾Diclofenac; Flurbiprofen; Ibuprofen; Indomethacin; Ketoprofen; Meclofenamate b; Mefenamic Acid; Naproxen; Piroxicam.

Vascular headache prophylactic¾Fenoprofen; Ibuprofen; Indomethacin; Mefenamic Acid; Naproxen.

Vascular headache suppressant¾Diclofenac; Diflunisal; Etodolac b; Fenoprofen ; Floctafenine; Ibuprofen; Indomethacin; Ketoprofen; Meclofenamate b; Mefenamic Acid; Naproxen.

Prostaglandin synthesis inhibitor, renal (Bartter"s syndrome)¾Indomethacin .

Indications

Note: Bracketed information in the Indications section refers to uses that are not included in U.S. product labeling.

Accepted

Rheumatic disease (treatment), such as

Arthritis, rheumatoid¾Diclofenac, 23, 158 diflunisal, 24, 165, 219 fenoprofen, 26, 27, 186, 187 flurbiprofen, 29, 126, 144, 169, 220 ibuprofen, 31, 38, 139, 181, 182, 183, 222 indomethacin, 32, 33, 175, 176 ketoprofen, 35, 36, 205, 206, 207 meclofenamate, 37, 178 nabumetone, 210, 211 naproxen, 1, 39, 40, 41, 142, 188, 189 oxaprozin, 163 phenylbutazone * , 42 piroxicam, 44, 45, 167, 168 sulindac, 46, 47, 160, 223 tenoxicam, 180 tiaprofenic acid, 48, 213 and tolmetin 49, 50, 215, 216 are indicated for the treatment of acute or chronic rheumatoid arthritis.

Osteoarthritis¾Diclofenac, 23, 156, 158 diflunisal, 24, 25, 165, 219 etodolac, 177 fenoprofen, 26, 27, 186, 187 flurbiprofen, 29, 126, 144, 169, 220 ibuprofen, 31, 78, 139, 181, 182, 183, 222 indomethacin, 32, 33, 175, 176 ketoprofen, 35, 36, 205, 206, 207 meclofenamate, 37, 178 meloxicam, 320 nabumetone, 211 naproxen, 1, 39, 40, 41, 142, 188, 189 oxaprozin, 163 phenylbutazone * , 42 piroxicam, 44, 45, 167, 168 sulindac, 46, 47, 160, 223 tenoxicam, 180 tiaprofenic acid, 48, 213 and tolmetin 49, 50, 215, 216 are indicated for relief of acute or chronic osteoarthritis.

Ankylosing spondylitis¾Diclofenac *, 58, 158 [diflunisal] * , 233 [fenoprofen] * , 233 [flurbiprofen] , 29, 126, 169, 220 [ibuprofen] * , 233 indomethacin, 32, 33, 175, 176 [ketoprofen] , 36, 206, 207 naproxen, 1, 39, 40, 41, 142, 188, 189 phenylbutazone, 42, 43 [piroxicam] , 45, 168 sulindac, 46, 47,

160, 223 tenoxicam, 180 and [tolmetin] 50, 216 are indicated for relief of acute or chronic ankylosing spondylitis.

Arthritis, juvenile¾Ibuprofen, 128, 129, 139 indomethacin * , 32 naproxen, 1, 39, 41, 142, 188, 189 and tolmetin 49, 50, 215, 216 are indicated for relief of acute or chronic juvenile arthritis.

[Arthritis, psoriatic] *¾Diflunisal, fenoprofen, ibuprofen, indomethacin, ketoprofen, meclofenamate, phenylbutazone, and tolmetin are used in the treatment of psoriatic arthritis. 233

[Reiter"s disease] *¾Indomethacin is used in the treatment of Reiter"s disease. 234

[Rheumatic complications associated with Paget"s disease of bone] *¾ Indomethacin is used in the treatment of this condition. 235

Although NSAIDs may be required for relief of [rheumatic complications occurring in association with systemic lupus erythematosus (SLE)] * , 227, 236 extreme caution is recommended because patients with SLE may be predisposed toward NSAID-induced central nervous system (CNS) and/or renal toxicity. 236 Several NSAIDs, including ibuprofen, 103, 104, 105, 107 sulindac, 109 and tolmetin, 108 have been shown to cause serious adverse effects, including aseptic meningitis, in patients with SLE. In addition, ibuprofen (although a causal relationship has not been established), 31 meclofenamate, 37 and phenylbutazone 43 have rarely been reported to cause an SLE-like syndrome and/or to exacerbate pre-existing SLE.
NSAIDs do not affect the progressive course of some forms of rheumatic disease. Some patients with rheumatoid arthritis may need additional treatment. 228

Pain (treatment)¾Diclofenac, 158, 218 diflunisal, 24, 25, 165, 219 etodolac, 177 fenoprofen * , 26, 186 floctafenine, 28, 174 ibuprofen, 31, 78, 139, 181, 182, 183, 222 ketoprofen, 35, 205, 206 meclofenamate, 127, 178 mefenamic acid, 38, 79, 208, 209 and naproxen 1, 39, 41, 142, 143, 188, 226 are indicated for relief of mild to moderate pain, especially when anti-inflammatory actions may also be desired, e.g., following dental, obstetric, or orthopedic surgery, and for relief of musculoskeletal pain due to soft tissue athletic injuries (strains or sprains). Only immediate-release dosage forms are recommended for relief of acute pain because of their more rapid onset of action relative to delayed-release or extended-release dosage forms. 240

Mefenamic acid is indicated for relief of mild to moderate pain when therapy will not exceed 1 week. 38, 209

Those NSAIDs indicated for relief of pain are also recommended for relief of mild to moderate bone pain caused by metastatic neoplastic disease. However, careful patient selection is necessary, especially in patients receiving chemotherapy, because of the potential gastrointestinal or renal toxicity and the platelet aggregation-inhibiting actions of these medications. 235

Gouty arthritis, acute (treatment) or

[Calcium pyrophosphate deposition disease, acute (treatment)] * 235¾[Diclofenac] *, 309 [diflunisal] * , 309 [etodolac] , 309 [fenoprofen] * , 237 floctafenine * , 309 [ibuprofen] * , 237 indomethacin, 32, 33, 175, 176 [ketoprofen] * , 238 [meclofenamate] , 309 [mefenamic acid] * , 309 naproxen * , 1, 142, 188 phenylbutazone, 42, 43, 224 [piroxicam] * , 235 and sulindac 46, 47, 160, 223 are indicated [or

used] for relief of the pain and inflammation of acute gouty arthritis and [acute calcium pyrophosphate deposition disease (pseudogout; chondrocalcinosis articularis; synovitis, crystal-induced)] *.

Only immediate-release dosage forms are recommended for relief of acute attacks because of their more rapid onset of action relative to delayed-release or extended-release dosage forms. 240

[Long-term prophylactic use of an NSAID may decrease the incidence or severity of recurrent acute gout attacks, especially during the early months of antihyperuricemic therapy. 237 The NSAIDs do not correct hyperuricemia (although diclofenac, 158 diflunisal, 164 etodolac, 177 oxaprozin, 253, 254 and phenylbutazone 224 have some uricosuric activity) and do not eliminate the need for administration of an antihyperuricemic agent for the long-term management of chronic gout. 237 Colchicine is the recommended agent for preventing acute gout attacks because, in low (prophylactic) doses, it is less toxic for long-term use than NSAIDs. 229 NSAIDs (other than phenylbutazone, which is not recommended for long-term treatment) 237 should be used only for patients unable to tolerate even prophylactic doses of colchicine. 229]

Inflammation, nonrheumatic (treatment)¾Most of the NSAIDs are indicated [or used] in the treatment of painful nonrheumatic inflammatory conditions, such as
Athletic injuries¾ Bursitis¾Capsulitis¾ Synovitis¾Tendinitis; or¾ Tenosynovitis¾[Flurbiprofen is indicated for relief of bursitis, tendinitis, and soft tissue injuries.] 145, 220 Indomethacin * 32, 176 and sulindac 46, 47, 160, 223 are indicated for treatment of bursitis and/or tendinitis of the shoulder. Naproxen 1, 39, 142, 143, 188 is indicated for treatment of bursitis and/or tendinitis of any joint. Tenoxicam is indicated for treatment of tendinitis, bursitis, and periarthritis of the shoulders or hips. 180 [Other NSAIDs, especially those approved by U.S. and/or Canadian regulatory agencies for relief of pain, are also used in the treatment of these and other painful inflammatory conditions.] * 239

Fever (treatment)¾Ibuprofen 137, 139, 183 and naproxen * 226 are indicated for reduction of fever.

[Fever, due to malignancy (treatment)] *¾Indomethacin (rapidly acting dosage forms only) is used to reduce fever in patients with Hodgkin"s disease, other lymphomas, and hepatic metastases of solid tumors. Indomethacin should be used only after aspirin and acetaminophen have proven ineffective. If antipyretic therapy at an adequate dosage is not effective within 48 hours, indomethacin should be discontinued. 234

Dysmenorrhea (treatment)¾Diclofenac, 59, 158, 218 [flurbiprofen] , 30, 169, 220 ibuprofen, 31, 78, 139, 181, 182, 183, 222 [indomethacin] * , 7, 225 ketoprofen, 35, 205, 206 meclofenamate, 178 mefenamic acid, 38, 79, 108, 209 naproxen, 1, 39, 80, 142, 143, 188, 226 and [piroxicam] 168 are indicated for relief of the pain and other symptoms of primary dysmenorrhea. [Other NSAIDs that have been approved by U.S. and/or Canadian regulatory agencies for relief of pain are also used to relieve dysmenorrhea.] * 240 Only immediate-release dosage forms are recommended for relief of dysmenorrhea because of their more rapid onset of action relative to delayed-release or extended-release dosage forms. 240

[Because of the high incidence of adverse effects with effective doses of indomethacin, 7 it is recommended that indomethacin be used only for severe primary dysmenorrhea unresponsive to other, less toxic, NSAIDs.] 241

Hypermenorrhea (treatment)¾Meclofenamate is indicated for treatment of idiopathic excessive menstrual bleeding. The absence of an underlying pathologic condition should be verified before meclofenamate therapy is instituted. 178 [NSAIDs that are used for relief of dysmenorrhea (see Dysmenorrhea , above) may also decrease excessive menstrual blood loss caused by an intrauterine device in addition to relieving other symptoms.] * 7

[Headache, vascular (prophylaxis)] * or

[Headache, vascular (treatment)] *¾Diclofenac, diflunisal, etodolac, fenoprofen, floctafenine, ibuprofen, indomethacin, ketoprofen, meclofenamate, mefenamic acid, and naproxen are used to relieve (when taken at the first sign of onset) migraine headache or other vascular headaches. Fenoprofen, ibuprofen, indomethacin, and naproxen are also used chronically to prevent recurrence of such headaches. Fenoprofen, ibuprofen, indomethacin, mefenamic acid, and naproxen may also be taken prior to and during menstruation to prevent migraine associated with menstruation. 242

[Bartter"s syndrome (treatment)] *¾Indomethacin is used in the treatment of Bartter"s syndrome. However, its use in this condition has been associated with adverse effects, including pseudotumor cerebri. Because long-term therapy is required, it has been suggested that other, less toxic, NSAIDs may be suitable alternatives to indomethacin. 234

[Pericarditis] *¾Indomethacin (rapidly acting dosage forms only) is used to relieve pain, fever, and inflammation associated with pericarditis. 240

Unaccepted

Except in the treatment of ankylosing spondylitis, for which it is a treatment of choice, and Bartter"s syndrome, indomethacin is not recommended as initial therapy because of its potential for causing severe side effects. 176 Also, although indomethacin, like other NSAIDs, has analgesic and antipyretic activity, it should not be used indiscriminately (because of its toxicity) to relieve pain or reduce fever. 241

Phenylbutazone is not recommended as initial therapy for any indication. Because of its potential for causing severe side effects, including agranulocytosis and aplastic anemia, it should be used only after less toxic treatments (including other, less toxic, NSAIDs) have been found ineffective. In many countries, phenylbutazone is approved only for treatment of severe ankylosing spondylitis unresponsive to other NSAIDs. Use of phenylbutazone to relieve the pain and inflammation of acute painful shoulder (i.e., peritendinitis, capsulitis, or bursitis of that joint) is no longer FDA-approved. It is strongly recommended that use of phenylbutazone be restricted to short-term treatment of severe flares of rheumatic disease, gout, or calcium pyrophosphate deposition disease. 42, 43, 236

* Not included in Canadian product labeling.

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Pharmacology/Pharmacokinetics

See Table 1.

See Table 2.

Physicochemical characteristics:

Chemical group¾Fenamate derivatives: Meclofenamate, mefenamic acid.
Indoleacetic acid derivative: Indomethacin. Indomethacin is chemically related to the pyrroleacetic acid derivatives sulindac and tolmetin and to the pyranoindoleacetic acid derivative etodolac.
Naphthylalkanone derivative: Nabumetone. 211

Oxicam derivative: Meloxicam, piroxicam, tenoxicam.
Phenylacetic acid derivative: Diclofenac.
Propionic acid derivatives: Fenoprofen, flurbiprofen, ibuprofen, ketoprofen, naproxen, oxaprozin, tiaprofenic acid.
Pyranoindoleacetic acid: Etodolac. 244 This medication is chemically related to the indoleacetic acid derivative indomethacin and to the pyrroleacetic acid derivatives sulindac and tolmetin.
Pyrazole derivative: Phenylbutazone.
Pyrroleacetic acid derivatives: Sulindac, tolmetin. These medications are chemically related to the indoleacetic acid derivative indomethacin and to the pyranoindoleacetic acid derivative etodolac.
Salicylic acid derivative: Diflunisal. However, diflunisal is not metabolized to salicylic acid in vivo
Molecular weight¾ 245

Diclofenac potassium: 334.24
Diclofenac sodium: 318.13
Diflunisal: 250.2
Etodolac: 287.36
Fenoprofen calcium: 558.64
Floctafenine: 406.36
Flurbiprofen: 244.26
Ibuprofen: 206.28
Indomethacin: 357.79
Ketoprofen: 254.28
Meclofenamate sodium: 336.15
Mefenamic acid: 241.29
Meloxicam: 351.4
Nabumetone: 228.29 Active nabumetone metabolite 6-methoxy-2-naphthylacetic acid (6-MNA)¾216.25 246

Naproxen: 230.26
Naproxen sodium: 252.24
Oxaprozin: 293.32
Phenylbutazone: 308.38
Piroxicam: 331.35
Sulindac: 356.41
Tenoxicam: 337.37
Tiaprofenic acid: 260.31
Tolmetin sodium: 315.3
Other characteristics¾Ketoprofen: Highly lipophilic.
Oxaprozin: Lipophilic.

pKa¾Diclofenac potassium: 4.0 158

Diclofenac sodium: 4.0 158

Diflunisal: 3.3 5

Etodolac: 4.65 177

Fenoprofen calcium: 4.5 (25 °C) 3

Flurbiprofen: 4.22 247

Ibuprofen: 4.43 247

Indomethacin: 4.5 32

Ketoprofen: 5.94 (in methanol:water [3:1]) 205

Mefenamic acid: 4.2 6

Meloxicam: 1.1 and 4.2 320

Naproxen: 4.2 7

Oxaprozin: 4.3 163

Piroxicam: 1.8 and 5.1 8

Tiaprofenic acid: 3.0 48

Tolmetin sodium: 3.5 9

Note: 6-MNA, the active metabolite of nabumetone, but not nabumetone itself, is acidic. Other NSAIDs not listed above are also acidic.

Mechanism of action/Effect:

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the activity of the enzyme cyclo-oxygenase, resulting in decreased formation of precursors of prostaglandins and thromboxanes from arachidonic acid. Also, meclofenamate and mefenamic acid have been shown to inhibit competitively the actions of prostaglandins. Although the resultant decrease in prostaglandin synthesis and activity in various tissues may be responsible for many of the therapeutic (and adverse) effects of NSAIDs, other actions may also contribute significantly to the therapeutic effects of these medications.
Antirheumatic (nonsteroidal anti-inflammatory)¾ Act via analgesic and anti-inflammatory mechanisms; the therapeutic effects are not due to pituitary-adrenal stimulation. These medications do not affect the progressive course of rheumatoid arthritis.

Analgesic¾ May block pain impulse generation via a peripheral action that may involve reduction of the activity of prostaglandins, and possibly inhibition of the synthesis or actions of other substances that sensitize pain receptors to mechanical or chemical stimulation. The antibradykinin activity of ketoprofen may also be involved in relief of pain, because bradykinin has been shown to act together with prostaglandins to cause pain. 248

Antigout agent¾ Act via analgesic and anti-inflammatory mechanisms; do not correct hyperuricemia.

Anti-inflammatory (nonsteroidal)¾ Exact mechanisms have not been determined. NSAIDs may act peripherally in inflamed tissue, probably by reducing prostaglandin activity in these tissues and possibly by inhibiting the synthesis and/or actions of other local mediators of the inflammatory response. Inhibition of leukocyte migration, inhibition of the release and/or actions of lysosomal enzymes, and actions on other cellular and immunological processes in mesenchymal and connective tissue may be involved. Indomethacin has been shown to inhibit phosphodiesterase, with a resultant increase in intracellular cyclic adenosine monophosphate (cAMP) concentration. Ketoprofen has been shown to inhibit leukotriene synthesis, inhibit bradykinin activity, and stabilize lysosomal membranes. 35

Antipyretic¾ Probably produce antipyresis by acting centrally on the hypothalamic heat-regulating center to produce peripheral vasodilation, resulting in increased blood flow through the skin, sweating, and heat loss. The central action probably involves reduction of prostaglandin activity in the hypothalamus.

Antidysmenorrheal¾ By inhibiting the synthesis and activity of intrauterine prostaglandins (which are thought to be responsible for the pain and other symptoms of primary dysmenorrhea), NSAIDs decrease uterine contractility 7 and uterine pressure, 31 increase uterine perfusion, and relieve ischemic as well as spasmodic pain. 7 The antibradykinin activity of ketoprofen may also be involved in relief of dysmenorrhea, because bradykinin has been shown to induce uterine contractions and to act together with prostaglandins to cause pain. 248 Also, NSAIDs may relieve to some extent extrauterine symptoms (such as headache, nausea, and vomiting) that may be associated with excessive prostaglandin production. 7

Vascular headache prophylactic and suppressant¾ Analgesic actions may be involved in relief of headache. Also, by reducing prostaglandin activity, NSAIDs may directly prevent or relieve certain types of headache thought to be caused by prostaglandin-induced dilation or constriction of cerebral blood vessels.

Prostaglandin synthesis inhibitor, renal¾ Inhibition of renal prostaglandin synthesis probably is responsible for indomethacin"s beneficial effect in patients with Bartter"s syndrome, which is thought to be caused by excessive production of renal prostaglandins.

Other actions/effects:

Most of the NSAIDs inhibit platelet aggregation. However, their antiplatelet effect, unlike that of aspirin, is reversible. 249 Single doses of 4 to 10 mg of flurbiprofen inhibit platelet aggregation. 29, 51, 61 Oxaprozin is as potent as aspirin in inhibiting platelet aggregation induced by epinephrine or collagen in vitro. 255, 256, 257 With diflunisal, the effect is clinically significant only with greater-than-recommended daily doses. 24 Also, usual doses of 55 diclofenac, 158, 218 meclofenamate, 37 mefenamic acid, 38 or nabumetone (as determined after administration of 1000 mg per day for 7 to 10

days) 210, 250, 251, 252 may not significantly alter platelet aggregability. Recovery of platelet function may occur within 1 day after discontinuation of diclofenac, 13, 57 diflunisal, 13 flurbiprofen, 51, 61 ibuprofen, indomethacin, or sulindac; 2 days after discontinuation of tolmetin; 4 days after discontinuation of naproxen; or 2 weeks following discontinuation of slowly eliminated agents such as oxaprozin 257 or piroxicam.
Diclofenac, 51 diflunisal, etodolac, 177 oxaprozin, 253, 254 and phenylbutazone 224 also have uricosuric activity.
Phenylbutazone also induces hepatic microsomal enzyme activity.
Studies have demonstrated that IgM rheumatoid factor production (which may be partially mediated by prostaglandins) may be decreased (but not totally inhibited) during NSAID therapy. 10, 11, 12 However, because these medications do not affect the progressive course of rheumatoid arthritis, the clinical significance of this effect has not been determined. 236

It has been proposed that the gastrointestinal toxicity of NSAIDs may be caused primarily by reduction of the synthesis and activity of prostaglandins (which exert a protective effect on the gastrointestinal mucosa) because upper gastrointestinal toxicity has been reported following rectal or parenteral administration of some of these medications. However, when administered orally, some of these acidic medications probably also exert a direct irritant or erosive effect on the mucosa. 14 Because nabumetone is a nonacidic prodrug, 210, 259 and the active metabolite 6-MNA is not formed until after absorption, 210, 250, 259 the risk of serious upper gastrointestinal tract toxicity may be lower with nabumetone than with other NSAIDs. 250, 260 Also, in one study, gastric and duodenal prostaglandin concentrations were not altered by 4 weeks of administration of therapeutic doses of etodolac. 261

The renal toxicity associated with NSAIDs (i.e., decreased renal perfusion, sodium and fluid retention, and decreased renal function) may be caused by inhibition of renal prostaglandins, which are directly involved in the maintenance of renal hemodynamics and sodium and fluid balance. Renal prostaglandins are especially important in maintaining renal function in the presence of generalized vasoconstriction or volume depletion. 14, 253, 258 Sulindac is a prodrug; its sulfide metabolite is the active substance. Because this active metabolite is not excreted via the kidneys, renal toxicity may be less likely with sulindac than with other NSAIDs. However, there have been reports of renal toxicity associated with sulindac therapy. 223 Etodolac has been shown to decrease some measures of renal function, 262, 263 with maximum effects occurring within 1.5 262, 263 to 2.5 263 hours after a dose. However, with administration of up to 500 mg every 12 hours, recovery of renal function occurred prior to administration of the next dose, even in patients with pre-existing mild to moderate renal function impairment (creatinine clearances ranging from 20 to 88 mL per minute). 262, 263 Whether more frequent administration of etodolac may cause cumulative effects on renal function has not been determined. 264

The analgesic, antipyretic, and anti-inflammatory effects of NSAIDs may mask symptoms of the onset and/or progression of an infection. 236

Therapeutic effect

When these medications are used in the treatment of arthritis, their analgesic actions may produce some relief of pain within the first day or two. Significant relief of other symptoms of inflammation usually occurs within a few days to a week; however, in severe cases, 2 weeks or more of continuous use may be required. 236

Drug and Indication	Onset of Action	Peak Effect	Duration of Action
Diclofenac			
Tablets			
Pain	30 min		Up to 8 hr
Diflunisal			
Pain	1 hr	2-3 hr	8-12 hr
Etodolac			
Pain	30 min	1-2 hr	
200 mg			4-5 hr
400 mg			5-6 hr, but 8-12 hr in some patients
Ibuprofen			
Fever		2-4 hr	
5 mg/kg			6 hr
10 mg/kg			8 hr or more
Pain	0.5 hr		4-6 hr
Indomethacin			
Gout	2-4 hr		
Heat, tenderness		2-3 days	
Swelling		3-5 days	
Meclofenamate			
Pain	1 hr		4-6 hr
Naproxen			
Gout		1-2 days	
Pain	1 hr	2-4 hr	Up to 7 hr
Piroxicam			
Gout	2-4 hr	3-5 days	24 hr

Synovial fluid concentrations

Studies with several of the NSAIDs have shown that these medications enter the synovial fluid and that, several hours after administration of a single dose, synovial fluid concentrations equal or exceed the simultaneously measured plasma concentration. 23, 35, 48, 51, 61, 68, 69, 70, 77, 93, 291 In addition, there is some evidence that ketoprofen, oxaprozin, 291 and possibly other NSAIDs, may accumulate in synovial fluid when administered chronically.

Drug and Dose	Concentration	Half-life a (hr)

	Time to Peak (hr)	Peak (mcg/mL)	
Diclofenac	3 b	0.28 b	Up to 6
Etodolac c	2.7-3.7	Total 2.6 Free (unbound) 44-84 nanograms/mL	6.5-7
Flurbiprofen			
100 mg b	5.2	4.4	4.6
Indomethacin			
50 mg	2	0.69	
Ketoprofen			
50 mg	2	0.7-0.9	
100 mg		0.7-0.9	
Nabumetone			
1000 mg	±8	20 d; 35 e	
Tenoxicam			
40 mg	10	1.82	
Tiaprofenic Acid			
Tablets			
200 mg b	4	5.3	
300 mg b	4	7.7	
Extended-release			
Capsules	8		8.6
Tolmetin			
400 mg b	2	5.6	6.9

a Elimination.

b Determined at steady-state, after administration of a single dose in patients receiving chronic therapy (for diclofenac-50 mg 3 times a day; for flurbiprofen-100 mg twice a day; for tiaprofenic acid-200 mg 3 times a day for 7 days or 300 mg twice a day for 7 days; for tolmetin-400 mg 4 times a day for 7 days).

c Determined at steady-state.

d Single dose; simultaneous plasma concentration 36 mcg/mL.

e Multiple doses (1000 mg every 12 hours on the first day, then 1000 mg per day for 3 days); simultaneous plasma concentration 41 mcg/mL.

Precautions to Consider

Cross-sensitivity and/or related problems

Patients sensitive to one of the nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, ketorolac, and NSAIDs no longer commercially available (such as oxyphenbutazone, suprofen, and zomepirac) may be sensitive to any of the other NSAIDs also.
NSAIDs may cause bronchoconstriction or anaphylaxis in aspirin-sensitive asthmatics, especially those with aspirin-induced nasal polyps, asthma, and other allergic reactions (the "aspirin triad"").
Patients with bronchospastic reactions to aspirin may be desensitized to this effect by administration of initially small and gradually increasing doses of aspirin. Desensitization must be carried out by physicians who are experienced with the technique, in a facility having personnel, equipment, and medications immediately available for treatment of any adverse reaction to the medication (especially anaphylaxis or severe bronchospasm). Desensitization to aspirin also desensitizes the patient to other NSAIDs. However, unless aspirin or another NSAID is then administered on a daily basis, sensitivity to these medications redevelops within a few days. 15

Carcinogenicity

Diclofenac¾ No oncogenic potential was demonstrated with diclofenac sodium in a 2-year carcinogenicity study in male mice given up to 0.3 mg per kg of body weight (mg/kg) (0.9 mg per square meter of body surface area [mg/m 2]) per day or in female mice given up to 1 mg/kg (3 mg/m 2) per day.

Diflunisal¾ No effect on the incidence or type of neoplasia was found in a 105-week study in rats 24, 219 given up to 40 mg/kg per day (approximately 1.3 times the maximum recommended human dose [MRHD]) or in long-term studies in mice given up to 80 mg/kg per day (approximately 2.7 times the MRHD). 219

Etodolac¾ No carcinogenicity was demonstrated in mice or rats receiving up to 15 mg/kg per day (corresponding to 45 mg/m 2 for mice and 89 mg/m 2 for rats) for 2 years or 18 months, respectively. 177

Floctafenine¾ No effect on the incidence of neoplasia was found in studies in CD-1 mice receiving up to 240 mg/kg per day. 28

Flurbiprofen¾ No evidence of carcinogenicity was found in an 80-week study in mice receiving up to 14 mg/kg per day or in a 2-year study in rats receiving up to 12 mg/kg per day for 32 weeks, then up to 5 mg/kg per day thereafter. 144

Indomethacin¾ No evidence of carcinogenicity was found in studies in mice receiving up to 1.5 mg/kg per day for 62 to 88 weeks or in studies in rats receiving up to 1.5 mg/kg per day for 73 to 110 weeks. 32, 176

Leukemia has been reported in a few patients receiving indomethacin; however, a causal relationship has not been established. 32

Ketoprofen¾ No evidence of carcinogenicity was found in studies in mice receiving up to 32 mg/kg (96 mg/m 2) per day (approximately 0.5 times the MRHD based on body surface area). 205

Meclofenamate¾ No evidence of carcinogenicity was found in an 18-month study in rats. 37, 178

Meloxicam¾ No carcinogenic effect was observed in a 104-week study in rats or in a 99-week study in mice 320.

Naproxen¾ No evidence of carcinogenicity was found in a 24-month study in rats. 1, 188

Oxaprozin¾ An increased incidence of hepatic adenomas and carcinomas occurred in 2-year studies in male CD mice, but not in female CD mice or in rats, given oxaprozin. The significance of this species-specific finding is not known. 163

Phenylbutazone¾ Leukemia has been reported in a few patients receiving phenylbutazone; however, a causal relationship has not been established.

Long-term studies in animals have not been done to determine whether phenylbutazone has carcinogenic activity. 42

Tenoxicam¾ No evidence of carcinogenicity was found in an 80-week study in mice receiving up to 5 mg/kg per day or in a 104-week study in rats receiving up to 6 mg/kg per day. 180

Tiaprofenic acid¾ No evidence of carcinogenicity was found in an 80-week study in mice receiving up to 30 mg/kg per day or in a 104-week study in rats receiving up to 30 mg/kg per day. 48, 213

Tolmetin¾ No evidence of carcinogenicity was found in an 18-month study in mice receiving up to 50 mg/kg per day or in a 24-month study in rats receiving up to 75 mg/kg per day. 49, 215

Tumorigenicity

Diclofenac¾ No tumorigenicity was demonstrated in studies in rats receiving up to 2 mg/kg per day (approximately the recommended human dose). 119 Although there was a slight increase in benign mammary fibroadenomas in female rats given 0.5 mg/kg (3 mg/m 2) per day, the increase was not significant. 158

Flurbiprofen¾ No tumorigenicity was demonstrated in a 2-year study in rats receiving up to 12 mg/kg per day for 32 weeks, then up to 5 mg/kg per day. 29

Indomethacin¾ No tumorigenicity was demonstrated in an 81-week study in rats receiving up to 1 mg/kg per day. 32, 176

Ketoprofen¾ No tumorigenicity was demonstrated in studies in rats receiving 6 mg/kg (36 mg/m 2) per day for 81 weeks or lower doses for 104 weeks. 205

Nabumetone¾ No tumorigenicity was demonstrated in 2-year studies in mice and rats. 211

Mutagenicity

Diclofenac¾ No mutagenic activity was demonstrated in in vitro tests using mammalian cells or bacteria (with or without microsomal activation) or in in vivo tests, including dominant lethal and male germinal epithelial chromosomal studies in mice and nucleus anomaly and chromosomal aberration studies in Chinese hamsters. 158

Diflunisal¾ No mutagenic activity was demonstrated in the dominant lethal assay, Ames microbial mutagen test, or V-79 Chinese hamster lung cell assay. 24

Etodolac¾ No mutagenic activity was demonstrated in in vitro tests performed with Salmonella typhimurium and mouse lymphoma cells or in an in vivo mouse micronucleus test. However, in the in vitro human peripheral lymphocyte test, concentrations of 50 to 200 mcg per mL (mcg/mL) of etodolac produced an increase in the number of gaps (3 to 5.3% unstained regions in the chromatid without dislocation, compared with 2% in controls). 177

Indomethacin¾ No mutagenic activity was demonstrated in in vitro tests (Ames test or E. coli , with or without metabolic activation) or in in vivo tests (host-mediated assay, sex-linked recessive lethals in Drosophila , and micronucleus test in mice). 32, 176

Ketoprofen¾ No mutagenic activity was demonstrated in the Ames test. 205

Meloxicam¾ No mutagenic activity was demonstrated in the Ames test 320.

Nabumetone¾ No mutagenic activity was demonstrated in the Ames test or in the mouse micronucleus test in vivo. However, chromosomal aberrations occurred in lymphocytes exposed in vitro to nabumetone or its active metabolite 6-methoxy-2-naphthylacetic acid (6-MNA) at concentrations of 80 mcg/mL (369.6 micromoles/L) or higher. 211

Oxaprozin¾ No mutagenic activity was demonstrated in the Ames test, forward mutation testing in yeast and Chinese hamster ovary cells, DNA repair testing in Chinese hamster ovary cells, micronucleus testing in mouse bone marrow, chromosomal aberration testing in human lymphocytes, or cell transformation testing in mouse fibroblasts. 163

Phenylbutazone¾ No mutagenic activity was demonstrated in tests in mice, Chinese hamsters, or rats given up to 33 times the maximum daily human dose, or in bacteria or fungi. However, in vitro tests using Chinese hamster fibroblast cells have shown that phenylbutazone concentrations exceeding 860 mg/L produce chromosome abnormalities. Although an increased incidence of chromosome anomalies has been reported in cultured leukocyte cells from patients receiving therapeutic doses of the medication, other similar studies in humans and in horses have yielded inconclusive or negative results. 43

Piroxicam¾ No mutagenic activity was demonstrated (test systems used not specified). 45

Tenoxicam¾ No mutagenic activity was demonstrated in studies in 3 bacterial systems and 4 eukaryotic test systems. 180

Tiaprofenic acid¾ No mutagenic activity was demonstrated in the Ames test or in the micronucleus test in mice. 48, 213

Tolmetin¾ No mutagenic activity was demonstrated in the Ames test. 49, 215

Pregnancy/Reproduction

Fertility¾Diclofenac¾ No impairment of fertility was demonstrated in reproduction studies in rats receiving up to 4 mg/kg (24 mg/m 2) per day. 158

Diflunisal¾ No impairment of fertility was demonstrated in reproduction studies in rats receiving up to 50 mg/kg per day. 24, 219

Etodolac¾ A reduction in the implantation of fertilized eggs was demonstrated in reproduction studies in rats receiving 8 mg/kg per day, but no impairment of fertility was demonstrated in male or female rats receiving up to 16 mg/kg (94 mg/m 2) per day. 177

Floctafenine¾ No impairment of fertility was demonstrated in reproduction studies in rats receiving up to 160 mg/kg per day. 28

Flurbiprofen¾ No impairment of fertility was demonstrated in reproduction studies in rats receiving 2.25 mg/kg per day. 29, 144

Indomethacin¾ No impairment of fertility was demonstrated in a 2-generation reproduction study in mice or in a 2-litter reproduction study in rats receiving up to 0.5 mg/kg per day. 32, 176

Ketoprofen¾ No impairment of fertility was demonstrated in reproduction studies in male rats receiving up to 9 mg/kg (54 mg/m 2) per day. However, a decrease in the number of implantation sites was demonstrated in female rats receiving 6 or 9 mg/kg (36 or 54 mg/m 2) per day. In other studies, high doses of ketoprofen caused abnormal spermatogenesis or inhibition of spermatogenesis in rats and dogs, and decreased testicular weight in dogs and baboons. 205

Mefenamic acid¾ Impairment of fertility was demonstrated in reproduction studies in rats receiving 10 times the human dose. 38, 209

Meloxicam¾ No impairment of fertility was demonstrated in male or female rats receiving 4.9 times the human dose 320.

Nabumetone¾ No impairment of fertility was demonstrated in male or female rats receiving 320 mg/kg (1888 mg/m 2) per day. 211

Naproxen¾ No impairment of fertility was demonstrated in mice, rats, or rabbits receiving up to 6 times the human dose. 1, 188

Oxaprozin¾ No impairment of fertility was demonstrated in male or female rats receiving up to 200 mg/kg (1180 mg per square meter of body surface area [mg/m 2]) per day. For comparison, the usual human dose is about 17 mg/kg (629 mg/m 2) per day. However, testicular degeneration occurred in beagle dogs given 37.5 mg/kg (750 mg/m 2) or more per day for 42 days or longer. This finding did not occur in other species, and the clinical relevance to humans is unknown. 163

Phenylbutazone¾ No impairment of fertility was demonstrated in reproduction studies in mice, Chinese hamsters, and rats receiving up to 33 times the maximum daily human dose. 42

Piroxicam and tolmetin¾ No impairment of fertility was demonstrated in animal reproduction studies. 44, 49, 215

Tenoxicam¾ No impairment of fertility was demonstrated in male rats receiving up to 8 mg per day for at least 63 days prior to mating. Administration of 8 mg per day, but not lower doses, to female rats from 14 days prior to, to 7 days after, mating resulted in a significant decrease in the number of corpora lutea and implantations, resulting in fewer live fetuses. 180

Tiaprofenic¾ No impairment of fertility was demonstrated in reproduction studies in female or 132 male rats receiving up to 20 mg/kg per day. However, an increased number of pre- and post-implantation losses was demonstrated in studies in female rats receiving 20 mg/kg per day, and a decrease in the number of implantation sites was demonstrated in studies in rabbits receiving 75 mg/kg per day. 48, 213

Pregnancy¾First trimester¾ Diclofenac:

Adequate and well-controlled studies in humans have not been done.

Diclofenac crosses the placenta in mice and rats. 158 Studies in rats receiving 2 or 4 mg/kg per day have shown that diclofenac is embryotoxic (causing low birth weight, a slightly decreased growth rate, and failure to survive, especially with the higher dose). Also, in studies in rabbits receiving 5 or 10 mg/kg per day, diclofenac caused increases in the resorption rates, decreased fetal weights, abnormal skeletal findings, and definite embryotoxicity with the higher dose. 218 However, no teratogenicity was demonstrated in reproduction studies in rabbits receiving up to 10 mg/kg (80 mg/m 2) per day, in mice receiving up to 20 mg/kg (60 mg/m 2) per day, or in rats receiving up to 10 mg/kg (60 mg/m 2) per day. 158

FDA Pregnancy Category B. 23, 93, 158

Diflunisal:

Adequate and well-controlled studies in humans have not been done.

Studies in animals have shown that diflunisal is teratogenic in rabbits (causing fetal vertebral and rib malformations at doses ranging from 40 to 50 mg/kg per day) but not in mice (in doses of 45 mg/kg per day) or rats (in doses of 100 mg/kg per day). Diflunisal also caused maternotoxicity and embryotoxicity (increased fetal resorptions) in rabbits receiving 60 mg/kg per day (2 times the maximum human dose).

FDA Pregnancy Category C. 219

Etodolac:

Adequate and well-controlled studies in humans have not been done.

Isolated alterations of limb development, including polydactyly (extra digits), oligodactyly (missing digits), syndactyly (digits attached by webbing), and unossified phalanges, occurred in rats receiving 2 to 14 mg/kg per day. Also, oligodactyly and synostosis of metatarsals occurred in rabbits receiving 2 to 14 mg/kg per day. However, the frequency and dosage group distribution in initial and repeated studies did not establish a clear drug- or dose-response relationship.

FDA Pregnancy Category C. 177

Fenoprofen, ibuprofen, naproxen, and tolmetin:

Adequate and well-controlled studies in humans have not been done.

Studies in animals have not shown that these agents cause adverse effects on fetal development. Naproxen was studied in mice, rats, and rabbits receiving up to 6 times the human dose. Tolmetin was studied in rats and rabbits receiving up to 50 mg/kg (1.5 times the maximum human dose). 181, 186, 188, 215

Naproxen: FDA Pregnancy Category B.
Tolmetin: FDA Pregnancy Category C.

Floctafenine:

Studies in mice receiving up to 320 mg/kg per day, rats receiving up to 240 mg/kg per day, and rabbits receiving up to 160 mg/kg per day have not shown that floctafenine is teratogenic. However, embryotoxicity (increased fetal losses in mice, decreased fetal weight in rats, and increased fetal losses in rabbits) was demonstrated with these high doses (but not at lower dosage levels). 28

Flurbiprofen:

Although adequate and well-controlled studies in humans have not been done, it has been shown that flurbiprofen crosses the placenta.

Studies in mice receiving up to 12 mg/kg per day, rats receiving up to 25 mg/kg per day, and rabbits receiving up to 7.5 mg/kg per day have not shown evidence of teratogenicity. 144 However, studies in rats have shown doses of 0.4 mg/kg per day or higher to be embryocidal (causing reduced weight or slower fetal growth, increased stillbirths, and decreased pup survival). Also, stillbirths, retained fetuses, and/or fetal distress occurred in studies in rats receiving as little as 0.2 mg/kg per day. In addition, fetotoxicity related to maternal toxicity (gastrointestinal ulceration, retardation of weight gain, intrauterine hemorrhage, and maternal deaths) occurred in rats receiving 25 mg/kg per day from Days 1 through 20 of pregnancy. With lower doses (0.2, 0.675, or 2.25 mg/kg per day), such effects did not occur when the medication was discontinued on Day 17 of pregnancy. Maternal deaths due to gastrointestinal ulceration also occurred in rabbits receiving the medication. 29, 30, 221

FDA Pregnancy Category B. 144

Indomethacin:

Although studies in humans have not been done, it has been shown that indomethacin crosses the placenta. 8

Studies in rats and mice have shown that indomethacin (at a dosage of 4 mg/kg per day) causes decreased average fetal weight and retarded ossification. In other studies in mice, higher doses (5 to 15 mg/kg per day) caused maternal toxicity and death, increased fetal resorptions, and fetal malformations. 176

Ketoprofen:

Adequate and well-controlled studies in humans have not been done.

Studies in animals have not shown evidence of teratogenicity or embryotoxicity in mice receiving up to 12 mg/kg (36 mg/m 2) per day or in rats receiving up to 9 mg/kg (54 mg/m 2) per day. In studies in rabbits, maternally toxic doses were embryotoxic but not teratogenic.

FDA Pregnancy Category B. 35, 205

Meclofenamate:

Adequate and well-controlled studies in humans have not been done.

Animal studies have shown meclofenamate to cause fetotoxicity, minor skeletal malformations (e.g., supernumerary ribs), and delayed ossification, but no major teratogenicity. 178

Mefenamic acid:

Although adequate and well-controlled studies in humans have not been done, it has been demonstrated that mefenamic acid metabolites readily cross the placenta.

Mefenamic acid caused increases in the number of resorptions in rabbits receiving 2.5 times the human dose and decreases in survival to weaning (possibly due to maternal neglect) in rats receiving 10 times the human dose. Although no fetal abnormalities were reported in these studies or in studies in dogs receiving up to 10 times the human dose, it has been recommended that mefenamic acid not be used during pregnancy.

FDA Pregnancy Category C. 209

Meloxicam:

Adequate and well-controlled studies in humans have not been done 320.

Meloxicam crosses the placenta in animals.

Meloxicam was not teratogenic in rats at a dose equivalent to 2.2 times the human dose when given throughout organogenesis. However, an increased incidence of embryolethality occurred when female rats were given half the human dose 2 weeks before mating and during early embryonic development. The number of live births and neonatal survival were reduced in rats give oral doses equivalent to 0.07 times the human dose during late gestation and lactation periods 320

Nabumetone:

Adequate and well-controlled studies in humans have not been done.

Nabumetone did not cause teratogenicity in rats receiving up to 400 mg/kg (2360 mg/m 2) per day or in rabbits receiving up to 300 mg/kg (3540 mg/m 2) per day. However, fetotoxicity (post-implantation losses) occurred in rats receiving 100 mg/kg (590 mg/m 2) per day or more. These doses are equivalent to the maximum recommended human dose of nabumetone.

FDA Pregnancy Category C. 211

Oxaprozin:

Adequate and well-controlled studies in humans have not been done. 163

Fetal malformations occurred infrequently in rabbits receiving 7.5 to 30 mg/kg per day (doses within the usual human dose range). However, no teratogenicity occurred in mice or rats receiving 50 to 200 mg/kg (225 to 900 mg/m 2) per day.

FDA Pregnancy Category C. 163

Phenylbutazone:

Adequate and well-controlled studies in humans have not been done.

Although studies in rats and rabbits have not shown that phenylbutazone (in doses up to 16 times the maximum daily human dose) is teratogenic, slightly reduced litter sizes were demonstrated in both species.

FDA Pregnancy Category C.

Piroxicam:

Studies in humans have not been done.

Studies in animals have not shown that piroxicam causes teratogenic effects in doses up to 10 mg/kg per day. 167

Sulindac:

Studies in humans have not been done.

Animal studies have shown that sulindac (at dosage levels of 20 and 40 mg/kg per day¾2.5 and 5 times the MRHD) causes decreased average fetal weight and an increased number of deaths (observed on the first day of the postpartum period). Also, some studies in rabbits have shown a low incidence of visceral and skeletal malformations with sulindac. However, these effects did not occur in repeat studies using the same or higher dosages. 46, 223

Tenoxicam:

Studies in mice receiving up to 8 mg/kg per day from Day 6 to Day 15 of gestation did not show tenoxicam to adversely affect the fetuses or neonates. Teratogenic effects did not occur in offspring of rats receiving up to 12 mg/kg per day from Day 7 to Day 17 of gestation. However, a higher mortality rate associated with panperitonitis, gastric lesions characteristic of NSAIDs, and uterine hemorrhage occurred in dams receiving 8 or 12 mg/kg, but not 4 mg/kg or less, per day. Tenoxicam was embryotoxic (causing increased resorptions), but not teratogenic, in rabbits receiving 32 mg/kg, but not 16 mg/kg or less, per day from Day 6 to Day 18 of gestation. 180

Tiaprofenic acid:

Tiaprofenic acid crosses the placenta.

Studies in mice receiving up to 100 mg/kg per day have not shown that the medication is teratogenic. However, an increase in the fetal loss rate was demonstrated in studies in mice receiving 100 mg/kg per day, rats receiving 10 or 25 (but not 5) mg/kg per day, and rabbits receiving 75 (but not 25 or 50) mg/kg per day. 48, 213

Second and third trimesters¾ All NSAIDs:

Although studies in humans have not been done with NSAIDs other than indomethacin, use of NSAIDs during the second half of pregnancy is not recommended because of possible adverse effects on the fetus, such as premature closure of the ductus arteriosus, which may lead to persistent pulmonary hypertension in the newborn. Studies in full-term pregnant rats have shown that diclofenac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, and tolmetin have a strong constrictive effect on the fetal ductus arteriosus, whereas floctafenine, phenylbutazone, piroxicam, sulindac, and tiaprofenic acid have a moderate constrictive effect. 16

Animal studies have also shown that administration of NSAIDs during late pregnancy may cause prolonged gestation, dystocia, and delayed parturition, possibly because of decreased uterine contractility resulting from inhibition of uterine prostaglandins. Decreases in pup survival rates also have been reported. Studies with piroxicam 45 and nabumetone (at a dose of 320 mg/kg per day) 211 have indicated that dystocia may cause an increased mortality rate in both offspring and dams, 45 and a study with tenoxicam showed a dose-dependent prolongation of gestation and decrease in neonatal viability with doses ranging between 0.5 and 2 mg/kg per day. 180 Also, delayed and prolonged parturition was associated with decreased pup survival in studies with etodolac 177 and with an increased number of stillbirths in studies with flurbiprofen 29 and tiaprofenic acid. 48 Administration of indomethacin to rats and mice during the last 3 days of gestation increased the incidence of neuronal necrosis in the diencephalon and caused maternal and fetal deaths. 176 Administration of oxaprozin to rats during late pregnancy resulted in decreased pup survival, 163 and administration of 3.5 times the maximum human daily dose of phenylbutazone to rats during late pregnancy and lactation resulted in an increased number of stillbirths and reduced survival of offspring. Studies in animals have also shown that administration of piroxicam during the third trimester may increase the risk of maternal gastrointestinal tract toxicity. 167

Indomethacin:

In addition to the adverse effects in animal studies described above, administration of indomethacin to pregnant women during the third trimester has caused closure of the ductus arteriosus, inhibition of platelet function resulting in bleeding, renal function impairment or failure with oligohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes in the fetus. 176

Breast-feeding

Problems in humans have not been documented with most of the NSAIDs.

Diclofenac¾ Diclofenac is distributed into breast milk. In one study, long-term use of 150 mg per day produced concentrations of 100 nanograms per gram in the breast milk. 158 An infant of 4 to 5 kg consuming one liter per day would therefore ingest approximately 0.03 mg/kg per day. 23

Diflunisal¾ Diflunisal is distributed into breast milk. Concentrations may reach 2 to 7% of the maternal plasma concentration. 24, 219

Etodolac, floctafenine, and tiaprofenic acid¾ It is not known whether these medications are distributed into breast milk. 28, 29, 48, 177, 209

Fenoprofen and mefenamic acid¾ Fenoprofen and mefenamic acid are distributed into breast milk in very small quantities. 26, 38, 209

Flurbiprofen¾ Flurbiprofen is distributed into breast milk in very small quantities. In one study, the peak concentration of 0.09 mcg/mL occurred 3 hours following a single 100-mg dose. A maximum of 0.07% of the dose appeared in breast milk within 24 hours after administration. 81 A nursing infant whose mother is taking 200 mg per day could receive approximately 0.1 mg of flurbiprofen per day. 144

Ibuprofen¾ Studies in humans have failed to detect ibuprofen in breast milk using methodology capable of detecting the medication in a concentration of 1 mcg/mL. The maternal dosage was 400 mg four times a day. 17, 31, 181, 182, 222

Indomethacin¾ Indomethacin is distributed into breast milk. 175, 176 Risk-benefit must be considered because convulsions were reported in one breast-fed infant whose mother received 200 mg of indomethacin per day, of which 0.5 to 2 mg per day was distributed into the breast milk.

Ketoprofen¾ It is not known whether ketoprofen is distributed into human breast milk; however, in animal studies, the concentration in the milk of lactating dogs was 4 to 5% of the maternal plasma concentration. In other studies, no adverse effect on perinatal development was observed in offspring of rats receiving 9 mg/kg (54 mg/m 2) per day, corresponding to 1.5 times the MRHD based on weight or 0.3 times the MRHD based on body surface area. 205

Meclofenamate¾ Trace amounts of meclofenamate are distributed into breast milk. Use of meclofenamate in nursing mothers is not recommended because animal studies have shown meclofenamate to interfere with normal development of the young before weaning. 178

Meloxicam¾ Studies of distribution of meloxicam into human breast milk have not been done 320.

However, meloxicam has been found in the milk of lactating rats at concentrations higher than those in plasma 320.

Nabumetone¾ It is not known whether nabumetone or its metabolites are distributed into human breast milk. 211 Problems in humans have not been documented. However, 6-MNA is distributed into the milk of lactating rats 211, 250 in concentrations approximately equal to those in plasma. 250

Naproxen¾ Naproxen is distributed into breast milk; concentrations may reach 1% of the maternal plasma concentration. 1, 198 The peak concentration in breast milk occurs 4 hours after a dose. 18

Oxaprozin¾ It is not known whether oxaprozin is distributed into human breast milk. However, it is distributed into the milk of lactating rats. 163

Phenylbutazone¾ Phenylbutazone is distributed into breast milk; 224 use by nursing mothers may cause severe adverse effects, including blood dyscrasias, in the infant.

Piroxicam¾ Piroxicam is distributed into breast milk; concentrations may reach 1 to 3% of the maternal plasma concentration. 168 Also, use of piroxicam by nursing mothers is not recommended because studies in rats have shown that piroxicam causes a dose-dependent inhibition of lactation. 45, 168

Sulindac¾ It is not known whether sulindac is distributed into human breast milk, but it is distributed into the milk of lactating rats. 46, 223

Tolmetin¾ Tolmetin is distributed into breast milk. 20, 215 In one study, an average concentration of 0.075 mcg/mL was measured, with the peak concentration occurring 1 hour following administration to the mother. The half-life in breast milk was 1.5 hours. 20

Pediatrics

Ibuprofen¾ Appropriate studies performed to date have not demonstrated pediatrics-specific problems that would limit the usefulness of ibuprofen in children 6 months of age or older. 139, 183 Safety and efficacy in infants younger than 6 months of age have not been established. 139, 183

Indomethacin¾ Although appropriate studies have not been done in the pediatric population, no pediatrics-specific problems have been documented to date (with the immediate-release capsule or oral suspension dosage form; the extended-release dosage form is not recommended for pediatric patients). 130, 176 However, because of indomethacin"s toxicity, it is recommended that its use be limited to patients unresponsive to (or intolerant of) other antirheumatic agents, 32, 176 that the patient be carefully monitored (especially for the presence of infection), and that the recommended pediatric doses not be exceeded. 32

Naproxen¾ Studies in children 2 years of age and older with juvenile arthritis have shown higher incidences of naproxen-induced skin rash and increased bleeding time as compared with adults. Studies in children younger than 2 years of age have not been done. 1, 188

Oxaprozin¾ Although a study with oxaprozin has been conducted in patients 3 to 16 years of age, 269 controlled studies have not been published. Preliminary evidence indicates that, although the risk of

overt hepatotoxicity appears to be minimal, elevated aspartate aminotransferase (AST [SGOT]) values during oxaprozin therapy may occur more often in patients treated for juvenile arthritis than in patients treated for other forms of arthritic disease. 287 Safety and efficacy in pediatric patients have not been established. 163

Phenylbutazone¾ Because of phenylbutazone"s toxicity, use in children younger than 15 years of age is not recommended. 224

Tolmetin¾ Appropriate studies performed to date have not demonstrated pediatrics-specific problems that would limit the usefulness of tolmetin in children 2 years of age or older. Studies in children younger than 2 years of age have not been done. 49, 215

Other NSAIDs¾ No information is available on the relationship of age to the effects of these medications in pediatric patients. Safety, efficacy, and appropriate dosages have not been established. 144, 145, 158, 164, 167, 168, 169, 174, 177, 178, 180, 186, 187, 205, 209, 210, 213, 219, 223

Geriatrics

All NSAIDs¾ Whether geriatric patients are at increased risk of serious gastrointestinal toxicity during NSAID therapy has not been established. However, NSAID-induced gastrointestinal ulceration and/or bleeding may be more likely to cause serious consequences, including fatalities, in geriatric patients than in younger adults. 144, 158, 159, 164, 167, 176, 178, 181, 186, 215 In addition, elderly patients are more likely to have age-related renal function impairment, which may increase the risk of NSAID-induced hepatic or renal toxicity and may also require dosage reduction to prevent accumulation of the medication. Some clinicians recommend that geriatric patients, especially those 70 years of age or older, be given one half of the usual adult dose initially. Also, careful monitoring of the patient is recommended. 294

Etodolac¾ Studies performed to date with 200 mg of etodolac twice a day 230, 231 have not shown differences in the pharmacokinetics of the medication in geriatric patients compared with younger adults. 177, 230, 231 Also, studies with 600 mg of etodolac per day 265 have not shown differences in the side effects profile of etodolac in geriatric patients compared with younger adults. 177, 265

Flurbiprofen¾ Studies have shown that the peak plasma concentration of flurbiprofen may be increased in females 74 to 94 years of age, but not in males 66 to 90 years of age.

Indomethacin¾ In addition to the increased risks of therapy with any NSAID as described above, geriatric patients are more likely to develop adverse CNS effects, especially confusion, while taking indomethacin.

Ketoprofen¾ Studies have shown that protein binding and clearance of ketoprofen may be reduced, leading to increased and prolonged serum concentration and elimination half-life. 35

Nabumetone¾ Studies in geriatric patients have not shown differences in the efficacy or safety of nabumetone compared with younger adults. 210, 211, 274 However, plasma concentrations of 6-MNA are higher in geriatric patients, and interpatient variability in the pharmacokinetic parameters for 6-MNA is greater in geriatric patients than in younger adults. 275, 276

Naproxen¾ Studies have shown that the unbound (free) fraction of naproxen, but not the total plasma concentration, may be increased in geriatric patients. 1, 75, 188 The steady-state concentration of unbound naproxen may be almost doubled in geriatric patients as compared with younger adults. 75

Oxaprozin¾ Studies have not demonstrated a need for adjustment of initial oxaprozin dosage in elderly patients on the basis of pharmacokinetic considerations. 163

The relationship of age to the risk of adverse effects in patients receiving oxaprozin has been examined using data from 3 studies in patients with rheumatoid arthritis and 1 study in patients with osteoarthritis. The data indicate that oxaprozin is more likely to cause a potentially significant decrease in renal function, adverse gastrointestinal effects, or a significant decrease in hemoglobin concentration in patients older than 60 years of age than in younger adults. 288 Although it has also been reported, with other NSAIDs, that geriatric patients seem to be more susceptible to NSAID-induced hepatotoxicity, 289 there were no significant age-related differences in measures of hepatic function in the 4 studies with oxaprozin. 288

Phenylbutazone¾ In patients 60 years of age and over, therapy should be limited to short periods (not to exceed 1 week if possible) because of the high risk of severe, possibly fatal, toxic reactions. Specifically, the risk of aplastic anemia and agranulocytosis is increased in elderly patients. 42

Piroxicam¾ Studies in geriatric patients have shown a tendency toward increased elimination half-life and steady-state plasma concentration in these patients, especially elderly females. 45

Tenoxicam¾ The risk of hyperkalemia may be increased in elderly patients. 180

Tiaprofenic acid¾ The risk of adverse renal effects reflected by hyperkalemia and/or an increase in blood urea nitrogen (BUN) may be increased in elderly patients; an increase in BUN occurred in 11.8% of elderly patients, but only 2.5% of all patients, in clinical trials. 213

Dental

NSAIDs may cause soreness, irritation, or ulceration of the oral mucosa.
Most of the NSAIDs may rarely cause leukopenia and/or thrombocytopenia, which may result in an increased incidence of microbial infection, delayed healing, and gingival bleeding. If leukopenia or thrombocytopenia occurs, dental work should be deferred until blood counts have returned to normal, and patients should be instructed in proper oral hygiene, including caution in use of regular toothbrushes, dental floss, and toothpicks. 123

Surgical

Caution is recommended in patients who require surgery. Most NSAIDs inhibit platelet aggregation and may prolong bleeding time, which may increase intra- and postoperative bleeding. The risk may be lower with usual doses of diclofenac, 158, 218 diflunisal, 24 meclofenamate, 37 mefenamic acid, 38 or nabumetone, 210, 250, 251, 252 which may not significantly alter platelet aggregability (although mefenamic acid-induced hypoprothrombinemia, if present, could be hazardous to the patient). Recovery of platelet function may occur within 1 day after discontinuation of diclofenac, 13, 57 diflunisal, 13 flurbiprofen, 51, 61 ibuprofen, indomethacin, or sulindac; 2 days after discontinuation of tolmetin; 4 days after discontinuation of naproxen; or 2 weeks following discontinuation of slowly

eliminated agents such as oxaprozin 257 or piroxicam. Consideration should be given to discontinuing NSAID treatment for an appropriate length of time prior to elective surgery, depending on the potency and duration of effect of the individual agent on platelet aggregability. In particular, it is recommended that treatment with oxaprozin, which is as potent as aspirin in inhibiting platelet aggregation, 255, 256, 257 be discontinued 1 to 2 weeks prior to elective surgery. 290

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with this medication.
In addition to the interactions listed below, the possibility should be considered that additive or multiple effects leading to impaired blood clotting and/or increased risk of bleeding may occur if any NSAID is used concurrently with any medication having a significant potential for causing hypoprothrombinemia, thrombocytopenia, or gastrointestinal ulceration or hemorrhage.
For all NSAIDs

Note: All of the following interactions have not been documented with every NSAID. However, they have been reported with several of these medications and should be considered potential precautions to the use of any NSAID, especially with chronic administration. 309

Acetaminophen

(prolonged concurrent use of acetaminophen with an NSAID may increase the risk of adverse renal effects; it is recommended that patients be under close medical supervision while receiving such combined therapy)
(concurrent use with diflunisal may also increase the risk of acetaminophen-induced hepatotoxicity because diflunisal may increase the acetaminophen plasma concentration by 50%)

Alcohol or

Corticosteroids, glucocorticoid or

Corticotropin (chronic therapeutic use) or

Potassium supplements

(concurrent use with an NSAID may increase the risk of gastrointestinal side effects, including ulceration or hemorrhage; however, concurrent use with a glucocorticoid or corticotropin in the treatment of arthritis may provide additional therapeutic benefit and permit reduction of glucocorticoid or corticotropin dosage)

>> Anticoagulants, coumarin- or indanedione-derivative or

>> Heparin or

>> Thrombolytic agents, such as:
Alteplase
Anistreplase
Streptokinase
Urokinase

(inhibition of platelet aggregation by NSAIDs, and the possibility of NSAID-induced gastrointestinal ulceration or bleeding, may be hazardous to patients receiving anticoagulant or thrombolytic therapy 320 ; although nabumetone may be less likely than other NSAIDs to increase the risk of bleeding because it may be less likely to cause gastrointestinal ulceration or hemorrhage 250, 260 and because it has minimal, if any, platelet aggregation-inhibiting activity, 210, 250, 251, 252 caution is recommended; 210 also, with usual doses, diclofenac, 158, 218 diflunisal, 24 meclofenamate, 37 and mefenamic acid may be less likely than other NSAIDs to significantly alter platelet aggregability)
(diflunisal, etodolac, fenoprofen, floctafenine, flurbiprofen, indomethacin, meclofenamate, mefenamic acid, phenylbutazone, piroxicam, sulindac, tiaprofenic acid, and tolmetin have been reported to potentiate the effects of coumarin- or indanedione-derivative anticoagulants; the effect of floctafenine on coagulation test results becomes apparent only after 2 weeks of concurrent use; potentiation may result from displacement of the anticoagulant from protein-binding sites and, with phenylbutazone, from inhibition of the metabolism of the anticoagulant; concurrent use of phenylbutazone with an anticoagulant is not recommended; if another NSAID is used concurrently, coagulation tests should be monitored and anticoagulant dosage adjustments made, if necessary, when NSAID therapy is initiated or discontinued)

Antidiabetic agents, oral or

Insulin

(NSAIDs may increase the hypoglycemic effect of these medications because prostaglandins are directly involved in regulatory mechanisms of glucose metabolism and possibly because of displacement of the oral antidiabetics from serum proteins; dosage adjustments of the antidiabetic agent may be necessary; glipizide and glyburide, due to their nonionic binding characteristics, may not be affected as much as the other oral antidiabetic agents; however, caution with concurrent use is recommended)
(diclofenac has also been reported to decrease the effects of these medications, leading to hyperglycemia)

Antihypertensives or

Diuretics, especially
>> Triamterene

(increased monitoring of the response to an antihypertensive agent may be advisable when any NSAID is used concurrently because flurbiprofen, 144 indomethacin, ibuprofen, naproxen, oxaprozin, and piroxicam have been shown to reduce or reverse the effects of antihypertensives, possibly by inhibiting renal prostaglandin synthesis and/or by causing sodium and fluid retention)
(NSAIDs may decrease the diuretic, natriuretic, and antihypertensive effects of diuretics, probably by inhibiting renal prostaglandin synthesis; flurbiprofen has also been shown to interfere with furosemide-induced kaliuresis 144 ; however, diflunisal does not decrease the diuretic effect of furosemide 219)

(indomethacin may block the increase in plasma renin activity [PRA] induced by bumetanide, furosemide, or indapamide)
(concurrent use of an NSAID and a diuretic may increase the risk of renal failure secondary to a decrease in renal blood flow caused by inhibition of renal prostaglandin synthesis; specifically, concurrent use of triamterene and indomethacin is not recommended because this combination has caused renal function impairment [azotemia and reduced creatinine clearance] and a few cases of renal failure requiring hemodialysis)
(concurrent use of a potassium-sparing diuretic with indomethacin or diclofenac, 156, 218 and possibly other NSAIDs, 180, 213 may increase the risk of hyperkalemia)
(diflunisal significantly increases the plasma concentration of hydrochlorothiazide and decreases the hyperuricemic effect of hydrochlorothiazide or furosemide)

>> Aspirin or

NSAIDs, two or more concurrently, especially
>> Diflunisal and indomethacin concurrently 175, 176, 219, 320 or

Salicylates other than aspirin and diflunisal

(concurrent use of two or more NSAIDs, including aspirin, is not recommended; concurrent therapy may increase the risk of gastrointestinal toxicity, including ulceration or hemorrhage, without providing additional symptomatic relief; specifically, concurrent use of diflunisal and indomethacin has resulted in fatal gastrointestinal hemorrhage)
(concurrent use of aspirin with other NSAIDs may also increase the risk of bleeding at sites other than the gastrointestinal tract because of additive inhibition of platelet aggregation)
(concurrent administration of two or more NSAIDs may alter the pharmacokinetic profile of at least one of the medications, which may alter the therapeutic effect and/or increase the risk of adverse effects; specifically, aspirin decreases protein binding of ketoprofen 205 and etodolac [but does not alter etodolac clearance], 177 increases plasma clearance of ketoprofen, 205 interferes with the formation and excretion of ketoprofen conjugates, decreases concentrations of the active sulfide metabolite of sulindac, 223 and decreases the bioavailability of diclofenac, 158, 218 diflunisal 219 , fenoprofen, 186 flurbiprofen [by 50%], 144 ibuprofen [by 50% in multiple-dose studies], 182 indomethacin [by 20%], 175, 176 meclofenamate, 178 piroxicam [by 20%], 167 a single dose of tenoxicam [by 20%], 180 and tolmetin. 216 Also, diflunisal decreases the renal clearance of indomethacin, resulting in significantly increased indomethacin plasma concentrations, 175, 176, 219 and decreases the concentration of the active sulfide metabolite of sulindac by 33%. 219, 223 Although studies to determine whether phenylbutazone alters etodolac clearance have not been done, phenylbutazone has been shown in vitro to decrease the protein binding of etodolac, leading to an 80% increase in the concentration of unbound etodolac 177)

Bone marrow depressants (See Appendix II)

(leukopenic and/or thrombocytopenic effects of these medications may be increased with concurrent or recent therapy if an NSAID causes the same effects; dosage adjustment of the bone marrow depressant, if necessary, should be based on blood counts)

>> Cefamandole or

>> Cefoperazone or

>> Cefotetan or

>> Plicamycin or

>> Valproic acid

(these medications may cause hypoprothrombinemia; in addition, plicamycin or valproic acid may inhibit platelet aggregation; concurrent use with an NSAID may increase the risk of bleeding because of additive interferences with platelet function and/or the potential occurrence of NSAID-induced gastrointestinal ulceration or hemorrhage)

Colchicine

(concurrent use with an NSAID may increase the risk of gastrointestinal ulceration or hemorrhage, and concurrent use with phenylbutazone may also increase the risk of adverse hematologic effects)
(inhibition of platelet aggregation by NSAIDs, added to colchicine"s effects on blood clotting mechanisms [colchicine may cause thrombocytopenia with chronic use and clotting defects, including disseminated intravascular coagulation, with overdose], may increase the risk of bleeding at sites other than the gastrointestinal tract)

>> Cyclosporine 158, 176, 177, 218, 219, 223 or

Gold compounds or

Nephrotoxic medications, other (See Appendix II)

(inhibition of renal prostaglandin activity by NSAIDs may increase the plasma concentration of cyclosporine and/or the risk of cyclosporine-induced nephrotoxicity; patients should be carefully monitored during concurrent use)
(the risk of adverse renal effects may also be increased when an NSAID is used concurrently with other nephrotoxic medications, possibly including gold compounds [although NSAIDs and gold compounds are commonly used concurrently in the treatment of arthritis])

Digitalis glycosides

(diclofenac and ibuprofen have been shown to increase serum digoxin concentrations, and indomethacin has increased digitalis concentrations in neonates being treated for patent ductus arteriosus; the possibility should be considered that some of the other NSAIDs may also increase digoxin concentrations, 177, 211 leading to an increased risk of digitalis toxicity; increased monitoring and dosage adjustments of the digitalis glycoside may be necessary during and following concurrent NSAID therapy; however, studies have failed to show that flurbiprofen, 144 ketoprofen, 205 piroxicam, 168 or tenoxicam 180 increases digoxin concentrations, and phenylbutazone may decrease digitalis concentrations [see individual For phenylbutazone listing, below])

>> Lithium

(diclofenac, ibuprofen, 182 indomethacin, meloxicam 320 naproxen, and piroxicam have been reported to increase the steady-state concentration of lithium, possibly by decreasing its renal clearance; with indomethacin, the steady-state lithium concentration was increased by up to 50%; other NSAIDs may have a similar effect; increased monitoring of lithium concentrations is recommended during and following concurrent use)

>> Methotrexate

(concurrent use with phenylbutazone may increase the risk of agranulocytosis or bone marrow depression and is not recommended)
(NSAIDs may decrease protein binding and/or renal elimination of methotrexate, resulting in increased and prolonged methotrexate plasma concentrations and an increased risk of toxicity, especially during high-dose methotrexate infusion therapy; indomethacin has caused toxicity with intermediate-dose methotrexate infusions; fatalities have been reported; it is recommended that NSAID therapy be withheld for varying periods of time, depending on the elimination half-life of the individual NSAID [12 to 24 hours for agents with a short elimination half-life to up to 10 or 12 days for agents with a very long elimination half-life] prior to administration of a high-dose methotrexate infusion [for indomethacin, an intermediate- or high-dose methotrexate infusion]; also, NSAID therapy should not be resumed following the infusion until the methotrexate plasma concentration has decreased to a nontoxic level, usually at least 12 hours)
(severe, sometimes fatal, methotrexate toxicity has also been reported when NSAIDs were used concurrently with low to moderate doses of methotrexate, including doses commonly used in the treatment of rheumatoid arthritis or psoriasis; 87, 88, 89 caution in concurrent use is recommended, with dosage of methotrexate being adjusted as determined by monitoring the plasma methotrexate concentration and/or adequacy of the patient"s renal function)

Photosensitizing medications, other

(concurrent use with photosensitizing NSAIDs may cause additive photosensitizing effects)

Platelet aggregation inhibitors, other (See Appendix II)

(concurrent use with an NSAID may increase the risk of bleeding because of additive inhibition of platelet aggregation, as well as the potential for NSAID-induced gastrointestinal ulceration or hemorrhage)
(concurrent use of sulfinpyrazone with NSAIDs may also increase the risk of gastrointestinal ulceration or hemorrhage)

>> Probenecid

(concurrent use of probenecid with ketoprofen is not recommended; probenecid decreases ketoprofen"s renal clearance [by approximately 66%] and protein binding [by 28%], and inhibits formation and renal clearance of ketoprofen conjugates, leading to greatly increased ketoprofen plasma concentration and risk of toxicity 205)
(probenecid has also been shown to decrease renal and biliary clearance of indomethacin, and to increase plasma concentrations of indomethacin and naproxen, leading to increased risk of toxicity and possibly to increased effectiveness of the NSAID; if concurrent use is necessary, it is recommended that

these NSAIDs be administered in reduced dosage and that increases in dosage be made slowly and in small increments 1, 32, 176)
(probenecid may also decrease excretion and increase serum concentrations of other NSAIDs, possibly enhancing effectiveness and/or increasing the potential for toxicity; a decrease in dosage of the NSAID may be necessary if adverse effects occur)
(probenecid may increase the plasma concentration of sulindac and its sulfone metabolite, and slightly decrease the plasma concentration of the active sulfide metabolite 223)

For diflunisal (in addition to those listed for all NSAIDs)

Antacids

(concurrent chronic use may significantly decrease the plasma concentration of diflunisal)

For fenoprofen (in addition to those listed for all NSAIDs)

Antacids

(concurrent chronic use may significantly decrease the plasma concentration of fenoprofen)

Phenobarbital

(phenobarbital may increase metabolism of fenoprofen by inducing hepatic microsomal enzymes, leading to a decrease in the elimination half-life of fenoprofen; fenoprofen dosage adjustment may be required)

For indomethacin (in addition to those listed for all NSAIDs)

Aminoglycosides

(administration of indomethacin to neonates being treated for a patent ductus has decreased the renal clearance and increased the plasma concentration of concurrently administered aminoglycoside antibiotics; although not documented, similar effects may occur in other patients, leading to increased risk of toxicity; adjustment of aminoglycoside dosage may be required)

>> Zidovudine

(indomethacin may competitively inhibit hepatic glucuronidation and decrease the clearance of zidovudine, possibly leading to potentiation of zidovudine toxicity; indomethacin toxicity may also be increased; concurrent use of the two medications should be avoided)

For phenylbutazone (in addition to those listed for all NSAIDs)

Note: Phenylbutazone induces hepatic microsomal enzymes and is itself metabolized by the same enzymes. It has been reported to increase the metabolism of several medications metabolized by hepatic microsomal enzymes and to decrease the metabolism of others. Although not documented, it has been proposed that, in some cases, phenylbutazone may compete with other medications for the enzymes.

Alcohol

(concurrent use of alcohol with phenylbutazone may increase the potential for impairment of psychomotor skills)

Anticonvulsants, hydantoin, especially
>> Phenytoin

(phenylbutazone may displace hydantoin anticonvulsants from their protein-binding sites and inhibit their metabolism, possibly leading to increased elimination half-life and toxicity; hydantoin dosage adjustment, based on monitoring of plasma concentrations and/or observed signs of toxicity, may be required)

Barbiturates or

Cortisone

(phenylbutazone may decrease the efficacy of these medications by inducing hepatic microsomal enzymes and increasing their metabolism; the possibility should be considered that corticosteroids other than cortisone may be similarly affected)

Cholestyramine

(cholestyramine may decrease absorption of phenylbutazone; administration of phenylbutazone 1 hour before or 4 to 6 hours after cholestyramine may decrease the risk of impaired absorption and of toxicity resulting from sudden increases in absorption and serum concentration of phenylbutazone if cholestyramine therapy is discontinued)

Contraceptives, estrogen-containing, oral

(concurrent long-term use with phenylbutazone may result in reduced contraceptive reliability and increased incidence of breakthrough bleeding)

Dermatitis-causing medications, especially
Chloroquine
Hydroxychloroquine

(concurrent use with phenylbutazone may increase the risk of severe dermatologic reactions)

>> Digitalis glycosides, possibly excepting digoxin

(phenylbutazone may increase the hepatic metabolism of digitalis, leading to a decrease in digitalis serum concentration; digitalis glycoside dosage adjustment may be necessary during and following concurrent use)

Hepatic enzyme inducers, other (See Appendix II)

(hepatic enzyme inducers may increase phenylbutazone metabolism and decrease its half-life)

Methylphenidate

(methylphenidate may inhibit metabolism of phenylbutazone, leading to increased plasma concentrations and toxicity; dosage adjustments may be necessary)

>> Penicillamine

(concurrent use with phenylbutazone may increase the risk of serious hematologic and/or renal adverse effects)

Sulfonamides

(sulfonamides may displace phenylbutazone from its protein binding sites and potentiate its effects; phenylbutazone has also been reported to potentiate the effects of sulfonamides)

Other medications, oral, especially:
>> Ciprofloxacin 277

>> Enoxacin 278

>> Itraconazole 279

>> Ketoconazole 280

>> Lomefloxacin 281

>> Norfloxacin 282

>> Ofloxacin 283

>> Tetracyclines, oral

(antacids present in buffered phenylbutazone formulations may decrease absorption of many other orally administered medications by forming nonabsorbable complexes and/or increasing intragastric pH; if used concurrently, buffered phenylbutazone should be taken at least 6 hours before or 2 hours after ciprofloxacin or lomefloxacin, 8 hours before or 2 hours after enoxacin, 2 hours after itraconazole, 3 hours before or after ketoconazole, 2 hours before or after norfloxacin or ofloxacin, 1 to 3 hours before or after tetracycline, and at least 1 to 2 hours before or after other orally administered medications)

For sulindac (in addition to those listed for all NSAIDs)

Antacids

(concurrent chronic use may significantly decrease the plasma concentration of sulindac)

Dimethyl sulfoxide (DMSO)

(topical application of DMSO to arthritic joints [not recommended because safety and efficacy are unproven] by patients receiving sulindac has been reported to cause peripheral neuropathy and to decrease the plasma concentration of sulindac"s active metabolite, thereby decreasing its efficacy)

For tenoxicam (in addition to those listed for all NSAIDs)

Cholestyramine

(cholestyramine decreased the average half-life of an intravenous dose of tenoxicam from 67.4 to 31.9 hours and increased the apparent clearance of tenoxicam by 105%) 180

For tiaprofenic acid (in addition to those listed for all NSAIDs)

Anticonvulsants, hydantoin, especially
>> Phenytoin

(tiaprofenic acid may displace hydantoin anticonvulsants from their protein-binding sites, which may lead to an increase in the concentration of the unbound fraction and to toxicity; hydantoin dosage adjustment, based on monitoring of plasma concentrations and/or observed signs of toxicity, may be required)

Laboratory value alterations

The following have been selected on the basis of their potential clinical significance (possible effect in parentheses where appropriate)¾not necessarily inclusive (>> = major clinical significance):
With diagnostic test results

For diflunisal

Salicylate concentrations, serum

(diflunisal may produce falsely elevated serum salicylate values determined via the Abbott TDx fluorescence polarization immunoassay, the Trinder colorimetric assay, or the Du Pont aca method, despite the fact that diflunisal is not metabolized to salicylate in vivo219)

For etodolac

Bilirubin, urine, determinations

(phenolic metabolites of etodolac may cause false-positive test results)

Ketones, urine, determinations

(false-positive test results may occur with dipstick method of determination)

For fenoprofen

Triiodothyronine (T 3) determinations

(fenoprofen may interfere with total and free T 3 determinations in the Amerlex-M kit assay; thyroid-stimulating hormone, total thyroxine, and thyrotropin-releasing hormone test responses are not affected 26)

For indomethacin

Dexamethasone suppression test for endogenous depression

(indomethacin may produce false-negative test results [i.e., no indication of endogenous depression] because plasma cortisol concentration is reduced to a greater extent than with dexamethasone alone)

5-Hydroxyindoleacetic acid (5-HIAA), urinary, determinations

(false 5-HIAA concentration values may be measured via the Goldenberg modification of Undenfriend"s method because indomethacin metabolites are structurally similar to 5-HIAA)

For ketoprofen

Albumin, urine, determinations and

Bile salts, urine, determinations and

17-Ketosteroid (17-KS), urine, determinations and

17-Hydroxycorticosteroid (17-OHCS), urine, determinations

(ketoprofen metabolites in urine may interfere with test procedures that rely on acid precipitation as an end point or on color reactions of carbonyl groups; no interference occurs in tests for urinary protein using commercially available dye-impregnated test strips)

For mefenamic acid

Bile, urinary, determinations

(false-positive test results may occur when the diazo tablet test is used; the Harrison test is not affected)

For naproxen

5-HIAA, urine, determinations

(naproxen may interfere with some assays)

Steroid, urine, determinations

(17-ketogenic steroid concentrations may be falsely increased by naproxen when m-dinitrobenzene reagent is used; although 17-hydroxycorticosteroid measurements are not significantly altered when the

Porter-Silber test is used, naproxen therapy should be discontinued 72 hours before adrenal function tests are performed)

For phenylbutazone

Thyroid function tests

(phenylbutazone may decrease 24-hour 131I thyroidal uptake [effect lasts about 14 days] or increase resin or red cell T 3 uptake)

For tolmetin

Protein, urine, determinations

(the metabolites of tolmetin in urine produce false-positive tests for urine protein when the sulfosalicylic acid method is used; no interference occurs in tests for urine protein when commercially available dye-impregnated reagent strips are used)

With physiology/laboratory test values

Bleeding time

(may be prolonged by most NSAIDs [with ketoprofen, by 3 to 4 minutes above baseline values] because of suppressed platelet aggregation; effects may persist for less than 1 day [flurbiprofen, ibuprofen, indomethacin, sulindac], 2 days [tolmetin], 4 days [naproxen], or 2 weeks [oxaprozin and piroxicam] following discontinuation of therapy)
(effects on platelet aggregation and bleeding time appear minimal with usual doses of diclofenac, 158, 218 meclofenamate, 37 or mefenamic acid, 38 up to 1000 mg twice a day of diflunisal, or up to 1000 mg per day of nabumetone 210, 250, 251, 252)

Glucose concentrations

(decrease in blood glucose concentration has been reported with ibuprofen, indomethacin, and piroxicam)
(increase in blood glucose concentration has been reported with indomethacin, phenylbutazone, piroxicam, and sulindac)
(increase in urine glucose concentration has also been reported with indomethacin)

Hematocrit or

Hemoglobin

(values may be decreased, possibly because of gastrointestinal bleeding or microbleeding and/or hemodilution caused by fluid retention 177)

Leukocyte count and

Platelet count

(may be decreased)

Liver function tests, including:
Alkaline phosphatase, serum
Lactate dehydrogenase (LDH), serum
Transaminases, serum

(values may be increased; liver function test abnormalities may return to normal despite continued use; however, if significant abnormalities occur, clinical signs and symptoms consistent with liver disease develop, or systemic manifestations such as eosinophilia or rash occur, the medication should be discontinued)
(the incidence of significantly increased transaminase values is higher with diclofenac than with other NSAIDs; in clinical trials with diclofenac, elevations to more than 3 times the upper limit of normal occurred with overall rates of 2% in patients treated for 2 months and 4% in patients treated for 2 to 6 months; values in excess of 8 times the upper limit of normal occurred in approximately 1% of the patients 158)

Plasma renin activity (PRA)

(indomethacin has been reported to decrease PRA and to block the increase in PRA usually produced by bumetanide, furosemide, or indapamide)

Potassium, serum, concentrations

(may be increased)

Protein, urine (including albumin) concentrations

(increases have been reported with diclofenac, diflunisal, indomethacin, phenylbutazone, piroxicam, sulindac, tenoxicam, and tolmetin)

Renal function tests, including:
Blood urea nitrogen (BUN)
Creatinine, serum
Electrolyte, blood and urine, concentrations
Urine volume

(NSAIDs may decrease renal function, resulting in increased BUN, serum creatinine, and serum electrolyte concentrations and in decreased urine volume and urine electrolyte concentrations; however, in some cases, water retention may exceed that of sodium, resulting in dilutional hyponatremia)

Uric acid concentrations

(serum concentrations may be decreased and urine concentrations increased by diclofenac, 51 diflunisal, 24 etodolac, 177 oxaprozin, 253, 254 and phenylbutazone 224 ; in clinical trials with etodolac, the serum concentration was usually decreased by 1 to 2 mg per 100 mL [59 to 118

micromoles/L] after 4 weeks of therapy with 600 to 1000 mg per day and the reduction was maintained during the study period 177)

For mefenamic acid only

Prothrombin time

(may be prolonged)

Medical considerations/Contraindications

The medical considerations/contraindications included have been selected on the basis of their potential clinical significance (reasons given in parentheses where appropriate)¾ not necessarily inclusive (>> = major clinical significance).
Except under special circumstances, this medication should not be used when the following medical problems exist

For all NSAIDs

>> Allergic reaction, severe, such as anaphylaxis or angioedema, induced by aspirin or other NSAIDs, history of or

>> Nasal polyps associated with bronchospasm, aspirin-induced

(high risk of severe allergic reactions because of cross-sensitivity)

For diclofenac (in addition to those listed for all NSAIDs)

>> Blood dyscrasias, active or history of or

>> Bone marrow depression

(diclofenac may induce or exacerbate these conditions)

For phenylbutazone (in addition to those listed for all NSAIDs)

>> Blood dyscrasias, active or history of or

>> Bone marrow depression

(phenylbutazone may induce or exacerbate these conditions)

>> Cardiac disease, severe or

>> Cardiac failure, incipient or

>> Cardiopulmonary disease, severe

(sodium and fluid retention caused by phenylbutazone may increase plasma volume and the risk of edema, acute pulmonary edema, and cardiac decompensation)

>> Hepatic disease, severe or

>> Renal disease, severe

(increased phenylbutazone blood concentrations and potential for toxicity may result from decreased clearance; also, potential for adverse renal effects may be increased in the presence of pre-existing severe hepatic or renal disease)

>> Peptic ulcer disease, active

(may be exacerbated; increased risk of perforation and/or bleeding)

Risk-benefit should be considered when the following medical problems exist

For all NSAIDs

Allergic reaction, mild, such as allergic rhinitis, urticaria, or skin rash, induced by aspirin or other NSAIDs, history of

(possibility of cross-sensitivity)

Anemia or

Asthma

(may be exacerbated)

Conditions predisposing to and/or exacerbated by fluid retention, such as:
Compromised cardiac function
Congestive heart disease
Edema, pre-existing
Hypertension
Renal function impairment or failure

(NSAIDs may cause fluid retention and edema)

Conditions predisposing to gastrointestinal toxicity, such as: 1

Alcoholism, active 295

>> Inflammatory or ulcerative disease of the upper or lower gastrointestinal tract, including Crohn"s disease, diverticulitis, peptic ulcer disease, or ulcerative colitis, active or history of 160, 168, 169, 174, 175, 182, 187, 189, 211, 213, 216, 218

Tobacco use, or recent history of 295

(NSAIDs should preferably not be given to patients with active peptic ulcer disease or gastrointestinal bleeding; if NSAID administration is considered essential, an antiulcer regimen should be administered concurrently 303)
(caution and close supervision are also recommended for other patients in whom there is a significant risk of gastrointestinal toxicity; misoprostol or sucralfate should be considered as prophylaxis for those at high risk 303)

Congestive heart failure or

Diabetes mellitus or

Edema, pre-existing or

Extracellular volume depletion or

Sepsis

(increased risk of renal failure)

>> Hemophilia or other bleeding problems including coagulation or platelet function disorders

(increased risk of bleeding because most NSAIDs inhibit platelet aggregation and may cause gastrointestinal ulceration or hemorrhage; although the risk of these problems is lower with nabumetone than with most other NSAIDs, caution is recommended 284)

Hepatic cirrhosis or

Hepatic function impairment

(risk of renal failure is increased in patients with hepatic function impairment)
(most NSAIDs are metabolized hepatically; impairment of metabolism may be particularly problematic for nabumetone, since metabolism to the active metabolite 6-MNA may be decreased 210, 211, 285 sufficiently to reduce efficacy 285)
(although stable hepatic cirrhosis does not alter the clearance of etodolac, the possibility should be considered that unstable hepatic disease or severe hepatic function impairment may do so 177)
(hepatic function impairment, especially if associated with chronic alcoholic cirrhosis, produces variability in ketoprofen pharmacokinetics and reduces ketoprofen protein binding; the concentration of unbound ketoprofen may be doubled; caution and careful monitoring are recommended; also, only immediate-release ketoprofen dosage forms should be used if the patient"s serum albumin is lower than 3.5 grams per deciliter 205)
(hepatic cirrhosis, especially if associated with chronic alcoholism, increases the concentration of unbound naproxen, even though the total plasma concentration may be decreased; the lowest effective dose should be administered and the patient carefully monitored 188)
(although the clearance of oxaprozin is not altered by well-compensated hepatic cirrhosis, caution is recommended in patients with severe hepatic function impairment 163)

(biotransformation of sulindac to the active sulfide metabolite is slowed; however, biliary elimination of the metabolite is greatly decreased, leading to increased and prolonged plasma concentrations and increased risk of toxicity; the patient should be carefully monitored and dosage adjusted as necessary)

Renal function impairment

(increased risk of hyperkalemia 180, 211, 218 and of adverse renal effects, including acute renal failure; especially careful monitoring of the patient is recommended)
(NSAIDs and/or their metabolites are excreted primarily via the kidneys; a reduction in dosage may be required to prevent accumulation)
(etodolac has not been shown to increase the risk of renal toxicity, and the pharmacokinetic profile of etodolac is not altered, when up to 500 mg of etodolac is administered every 12 hours to patients with mild to moderate renal function impairment; however, the possibility of renal toxicity associated with a reduction of renal prostaglandin synthesis leading to a decrease in renal blood flow cannot be discounted; caution and monitoring of patients considered to be at risk are recommended 177, 232, 262, 263)
(although less than 1% of the active 6-MNA metabolite of nabumetone is eliminated in the urine unchanged, 250 and increased concentrations of 6-MNA were not measured after administration of a single dose, 286 caution is recommended in patients with renal function impairment because the extent to which metabolites may accumulate and cause adverse effects has not been determined 210)
(in end-stage renal disease, conversion of sulindac to its active metabolite is decreased)

>> Renal function impairment

(the risk of toxicity associated with accumulation of the NSAID and/or the risk of adverse renal effects may be higher with diflunisal, fenoprofen, indomethacin, and piroxicam than with other NSAIDs; individualization of dosage and especially careful monitoring of the patient are recommended)

>> Stomatitis

(may be induced by NSAIDs; this symptom of possible NSAID-induced blood dyscrasias may be masked by pre-existing stomatitis)

Systemic lupus erythematosus (SLE)

(patient may be predisposed to NSAID-induced central nervous system and/or renal adverse effects)

>> Caution is also recommended in geriatric patients, who may be more likely to develop adverse hepatic or renal effects with these medications and in whom gastrointestinal ulceration or bleeding is more likely to cause serious consequences, including fatalities.

Caution is also recommended when an NSAID, especially fenoprofen, is used in patients who developed genitourinary tract problems such as dysuria, cystitis, hematuria, nephritis, or nephrotic syndrome during treatment with another NSAID.

The sodium content of diclofenac sodium, meclofenamate sodium, naproxen sodium, naproxen oral suspension, and tolmetin sodium should be considered when selecting an NSAID for patients who must restrict their sodium intake.

For diclofenac (in addition to those listed for all NSAIDs)

Porphyria, hepatic

(diclofenac may precipitate an acute attack 158, 218)

For indomethacin (in addition to those listed for all NSAIDs)

Epilepsy or

>> Mental depression or other psychiatric disturbances or

Parkinsonism

(indomethacin may aggravate these conditions)

For mefenamic acid (in addition to those listed for all NSAIDs)

>> Hypoprothrombinemia, when prothrombin activity is 10 to 20% of normal

(increased risk of bleeding, since mefenamic acid may further increase the prothrombin time 209)

For phenylbutazone (in addition to those listed for all NSAIDs)

>> Polymyalgia rheumatica or

>> Temporal arteritis

(phenylbutazone may aggravate these conditions)

For sulindac (in addition to those listed for all NSAIDs)

>> Renal calculus or history of

(renal calculi containing sulindac metabolites have occurred, rarely, in patients receiving sulindac; it is recommended that the medication be used with caution, and in conjunction with adequate fluid intake, in patients who may be predisposed to calculus formation 223, 306)

For rectal administration (in addition to those listed as applying to oral use of the NSAIDs with rectal dosage forms)

>> Bleeding, rectal or anal, active or recent history of or

>> Hemorrhoids or

>> Lesions, inflammatory, of anus or rectum or

>> Proctitis or recent history of

(may be exacerbated or reactivated)

Patient monitoring

The following may be especially important in patient monitoring (other tests may be warranted in some patients, depending on condition; >> = major clinical significance):
Blood urea nitrogen (BUN) determinations or

Creatinine concentrations, serum and/or

Potassium concentrations, serum

(monitoring may be required at periodic intervals during therapy, especially in patients with documented hepatic or renal function impairment, other patients known or suspected to be at risk for renal function impairment, and/or those taking diuretics concurrently; also, may be required if signs of possible renal toxicity, such as substantial increases in blood pressure, fluid retention, or rapid weight gain occur)

Complete physical examinations, including urinalyses

(recommended prior to and at regular frequent intervals during phenylbutazone therapy)

Hematocrit determinations and/or

Hemoglobin determinations and/or

Stool tests for occult blood loss

(may be performed at one- to six-month intervals to detect blood loss during prolonged therapy, depending on the individual patient"s risk of developing gastrointestinal toxicity; however, these tests [unlike endoscopy, which is not recommended on a routine basis] are not capable of detecting ulcerations that are developing asymptomatically or of predicting whether severe gastrointestinal bleeding is likely to occur 304)

>> Hematologic determinations

(recommended prior to initiation of phenylbutazone therapy and at regular intervals of 3 to 4 weeks during therapy for patients receiving the medication for periods longer than 1 week)
(although routine monitoring is not necessary during therapy with other NSAIDs, appropriate testing should be performed if symptoms of blood dyscrasias occur)

Liver function tests, especially determination of transaminase (AST [SGOT]; ALT [SGPT]) values

(may be required at periodic intervals during indomethacin therapy; also, it is recommended that hepatic function tests be performed within eight weeks following initiation of diclofenac therapy and periodically thereafter 119)

(may also be required at periodic intervals during therapy with other NSAIDs if the patient is known or suspected to be at increased risk of developing hepatic adverse effects)
(although routine monitoring is not necessary for most patients during therapy with NSAIDs other than diclofenac or indomethacin, appropriate tests should be performed if signs and/or symptoms of hepatotoxicity occur)

Ophthalmologic examinations

(may be required if vision problems such as blurred vision occur during therapy)

Upper gastrointestinal diagnostic tests

(recommended for patients with persistent or severe dyspepsia or other signs of possible gastrointestinal toxicity)

Side/Adverse Effects

See Table 3.

Note: Hypersensitivity reactions with these medications may be similar to those reported for aspirin, i.e., rhinosinusitis/asthma or angioedema/urticaria. Anaphylaxis has also been reported, both in aspirin-sensitive patients and in those without known hypersensitivity to any of these agents. The risk of anaphylaxis, characterized by respiratory distress, circulatory collapse, and angioedema and/or urticaria with or without pruritus, may be increased when previously discontinued therapy with one of these medications is reinstituted. Although anaphylaxis occurs rarely with these agents, several reports have indicated a higher incidence of anaphylactic reactions with tolmetin than with the others.
Other hypersensitivity reactions affecting multiple body systems have also been reported with several of the NSAIDs. A hypersensitivity syndrome consisting of fever and chills, skin rashes or other cutaneous manifestations, hepatotoxicity, renal toxicity (including renal failure), leukopenia, thrombocytopenia, eosinophilia, inflamed glands or lymph nodes, and arthralgias has been reported rarely with diflunisal and with sulindac. Fever, skin rashes, and arthralgias have also preceded fenoprofen-induced renal toxicity. 3 In addition, a syndrome of fever and chills, nausea, vomiting, and abdominal pain has been reported with ibuprofen, 31 and a serum sickness- or influenza-like syndrome that may consist of troubled breathing, arthralgias, fever and chills, fatigue, pruritus, and/or skin rash or other cutaneous manifestations, has been reported with ibuprofen (although a positive causal relationship has not been established), meclofenamate, phenylbutazone, piroxicam, and tolmetin. 44, 45

The antipyretic, analgesic, and anti-inflammatory actions of NSAIDs may mask symptoms of the occurrence or worsening of infections. Reactivation of latent pulmonary tuberculosis has been reported in a few patients receiving indomethacin. 32, 131

Two cases of biliary obstruction associated with sulindac therapy have been reported. The obstruction was caused in each case by the presence in the common bile duct of a "sludge"" of crystals containing a sulindac metabolite. 305, 308

Metabolic acidosis and respiratory alkalosis have also been reported rarely (incidences < 1%) with phenylbutazone.

Patients 40 years of age and older may be more susceptible to the toxic effects of phenylbutazone. In patients 60 years of age and older, there is an increased risk of severe, possibly fatal, toxic reactions.
Phenylbutazone-induced agranulocytosis may occur with a rapid onset, especially in relatively young patients. Aplastic anemia may occur more frequently in patients receiving prolonged therapy, especially older female patients. Both agranulocytosis and aplastic anemia are more likely to occur in geriatric patients.
Because diflunisal is a salicylic acid derivative, the possibility that it may be associated with the development of Reye"s syndrome in children, teenagers, or young adults with acute febrile illnesses, especially influenza or varicella, should be kept in mind. 24

Overdose

For specific information on the agents used in the management of anti-inflammatory agents, nonsteroidal overdose, see:
· Diazepam in Benzodiazepines (Systemic) monograph;
· Dopamine or Dobutamine in Sympathomimetic Agents¾Cardiovascular Use (Parenteral-Systemic) monograph; and/or
· Vitamin K 1¾Phytonadione in Vitamin K (Systemic) monograph.
For more information on the management of overdose or unintentional ingestion, contact a Poison Control Center (see Poison Control Center Listing).

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance (possible signs and symptoms in parentheses where appropriate)¾not necessarily inclusive:
Acute and chronic

For phenylbutazone

Bluish color of fingernails, lips, or skin; convulsions, especially in children; difficulty in hearing or ringing or buzzing in the ears; dizziness or lightheadedness; hallucinations; headache, severe and continuing; increase or decrease in blood pressure; mood or mental changes; nausea, vomiting, or stomach pain, severe; periorbital edema (swelling around the eyes); shortness of breath, troubled breathing, or unusually slow, fast, or irregular breathing; swelling of face, hands, feet, or lower legs

Note: The lowest fatal doses reported for phenylbutazone are 14 grams (in an adult) and 2 grams (in a 3-year-old child). The highest doses reported to have been survived are 40 grams (in a young adult) and 5 grams (in a 3-year-old child).
Laboratory findings in overdose may reveal respiratory or metabolic acidosis or alkalosis, other electrolyte disturbances, impaired hepatic or renal function, and abnormalities of formed blood elements.
Late manifestations of massive overdosage may occur 2 to 7 days following ingestion and may include hepatomegaly, jaundice, electrocardiographic abnormalities, blood dyscrasias, and ulceration of the buccal or gastrointestinal mucosa.

For other NSAIDs

Note: The symptoms of overdose of most of the other NSAIDs have not been described as completely as for phenylbutazone. Reported symptoms have generally reflected the gastrointestinal, renal, and CNS toxicities of these medications. Following overdosage with a propionic acid derivative or indomethacin, patients may remain asymptomatic or experience only relatively mild CNS effects (e.g., lethargy, drowsiness) or gastrointestinal symptoms (e.g., abdominal pain, nausea, vomiting). However, more serious effects, such as gastrointestinal hemorrhage, acute renal failure, convulsions, and coma have been reported with these, as well as other, NSAIDs. Convulsions may be especially likely to occur following mefenamic acid overdose. Also, hypoprothrombinemia has been reported following overdose of several NSAIDs. 95

Treatment of overdose

To decrease absorption¾Emptying the stomach via induction of emesis (in alert patients only) or gastric lavage. However, syrup of ipecac may induce symptoms similar to those of NSAID toxicity, which may complicate diagnosis, and is therefore not recommended for induction of emesis. 95

Administering activated charcoal. The efficacy of activated charcoal in decreasing absorption of these medications when given more than 2 hours (6 hours for piroxicam) following ingestion of the overdose has not been determined. However, there is some evidence that repeated administration of activated charcoal may interrupt enterohepatic circulation and/or bind any of the medication that has diffused from the circulation into the intestine, thereby increasing nonrenal excretion. 95

To enhance elimination¾Administering antacids or other urinary alkalizers may increase diflunisal or sulindac excretion. Antacids may also relieve adverse gastrointestinal effects.
Inducing diuresis may be helpful in overdosage with fenoprofen, ibuprofen, or tolmetin; however, furosemide does not lower fenoprofen blood concentration.
Hemodialysis may be necessary to treat renal failure, but cannot be relied upon to decrease plasma concentrations of most NSAIDs because of their high degree of protein binding. Studies have shown that diclofenac and ketoprofen are dialyzable, but that diflunisal, etodolac, ibuprofen, indomethacin, and oxaprozin are not.
Specific treatment¾For severe hypotension plasma:
Use of volume expanders
For convulsions:
Diazepam or other appropriate benzodiazepine anticonvulsants. See the package insert or Diazepam in Benzodiazepines (Systemic) for specific dosing guidelines for use of this product.
For hypoprothrombinemia:
Use of Vitamin K 1. See the package insert or Vitamin K 1¾Phytonadione in Vitamin K (Systemic) monograph for specific dosing guidelines for use of this product.
For prevention or reversal of early indications of, renal failure:
Use of dopamine plus dobutamine intravenously 95.

See the package insert or Dopamine or Dobutamine in Sympathomimetic Agents¾Cardiovascular Use (Parenteral-Systemic) monograph for specific dosing guidelines for use of this product.
Instituting symptomatic and other supportive treatment as necessary. Certain adverse effects of NSAIDs, including nephritis or nephrotic syndrome, thrombocytopenia, hemolytic anemia, and severe cutaneous or other hypersensitivity reactions, may respond to glucocorticoid administration. 96, 97

Monitoring¾The possibility must be considered that gastrointestinal ulceration or hemorrhage, and phenylbutazone-induced blood dyscrasias, may occur several days after ingestion of an overdose. Patients being discharged after initial treatment should be informed of possible presenting symptoms and advised to seek immediate treatment if they occur.
Supportive care¾Monitoring and supporting vital functions. If respiratory support is required following phenylbutazone overdose, respiratory stimulants should not be used. Patients in whom intentional overdose is known or suspected should be referred for psychiatric consultation.

Patient Consultation

As an aid to patient consultation, refer to Advice for the Patient, Anti-inflammatory Drugs, Nonsteroidal (Systemic).
In providing consultation, consider emphasizing the following selected information (>> = major clinical significance):
Before using this medication

>> Conditions affecting use, especially:

Allergies to aspirin or any of the nonsteroidal anti-inflammatory drugs (NSAIDs)
Pregnancy¾Use of an NSAID during second half of pregnancy not recommended because of potential adverse effect on fetal blood flow and possible prolongation of pregnancy, dystocia, and difficult and/or delayed delivery
Breast-feeding¾For indomethacin: Has caused convulsions in a nursing infant
For meclofenamate and piroxicam: These NSAIDs have caused adverse effects in animal studies
For phenylbutazone: May cause blood dyscrasias or other adverse effects in the infant
Use in children¾For indomethacin: Because of toxicity, should be used with caution and only in patients unresponsive to less toxic NSAIDs
For naproxen: Skin rash more common in pediatric patients
For phenylbutazone: Because of toxicity, not recommended in children < 15 years of age
Use in the elderly¾Increased risk of toxicity; initial dosage should be reduced and patients carefully monitored
Other medications, especially¾(For all NSAIDs: Anticoagulants, aspirin, cephalosporins that may induce hypoprothrombinemia, cyclosporine, lithium, methotrexate, plicamycin, probenecid, triamterene, and valproic acid)

(For indomethacin (in addition to those applying to all NSAIDs): Zidovudine)

(For phenylbutazone (in addition to those applying to all NSAIDs): Digitalis, penicillamine, and phenytoin)

(For buffered phenylbutazone (in addition to those applying to all NSAIDs and to phenylbutazone): Ciprofloxacin, enoxacin, itraconazole, ketoconazole, lomefloxacin, norfloxacin, ofloxacin, and oral tetracyclines)

(For tiaprofenic acid (in addition to those applying to all NSAIDs): Phenytoin)

Other medical problems, especially¾For all NSAIDs: Blood dyscrasias, bone marrow depression, cardiac or cardiopulmonary disease or predisposition to, clotting defects, hepatic disease, peptic ulcer or other

inflammatory or ulcerative gastrointestinal tract disease or predisposition to, renal disease or predisposition to, and stomatitis
For indomethacin (in addition to those applying to all NSAIDs): Epilepsy, mental illness, and parkinsonism
For phenylbutazone (in addition to those applying to all NSAIDs): Polymyalgia rheumatica and temporal arteritis
For sulindac (in addition to those applying to all NSAIDs): Renal calculus or history of
For rectal dosage forms (in addition to those applying to oral use of the NSAIDs with rectal dosage forms): Anal or rectal bleeding, hemorrhoids, inflammatory lesions of anus or rectum, and proctitis or recent history of
Proper use of this medication

For all NSAIDs

>> Not taking more medication than prescribed or recommended on OTC package label

>> For use in arthritis¾Compliance with therapy; noticeable improvement in condition usually requires a few days to a week of treatment (but up to 2 weeks, and sometimes even longer, in severe cases) and maximum effectiveness may require several weeks of treatment

>> Proper dosing
Missed dose (scheduled dosing): If dosing schedule is¾Once or twice a day: Taking as soon as possible if remembered within one or two hours after dose should have been taken; skipping dose if not remembered until later
More than twice a day: Taking as soon as possible; not taking if almost time for next dose; not doubling doses
>> Proper storage
For all capsule and tablet dosage forms

Taking with a full glass of water and not lying down for 15 to 30 minutes after taking

For indomethacin, mefenamic acid, phenylbutazone, and piroxicam

>> Taking oral dosage forms with meals or antacids (a magnesium- and aluminum-containing antacid may be preferred) to reduce gastrointestinal irritation

For flurbiprofen extended-release tablets, nabumetone, and naproxen extended-release tablets

Taking with food or antacids (a magnesium- and aluminum-containing antacid may be preferred) to reduce gastrointestinal irritation; taking with food also increases absorption

For immediate-release and extended-release oral dosage forms of NSAIDs not listed above

Taking with food or antacids (a magnesium- and aluminum-containing antacid may be preferred) to reduce gastrointestinal irritation, although when used for acute conditions (e.g., pain, gout, fever, or dysmenorrhea) the first 1 or 2 doses may be taken on an empty stomach to speed the onset of action

For oral suspensions

Not mixing suspension with an antacid or other liquid prior to use

For delayed-release (enteric-coated) or extended-release dosage forms, diflunisal tablets, and all phenylbutazone tablet formulations

Swallowing whole; not breaking, chewing or crushing before swallowing

For all suppository dosage forms

Proper administration technique

For indomethacin suppositories

Retaining in rectum for 1 full hour to ensure maximum absorption

For nonprescription use of ibuprofen or naproxen

>> Reading patient information sheet provided in package

For phenylbutazone

>> Taking for prescribed indications only; not taking to relieve other aches and pains

For mefenamic acid

>> Not taking longer than 7 days at a time unless otherwise directed by physician

Precautions while using this medication

>> Regular visits to physician during prolonged therapy

>> Possibility that use of alcohol may increase the risk of ulceration and, with phenylbutazone, depressant effects

>> Checking with physician if you consume 3 or more alcohol-containing beverages per day; alcohol consumption may increase the risk of NSAID-induced gastrointestinal toxicity

Not taking 2 or more NSAIDs, including ketorolac, concurrently, and not taking acetaminophen or aspirin or other salicylates for more than a few days while receiving NSAID therapy, unless concurrent use is prescribed by, and patient remains under the care of, a physician or dentist

Caution if any surgery is required because of possible enhanced bleeding (although may be less of a problem with diclofenac, diflunisal, meclofenamate, mefenamic acid, and nabumetone)

Caution if confusion, dizziness or lightheadedness, drowsiness, or vision problems occur

>> Possibility of photosensitivity

Possibility of gastrointestinal ulceration and bleeding

>> Notifying physician immediately if influenza-like symptoms (chills, fever, or muscle aches and pains) occur shortly prior to or together with a skin rash; rarely, these symptoms may indicate a serious reaction to the medication

Possibility of anaphylaxis

For buffered phenylbutazone

>> Not taking within:
¾6 hours before or 2 hours after ciprofloxacin or lomefloxacin
¾8 hours before or 2 hours after enoxacin
¾2 hours after itraconazole
¾3 hours before or after ketoconazole
¾2 hours before or after norfloxacin or ofloxacin
¾1 to 3 hours before or after an oral tetracycline

For mefenamic acid

Discontinuing use and checking with physician if severe diarrhea occurs

For nonprescription use of ibuprofen or naproxen

Checking with health care professional if symptoms do not improve or if they worsen, if using for fever and fever lasts more than 3 days or returns, or if painful area is red or swollen

Side/adverse effects

>> Stopping medication and obtaining emergency treatment if symptoms of any of the following occur

For all NSAIDs

Anaphylaxis, angioedema, or bronchospasm

>> Stopping medication and checking with physician immediately if symptoms of the following occur

For all NSAIDs

Spitting up blood, unexplained nosebleeds, chest pain, convulsions, fainting, gastrointestinal ulceration or bleeding, and blood dyscrasias

For mefenamic acid (in addition to those applying to all NSAIDs)

Diarrhea

For phenylbutazone (in addition to those applying to all NSAIDs)

Edema

Signs and symptoms of other potential side effects, especially

For all NSAIDs

Dysarthria, hallucinations, aseptic meningitis, migraine, mood or mental changes, peripheral neuropathy, syncope, or other central nervous system effects; dermatitis (allergic or exfoliative), Stevens-Johnson syndrome, or other dermatologic effects; colitis, dysphagia, esophagitis, gastritis, gastroenteritis, or other digestive system effects; crystalluria, urinary tract irritation or infection, or other genitourinary effects; anemia or hypocoagulation; hepatitis; angiitis, fever, allergic rhinitis, or other hypersensitivity reactions not listed previously; loosening or splitting of fingernails; lymphadenopathy; vision problems, conjunctivitis, or other ocular effects; stomatitis, glossitis, or other oral/perioral effects; hearing problems or tinnitus; pancreatitis; and edema, hyperkalemia, polyuria, renal impairment or failure, or other renal effects

For indomethacin (in addition to those applying to all NSAIDs) Headache (severe), especially in the morning

Possibility that the following may occur many days or weeks after medication is discontinued

For phenylbutazone

Blood dyscrasias

General Dosing Information

The sodium content of diclofenac sodium, meclofenamate sodium, naproxen sodium, naproxen oral suspension, and tolmetin sodium should be considered when selecting a nonsteroidal anti-inflammatory drug (NSAID) for patients who must restrict their sodium intake. Also, the sucrose content of ibuprofen and naproxen suspensions must be considered when selecting an NSAID for patients who must restrict their sucrose intake.

Patients who do not respond to one NSAID may respond to another. In responsive patients, partial symptomatic relief of arthritic symptoms usually occurs within 1 or 2 weeks, although maximum effectiveness may occur only after several weeks of therapy.

A reduction of initial dosage, possibly to as low as one-half the usual adult dose, is recommended for geriatric patients, especially those 70 years of age or older. However, if the reduced dose fails to produce an adequate clinical response and the medication is well tolerated, dosage may be increased as required and tolerated.

A reduction of dosage may also be required to prevent accumulation of NSAIDs and/or their metabolites (some of which may be unstable and may be hydrolyzed to the parent compound when their excretion is delayed) in patients with renal function impairment.

Long-term use of NSAIDs in doses that approach or exceed maximum dosage recommendations should be considered only if the clinical benefit is increased sufficiently to offset the higher risk of gastrointestinal toxicity or other adverse effects. 123

Indomethacin, mefenamic acid, phenylbutazone, and piroxicam should be administered immediately after meals or with food or antacids to reduce gastrointestinal irritation. Flurbiprofen extended-release capsules, nabumetone, or naproxen extended-release tablets should also be taken with food to increase absorption as well as reduce gastrointestinal irritation. The other NSAIDs (except for delayed-release [enteric-coated] and rectal dosage forms) are also preferably taken after meals or with food or antacids to reduce gastrointestinal irritation, especially during chronic use; however, for faster absorption when a rapid initial effect is required (as for analgesic or antipyretic use), the first 1 or 2 doses may be taken 30 minutes before meals or at least 2 hours after meals. If an antacid is taken concurrently, an aluminum- and magnesium-containing formulation may be preferred, since studies have shown that this formulation does not adversely affect absorption of most NSAIDs (See Table 1.

It is recommended that solid oral dosage forms of NSAIDs be taken with a full glass (240 mL) of water and that the patient remain in an upright position for 15 to 30 minutes after administration. These measures may reduce the risk of tablets or capsules becoming lodged in the esophagus, which has been reported to cause prolonged esophageal irritation and difficulty in swallowing in some patients receiving these medications.

In the treatment of primary dysmenorrhea, maximum benefit is achieved by initiating NSAID therapy as rapidly as possible after the onset of menses. 7, 31, 38 Prophylactic therapy (i.e., starting NSAID administration a few days prior to the expected onset of the menstrual period) has not been found to provide additional therapeutic benefit. 7

Concurrent use of an NSAID with an opioid analgesic provides additive analgesia and may permit lower doses of the opioid analgesic to be utilized.

The analgesic activity of non-opioid analgesics is subject to a ceiling effect. Therefore, administration of an NSAID in higher-than-recommended analgesic doses may not provide additional therapeutic benefit in the treatment of pain not associated with inflammation.

In the treatment of arthritis, most of these agents have been shown to provide additional symptomatic relief when administered concurrently with gold compounds or glucocorticoids. NSAIDs may permit reduction of glucocorticoid dosage; however, reductions of glucocorticoid dosage, especially following long-term use, should be gradual to avoid symptoms associated with adrenal insufficiency or other manifestations of too-sudden withdrawal.

DICLOFENAC

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. Immediate-release tablets only indicated for pain and primary dysmenorrhea, and may also be used to relieve acute attacks of gout or calcium pyrophosphate deposition disease (pseudogout) and pain associated with nonrheumatic inflammatory conditions or vascular headaches.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A phenylacetic acid derivative.

Other actions/effects¾ With usual doses, has lesser effect on platelet aggregation than most NSAIDs. Also has uricosuric activity.

Biotransformation¾Almost 50% of a dose eliminated via first-pass metabolism.

Half-life¾Elimination: 1.2-2 hours.

Onset of action¾Pain: Tablets¾30 minutes.

Duration of action¾Pain: Tablets¾Up to 8 hours.

Precautions¾ Pregnancy/reproduction¾Embryotoxicity and other adverse effects, but not teratogenicity, demonstrated in animal studies.

Surgical¾With recommended doses may be less likely than most other NSAIDs to increase perisurgical bleeding.

Drug interactions and/or related problems¾ Also, reported to increase digoxin plasma concentrations.

Also, concurrent use with potassium-sparing diuretics may cause hyperkalemia.

Also, reported to decrease effects of antidiabetic agents or insulin.

Laboratory value alterations¾ With usual doses is less likely than most other NSAIDs to increase bleeding time significantly.

Higher incidence of transaminase values being elevated to > 3 times the upper limit of normal than with other NSAIDs.

Also, may decrease plasma concentration and increase urine concentration of uric acid.

Medical considerations/contraindications¾ Not recommended for patients with blood dyscrasias (or history of) or bone marrow depression.

Caution also required in patients with hepatic porphyria; may precipitate an acute attack.

Caution with diclofenac sodium-containing dosage forms in patients who must restrict their sodium intake.

Patient monitoring¾Routine liver function tests recommended.

Side/adverse effects¾ See Table 3.

Additional Dosing Information

See also General Dosing Information.

Diclofenac therapy should be discontinued if gastrointestinal bleeding or ulceration occurs.

For oral dosage forms only

The delayed-release tablets and the extended-release tablets are to be swallowed whole, not crushed or chewed.

Oral Dosage Forms

DICLOFENAC POTASSIUM TABLETS

Usual adult dose

Analgesic and
Antidysmenorrheal¾Oral, 50 mg three times a day as needed. If necessary, 100 mg may be administered for the first dose only. 158, 215

Rheumatoid arthritis¾Oral, 150 to 200 mg per day in three or four divided doses, initially. 158 After a satisfactory response has been obtained, dosage should be reduced to the minimum dose that provides continuing control of symptoms, 23, 119, 158, 217 usually 75 to 100 mg a day in three divided doses. 23, 217

Osteoarthritis¾ Oral, 100 to 150 mg per day in two or three divided doses, initially. 119, 158, 217 After a satisfactory response has been obtained, dosage should be reduced to the minimum dose that provides continuing control of symptoms. 23, 119, 158, 217

Ankylosing spondylitis *¾ Oral, 100 to 125 mg a day in four or five divided doses, initially. After a satisfactory response has been obtained, dosage should be reduced to the minimum dose that provides continuing control of symptoms. 119, 158

Usual adult prescribing limits

Analgesic and
Antidysmenorrheal¾Up to 200 mg on the first day, then 150 mg per day thereafter. 158, 218

Rheumatoid arthritis¾ 225 mg per day. 158

Osteoarthritis¾ 150 mg per day; 218 higher doses have not been studied. 158

Usual pediatric dose

Safety and efficacy have not been established. 158

Strength(s) usually available

U.S.¾25 mg (Rx)[Cataflam 158 (calcium phosphate) (colloidal silicon dioxide) (iron oxides) (magnesium stearate) (microcrystalline cellulose) (polyethylene glycol) (povidone) (sodium starch glycolate) (starch) (sucrose) (talc) (titanium dioxide)]

50 mg (Rx)[Cataflam 158 (calcium phosphate) (colloidal silicon dioxide) (iron oxides) (magnesium stearate) (microcrystalline cellulose) (polyethylene glycol) (povidone) (sodium starch glycolate) (starch) (sucrose) (talc) (titanium dioxide)]

Canada¾50 mg[Voltaren Rapide 218 (carnauba wax) (cellulose) (colloidal silicon dioxide) (corn starch) (ferric oxide) (magnesium stearate) (polyethylene glycol) (povidone) (sodium carboxymethyl starch) (sucrose) (talc) (titanium dioxide) (tribasic calcium phosphate) (white ink)]

Packaging and storage:

Store below 30 °C (86 °F), in a tight container, unless otherwise directed by manufacturer. Protect from moisture.

Auxiliary labeling:

- Take with food.
- Take with a full glass of water.
- Avoid alcoholic beverages.

DICLOFENAC SODIUM DELAYED-RELEASE TABLETS

Usual adult dose

Analgesic
and Antidysmenorrheal¾The delayed-release formulation is not recommended. See Diclofenac Potassium Tablets , which should be used for these indications.
Antirheumatic (nonsteroidal anti-inflammatory) ¾See Diclofenac Potassium Tablets .

Usual pediatric dose

Safety and efficacy have not been established. 158

Strength(s) usually available

U.S.¾25 mg (Rx)[Voltaren 158 (hydroxypropyl methylcellulose) (iron oxide) (lactose) (magnesium stearate) (methacrylic acid copolymer) (microcrystalline cellulose) (polyethylene glycol) (povidone) (propylene glycol) (sodium hydroxide) (sodium starch glycolate) (talc) (titanium dioxide) (D&C Yellow #10 Aluminum Lake)]

50 mg (Rx)[Voltaren 158 (hydroxypropyl methylcellulose) (iron oxide) (lactose) (magnesium stearate) (methacrylic acid copolymer) (microcrystalline cellulose) (polyethylene glycol) (povidone) (propylene glycol) (sodium hydroxide) (sodium starch glycolate) (talc) (titanium dioxide) (FD&C Blue #1 Aluminum Lake)]

75 mg (Rx)[Voltaren (hydroxypropyl methylcellulose) (iron oxide) (lactose) (magnesium stearate) (methacrylic acid copolymer) (microcrystalline cellulose) (polyethylene glycol) (povidone) (propylene glycol) (sodium hydroxide) (sodium starch glycolate) (talc) (titanium dioxide)]

Canada¾25 mg (Rx)[Apo-Diclo 146 (sodium <1 mmol [1.81 mg])] [Novo-Difenac 191] [Nu-Diclo 199 (sodium <1 mmol)] [Voltaren 217 (lactose) (sodium < 1 mmol [2.03 mg])]

50 mg (Rx)[Apo-Diclo 146 (sodium <1 mmol [3.62 mg])] [Novo-Difenac 191] [Nu-Diclo 199 (sodium <1 mmol)] [Voltaren 217 (lactose) (sodium < 1 mmol [4.06 mg])]

Packaging and storage:

Store below 30 °C (86 °F), in a tight container, unless otherwise specified by manufacturer. Protect from moisture.

Auxiliary labeling:

· Swallow tablets whole.
· Take with a full glass of water.
· Avoid alcoholic beverages.

DICLOFENAC SODIUM EXTENDED-RELEASE TABLETS

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 75 or 100 mg once a day, in the morning or evening, or 75 mg two times a day, in the morning and evening. 217

Note: The extended-release dosage form is not intended as initial therapy; the daily maintenance dose should be determined using an immediate- or delayed-release formulation. 217 The extended-release dosage form may then be used, if desired, provided that the required dose can be achieved with the available strengths.

Usual pediatric dose

Safety and efficacy have not been established.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾75 mg (Rx)[Voltaren SR 217 (sodium < 1 mmol [6.1 mg])]

100 mg (Rx)[Novo-Difenac SR 191] [Voltaren SR 217 (sodium < 1 mmol [8.13 mg])]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Swallow tablets whole.
· Take with a full glass of water.
· Avoid alcoholic beverages.

Rectal Dosage Forms

DICLOFENAC SODIUM SUPPOSITORIES

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Rectal, 50 or 100 mg, as a substitute for the last oral dose of the day. 23, 217

Usual adult prescribing limits

Total daily dosage (oral and rectal) should not exceed 150 mg. 23, 217

Usual pediatric dose

Safety and efficacy have not been established.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾50 mg (Rx)[Voltaren 217 (sodium < 1 mmol [4.06 mg])]

100 mg (Rx)[Voltaren 217 (sodium < 1 mmol [8.13 mg])]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Auxiliary labeling:

· Avoid alcoholic beverages.
· For rectal use.

* Not included in Canadian product labeling.

DIFLUNISAL

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and psoriatic arthritis, and pain. May also be used to relieve acute attacks of gout or calcium pyrophosphate deposition disease (pseudogout), dysmenorrhea, and pain associated with nonrheumatic inflammatory conditions or vascular headaches.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A salicylate derivative, although not metabolized to salicylate in vivo .
Other actions/effects¾ Platelet aggregation inhibition significant only with greater-than-recommended doses.
Also has uricosuric activity.
Half-life¾Elimination: 8-12 hours; greatly prolonged by renal function impairment.
Onset of action¾Pain: 1 hour.
Duration of action¾Pain: 8-12 hours.

Precautions¾ Pregnancy/reproduction¾Embryotoxic and teratogenic effects demonstrated in rabbits, but not found to be teratogenic in mice.
Surgical¾With recommended doses may be less likely than most other NSAIDs to increase perisurgical bleeding.
Drug interactions and/or related problems¾ Also, may increase risk of acetaminophen-induced hepatotoxicity.
Also, chronic concurrent use of antacids significantly decreases diflunisal plasma concentration.
Diflunisal also increases plasma concentration of hydrochlorothiazide and decreases hyperuricemic effect of hydrochlorothiazide or furosemide, but has not been shown to decrease furosemide-induced diuresis.

Laboratory value alterations¾ Interference with salicylate determinations; may cause falsely elevated salicylate values.

With usual doses is less likely than most other NSAIDs to increase bleeding time significantly.

May decrease plasma concentrations and increase urine concentrations of uric acid.

Medical considerations/contraindications¾Higher risk than with most other NSAIDs in patients with renal function impairment.

Side/adverse effects¾ Reported to cause a characteristic hypersensitivity syndrome.

Possibility of Reye's syndrome in children and adolescents with acute febrile illness should be considered (as with other salicylates).

See also Table 3.

Additional Dosing Information

See also General Dosing Information.

Administration of a 1-gram initial loading dose is recommended to provide faster onset of analgesic action, shorter time to peak analgesic effect, and greater peak analgesic action. For long-term use, the initial loading dose decreases the time needed to reach steady-state plasma concentrations; if a loading dose is not administered, 2 to 3 days may be required to evaluate changes in treatment regimens.

In patients with impaired renal function, especially if renal function is decreased to 1/2 the normal value or below, a reduction in dosage and/or an increase in the dosing interval may be necessary to prevent diflunisal accumulation.

Tablets are to be swallowed whole, not crushed or chewed.

Because diflunisal is not hydrolyzed to salicylic acid in vivo , serum salicylate concentration cannot be used as a guide to dosage or potential toxicity during therapy.

Oral Dosage Forms

DIFLUNISAL TABLETS USP

Usual adult dose 24, 164, 165, 219, 267

Rheumatoid arthritis or
Osteoarthritis¾Oral, 250 to 500 mg two times a day; dosage may be increased or decreased according to patient response.

Analgesic¾Oral, 1 gram initially, followed by 500 mg every eight to twelve hours as needed.

Note: For some patients, 500 mg initially followed by 250 mg every eight to twelve hours may be appropriate, depending on the severity of pain or the age, weight, or response of the patient.

Usual adult prescribing limits

Up to 1.5 grams daily. 24, 164, 219

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾250 mg (Rx)[Dolobid 164] [Generic] 219

500 mg (Rx)[Dolobid 164] [Generic] (talc) (titanium dioxide) 219

Canada¾250 mg (Rx)[Apo-Diflunisal 267] [Dolobid 165] [Novo-Diflunisal 268]

500 mg (Rx)[Apo-Diflunisal 267] [Dolobid 165] [Novo-Diflunisal 268]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F). Store in a well-closed container.

Auxiliary labeling:

· Take with food.
· Swallow tablets whole.
· Take with a full glass of water.
· Avoid alcoholic beverages.

ETODOLAC

Summary of Differences

Indications¾ Indicated for treatment of osteoarthritis and for pain. May also be used to relieve acute attacks of gout or calcium pyrophosphate deposition disease (pseudogout), dysmenorrhea, and pain associated with nonrheumatic inflammatory conditions or vascular headaches.

Pharmacology¾ Physicochemical characteristics¾Chemical group: A pyranoindoleacetic acid derivative.
Other actions/effects¾Also has uricosuric activity.
Decreases renal function, but with administration of up to 500 mg every 12 hours recovery occurs prior to administration of next dose.
Half-life¾Elimination:
Single dose¾6-7 hours.
At steady-state¾7.3±4 hours.
Onset of action¾Pain: 30 minutes.
Time to peak effect¾Pain: 1-2 hours.
Duration of action¾Pain:
200-mg single dose¾4-5 hours.
400-mg single dose¾Generally 5-6 hours; up to 8-12 hours in some patients.

Precautions¾ Pregnancy/reproduction¾Alterations of limb development demonstrated in animal studies, but drug- or dose-response relationship not established.
Geriatrics¾No differences relative to younger adults in pharmacokinetic profile with 200 mg twice a day or in side effects profile with 600 mg per day.

Laboratory value alterations¾May cause false-positive test results in urinary bilirubin and urinary ketone determinations.

Decrease in serum uric acid concentration may be expected.

Medical considerations/contraindications: Significant problems have not been demonstrated in patients with mild to moderate renal function impairment receiving up to 500 mg every 12 hours.

Side/adverse effects¾ See Table 3.

Oral Dosage Forms

ETODOLAC CAPSULES

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 400 mg two or three times a day or 300 mg three or four times a day, initially. After a satisfactory response has been obtained, dosage should be individualized according to patient tolerance and response. Most patients are maintained on 600 to 1200 mg per day. However, as little as 200 mg two times a day has been effective in some patients. 177

Note: Although doses of up to 1 gram per day have been effective when administered in two divided doses (500 mg every twelve hours), administration on a three-dose-a-day schedule may provide greater benefit. 177

Analgesic¾Oral, 400 mg initially, then 200 to 400 mg every six to eight hours as needed. If a 400-mg dose fails to provide eight hours of analgesia, a regimen of 300 mg every six hours may be effective. 177

Usual adult prescribing limits

Patients weighing less than 60 kg¾20 mg per kg of body weight per day. 177

Patients weighing 60 kg or more¾1.2 grams per day. 177

Usual pediatric dose

Safety and efficacy have not been established. 177

Usual geriatric dose

See Usual adult dose .

Strength(s) usually available

U.S.¾200 mg (Rx)[Lodine 177 (cellulose) (gelatin) (iron oxides) (lactose) (magnesium stearate) (povidone) (sodium lauryl sulfate) (sodium starch glycolate) (titanium dioxide)]

300 mg (Rx)[Lodine 177 (cellulose) (gelatin) (iron oxides) (lactose) (magnesium stearate) (povidone) (sodium lauryl sulfate) (sodium starch glycolate) (titanium dioxide)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

ETODOLAC TABLETS

Usual adult dose

See Etodolac Capsules .

Usual adult prescribing limits

See Etodolac Capsules .

Usual pediatric dose

Safety and efficacy have not been established. 177

Usual geriatric dose

See Etodolac Capsules .

Strength(s) usually available

U.S.¾400 mg (Rx)[Lodine 177 (cellulose) (FD&C Yellow #10) (FD&C Blue #2) (FD&C Yellow #6) (hydroxypropyl methylcellulose) (lactose) (magnesium stearate) (polyethylene glycol) (polysorbate 80) (povidone) (sodium starch glycolate) (titanium dioxide)]

500 mg 317 (Rx)[Lodine 318 (cellulose) (FD&C Yellow #10) (FD&C Blue #2) (FD&C Yellow #6) (hydroxypropyl methylcellulose) (lactose) (magnesium stearate) (polyethylene glycol) (polysorbate 80) (povidone) (sodium starch glycolate) (titanium dioxide)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

ETODOLAC EXTENDED-RELEASE TABLETS

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 400 to 1000 mg once a day 316.

Usual adult prescribing limits

1000 mg a day 316.

Usual pediatric dose

Safety and efficacy have not been established 316.

Usual geriatric dose

See Usual adult dose 316.

Strength(s) usually available

U.S.¾400 mg (Rx)[Lodine XL 316 (dibasic sodium phosphate) (ethylcellulose) (FD&C Red #40) (FD&C Yellow #6) (hydroxypropyl methylcellulose) (lactose) (magnesium stearate) (polyethylene glycol) (polysorbate 80) (titanium dioxide)]

600 mg (Rx)[Lodine XL 316 (dibasic sodium phosphate) (ethylcellulose) (FD&C Red #40) (FD&C Yellow #6) (hydroxypropyl cellulose) (hydroxypropyl methylcellulose) (iron oxide) (lactose) (magnesium stearate) (polyethylene glycol) (polysorbate 80) (titanium dioxide)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer 316.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

FENOPROFEN

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and psoriatic arthritis; pain; and acute attacks of gout or calcium pyrophosphate deposition disease (pseudogout). May also be used to relieve dysmenorrhea and pain associated with nonrheumatic inflammatory conditions or vascular headaches. Also used for vascular headache prophylaxis.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A propionic acid derivative.

Half-life¾Elimination: 3 hours.

Precautions¾ Pregnancy/reproduction¾No teratogenic or other adverse effects demonstrated in animal studies.

Drug interactions and/or related problems¾Concurrent chronic use with antacids significantly decreases fenoprofen plasma concentration.

Also, phenobarbital may increase metabolism and decrease half-life of fenoprofen.

Laboratory value alterations¾Interference with triiodothyronine (T 3) determinations using the Amerlex-M kit assay.

Medical considerations/contraindications¾Higher risk than with most other NSAIDs in patients with renal function impairment.

Side/adverse effects¾ See Table 3.

Additional Dosing Information

See also General Dosing Information.

In the treatment of arthritis, improvement in condition may occur within a few days, but 2 to 3 weeks of continuous use on a regular basis may be required for maximum effectiveness.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling. The dosing and strengths of the available dosage forms are expressed in terms of the free acid (not the calcium salt).

FENOPROFEN CALCIUM CAPSULES USP

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 300 to 600 mg (free acid), depending on the severity of the symptoms, three or four times a day, then adjusted as needed. 186

Note: Higher doses generally are required in rheumatoid arthritis than in osteoarthritis.
Analgesic * or
[Antidysmenorrheal] *¾Oral, 200 mg (free acid) every four to six hours as needed. 186

Usual adult prescribing limits

Antirheumatic (nonsteroidal anti-inflammatory) ¾Up to 3.2 grams (free acid) daily. 26, 186

Usual pediatric dose

Safety and dosage have not been established. 186

Strength(s) usually available

U.S.¾200 mg (free acid) (Rx)[Nalfon 200 186] [Generic]

300 mg (free acid) (Rx)[Nalfon 186] [Generic]

Canada¾300 mg (free acid) (Rx)[Nalfon 187]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F). Store in a well-closed container.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· May cause drowsiness.
· Avoid alcoholic beverages.

FENOPROFEN CALCIUM TABLETS USP

Usual adult dose

See Fenoprofen Calcium Capsules USP .

Usual adult prescribing limits

See Fenoprofen Calcium Capsules USP .

Usual pediatric dose

Safety and dosage have not been established. 186

Strength(s) usually available

U.S.¾600 mg (free acid) (Rx)[Nalfon 186 (scored)] [Generic] 161

Canada¾600 mg (free acid) (Rx)[Nalfon 187]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F). Store in a well-closed container.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· May cause drowsiness.
· Avoid alcoholic beverages.

* Not included in Canadian product labeling.

FLOCTAFENINE

Summary of Differences

Indications¾ Indicated for relief of pain. May also be used to relieve acute attacks of gout or calcium pyrophosphate deposition disease (pseudogout), dysmenorrhea, and pain associated with nonrheumatic inflammatory conditions or vascular headaches.

Precautions¾ Pregnancy/reproduction¾Embryotoxicity but not teratogenicity demonstrated in animal studies.
Drug interactions and/or related problems¾Floctafenine-induced increase in effect of coumarin- or indanedione-derivative anticoagulants may not become apparent until after 2 weeks of concurrent use.

Side/adverse effects¾ See Table 3.

Additional Dosing Information

See also General Dosing Information.

Because the safety and efficacy of floctafenine for long-term administration has not been established, this medication is recommended for short-term use only.

Oral Dosage Forms

FLOCTAFENINE TABLETS

Usual adult dose

Analgesic¾Oral, 200 to 400 mg every six to eight hours, as needed. 28, 174

Usual adult prescribing limits

Dosage should not exceed 1.2 grams per day. 28, 174

Usual pediatric dose

Use is not recommended. 174

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾200 mg (Rx)[Idarac 174 (corn starch)]

400 mg (Rx)[Idarac 174 (corn starch)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from light.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· May cause drowsiness.
· Avoid alcoholic beverages.

FLURBIPROFEN

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, bursitis, tendinitis, soft tissue injuries, and dysmenorrhea.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A propionic acid derivative.
Half-life¾Elimination: 5.7 hours.
Peak plasma concentration¾Extended-release capsules: Increased by food.

Precautions¾ Pregnancy/reproduction¾Embryocidal and fetotoxic, but not teratogenic, effects demonstrated in animal studies.
Geriatrics¾Peak plasma concentrations increased in elderly females.
Drug interactions and/or related problems¾Studies failed to show that flurbiprofen increases digoxin plasma concentrations.

Side/adverse effects¾ See Table 3.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

FLURBIPROFEN EXTENDED-RELEASE CAPSULES

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 200 mg once a day in the evening. 169

Note: The extended-release dosage form is not intended as initial therapy; the daily maintenance dose should be determined using the immediate-release formulation. 169 The extended-release dosage form may then be used, if desired, provided that the required dose can be achieved with the available strength.

Usual pediatric dose

Safety and efficacy have not been established.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾200 mg (Rx)[Froben SR 169]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Auxiliary labeling:

- Take with food.
- Swallow capsules whole.
- Take with a full glass of water.
- Avoid alcoholic beverages.

FLURBIPROFEN TABLETS USP

Usual adult dose

Rheumatoid arthritis or
Osteoarthritis¾ Oral, 200 to 300 mg a day in two to four divided doses, initially. Dosage may then be individualized according to the severity of the disease and patient response. 126, 144

[Ankylosing spondylitis] ¾Oral, 200 mg a day in four divided doses, initially, although some patients may require 250 to 300 mg a day. 169

Note: After a satisfactory response has been obtained, dosage should be decreased to the lowest dose that provides continuing control of symptoms. 169

[Antidysmenorrheal]¾Oral, 50 mg four times a day. 30, 145, 169

[Anti-inflammatory (nonsteroidal)]¾Oral, 50 mg every four to six hours as needed. 145, 220

Usual adult prescribing limits

The maximum recommended single dose is 100 mg. 126, 144 Total daily dosage should not exceed 300 mg. 144, 169 This maximum dose is recommended for short-term use only, i.e., for initiation of therapy or for treating acute exacerbations of symptoms; it should not be used as a maintenance dose. 29, 145, 169

Usual pediatric dose

Safety and efficacy have not been established.

Strength(s) usually available

U.S.¾50 mg (Rx)[Ansaid 144 (lactose)] [Generic]

100 mg (Rx)[Ansaid 144 (lactose)] [Generic]

Canada¾50 mg (Rx)[Ansaid 144] [Apo-Flurbiprofen 147] [Froben 169] [Novo-Flurprofen 292] [Nu-Flurbiprofen 220] [Generic]

100 mg (Rx)[Ansaid 144] [Apo-Flurbiprofen 147] [Froben 169] [Novo-Flurprofen 292] [Nu-Flurbiprofen 220] [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

IBUPROFEN

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, juvenile arthritis, and psoriatic arthritis; pain; gouty arthritis or calcium pyrophosphate deposition disease (pseudogout); fever; and dysmenorrhea. May also be used for prophylaxis and treatment of vascular headaches.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A propionic acid derivative.
Half-life¾Elimination: 1.8-2 hours
Onset of action¾Pain: 0.5 hour.

Time to peak effect¾Fever: 2-4 hours.
Duration of action¾ Fever:
5-mg/kg dose¾6 hours.
10-mg/kg dose¾8 hours or more.
Pain: 4-6 hours.

Precautions¾ Pregnancy/reproduction¾Teratogenic effects in animals have not been shown.
Breast-feeding¾Methodology capable of detecting 1 mcg/mL failed to show that ibuprofen is distributed into breast milk.
Pediatrics¾Studied in children 6 months of age and older; pediatrics-specific problems have not been demonstrated.
Drug interactions and/or related problems¾Also, reported to increase digoxin plasma concentrations.
Laboratory value alterations¾Also, may decrease blood glucose concentrations.

Side/adverse effects¾ Reported to cause a characteristic hypersensitivity syndrome.
Reported to cause a serum sickness- or influenza-like syndrome.
See also Table 3.

Additional Dosing Information

See also General Dosing Information.

In the treatment of arthritis, improvement in condition may occur within 7 days, but 1 to 2 weeks of continuous use on a regular basis may be required for maximum effectiveness.

Oral Dosage Forms

IBUPROFEN ORAL SUSPENSION

Usual adult and adolescent dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 1200 to 3200 mg a day in three or four divided doses. After a satisfactory response has been obtained, dosage should be reduced to the lowest maintenance dose that provides continuing control of symptoms. 129, 130, 183, 222

Note: Higher doses generally are required in rheumatoid arthritis than in osteoarthritis.
Analgesic (mild to moderate pain)
Antipyretic or
Antidysmenorrheal¾Oral, 200 to 400 mg every four to six hours as needed. 31, 128, 129, 137, 138

Usual adult prescribing limits

Antirheumatic (nonsteroidal anti-inflammatory) ¾Up to 3600 mg per day. The maximum dosage should be used only if the clinical benefit is increased sufficiently to offset the higher risk of adverse effects. 31, 183, 222

Analgesic
Antipyretic; or

Antidysmenorrheal¾For patient self-medication (over-the-counter use): Not to exceed 1200 mg per day. 137

Usual pediatric dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Infants up to 6 months of age: Safety and efficacy have not been established. 128, 139

Children 6 months to 12 years of age: Oral, initially 30 to 40 mg per kg of body weight a day in three or four divided doses, although 20 mg per kg of body weight per day may be sufficient for patients with mild disease. After a satisfactory response has been achieved, dosage should be reduced to the lowest dose needed to control disease activity. 128, 139

Antipyretic¾Infants up to 6 months of age: Safety and efficacy have not been established. 129

Children 6 months to 12 years of age: Oral, 5 mg per kg of body weight for fevers less than 39.17 °C (102.5 °F) and 10 mg per kg of body weight for higher fevers. Dosage may be repeated, if necessary, at intervals of 4 to 6 hours or more. 128, 129, 139, 183

Usual pediatric prescribing limits

Antirheumatic¾Oral, 50 mg per kg of body weight per day. 128, 139

Antipyretic¾Oral, 40 mg per kg of body weight per day. 128, 129, 139, 183

Strength(s) usually available

U.S.¾40 mg per mL (OTC)[Motrin, Children's Oral Drops 314]

40 mg per mL (Rx)[Motrin, Children's Oral Drops 314]

100 mg per 5 mL (OTC)[Advil, Children's 139 (sucrose) (cellulose gum) (citric acid) (disodium EDTA) (FD&C Red #40) (glycerin) (microcrystalline cellulose) (polysorbate 80) (sodium benzoate) (sorbitol) (xanthan gum)]

100 mg per 5 mL (Rx)[Advil, Children's 139 (sucrose) (cellulose gum) (citric acid) (disodium EDTA) (FD&C Red #40) (glycerin) (microcrystalline cellulose) (polysorbate 80) (sodium benzoate) (sorbitol) (xanthan gum)]

100 mg per 5 mL (OTC)[Motrin, Children's (sucrose) (citric acid) (glycerin) (polysorbate 80) (sodium benzoate) (starch) (xanthan gum) (yellow #10) (red #40)]

100 mg per 5 mL (Rx)[Motrin, Children's (sucrose) (citric acid) (glycerin) (polysorbate 80) (sodium benzoate) (starch) (xanthan gum) (yellow #10) (red #40)]

Canada¾Not commercially available.

Packaging and storage:

Store between 15 and 30 °C (59 to 86 °F). Protect from freezing.

Auxiliary labeling:

· Take with food or antacids.
· Shake well.
· Avoid alcoholic beverages.

IBUPROFEN TABLETS USP

Usual adult and adolescent dose

See Ibuprofen Oral Suspension .

Usual adult prescribing limits

See Ibuprofen Oral Suspension .

Usual pediatric dose

See Ibuprofen Oral Suspension .

Usual pediatric prescribing limits

See Ibuprofen Oral Suspension .

Strength(s) usually available

U.S.¾100 mg (Rx)[Motrin, Junior Strength Caplets 314]

100 mg (OTC)[Motrin, Junior Strength Caplets 315]

200 mg (OTC)[Advil 137] [Advil Caplets 137] [Bayer Select Ibuprofen Pain Relief Formula Caplets 157] [Cramp End 162] [Excedrin IB 166] [Excedrin IB Caplets 166] [Genpril 161] [Genpril Caplets 161] [Haltran 170] [Ibu-200 161] [Ibuprin 161] [Ibuprohm 172] [Ibuprohm Caplets 172] [Ibu-Tab 173] [Medipren] [Medipren Caplets] [Midol IB 179] [Motrin-IB 184] [Motrin-IB Caplets 184] [Nuprin 204] [Nuprin Caplets 204] [Pamprin-IB] [Q-Profen 161] [Trendar 161] [Generic] 161

300 mg (Rx)[Motrin 181] [Generic] 161

400 mg (Rx)[Dolgesic 161] [Ibu 171] [Ibu-4 161] [Ibuprohm 172] [Ibu-Tab 173] [Motrin 181] [Rufen 161] [Generic] 161

600 mg (Rx)[Ibifon 600 Caplets 161] [Ibren 161] [Ibu 171] [Ibu-6 161] [Ibu-Tab 173] [Motrin 181] [Rufen 161] [Generic] 161

800 mg (Rx)[Ibu 171] [Ibu-8 161] [Ibu-Tab 173] [Motrin 181] [Rufen 161] [Generic] 161

Canada¾200 mg (OTC)[Actiprofen Caplets 136] [Advil 138] [Advil Caplets 138] [Apo-Ibuprofen 148] [Medipren Caplets 273] [Motrin-IB 185] [Motrin-IB Caplets 185] [Novo-Profen 197] [Generic]

300 mg (Rx)[Apo-Ibuprofen 148] [Motrin 182] [Novo-Profen 197] [Nu-Ibuprofen 271] [Generic]

400 mg (Rx)[Apo-Ibuprofen 148] [Motrin 182] [Novo-Profen 197] [Nu-Ibuprofen 271] [Generic]

600 mg (Rx)[Apo-Ibuprofen 148] [Motrin 182] [Novo-Profen 177] [Nu-Ibuprofen 271] [Generic]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), in a light-resistant container, unless otherwise specified by manufacturer. Store in a well-closed container.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· May cause drowsiness.
· Avoid alcoholic beverages.

IBUPROFEN TABLETS (CHEWABLE)

Usual adult and adolescent dose

See Ibuprofen Oral Suspension .

Usual adult prescribing limits

See Ibuprofen Oral Suspension .

Usual pediatric dose

See Ibuprofen Oral Suspension .

Usual pediatric prescribing limits

See Ibuprofen Oral Suspension .

Strength(s) usually available

U.S.¾50 mg (Rx)[Motrin Chewables 314]

100 mg (Rx)[Motrin Chewables 314]

Canada¾Not commercially available.

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), in a well-closed, light-resistant container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· May cause drowsiness.
· Avoid alcoholic beverages.

INDOMETHACIN

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis, psoriatic arthritis, Reiter's disease, and rheumatic complications associated with Paget's disease of bone; acute gouty arthritis and calcium pyrophosphate deposition disease (pseudogout); bursitis and tendinitis; fever associated with malignancy; dysmenorrhea; prevention and treatment of vascular headaches; Bartter's disease; and pericarditis.

Drug of first choice in ankylosing spondylitis; for other indications (except Bartter's syndrome), recommended only for patients unresponsive to less toxic NSAIDs or, in the case of fever, to other antipyretic agents.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: An indoleacetic acid derivative.

Absorption¾Oral: Capsules and oral suspension¾90% of a dose absorbed within 4 hours.

Extended-release capsules¾90% of a dose absorbed within 12 hours.

Rectal: 80 to 90% of a dose absorbed; incomplete absorption may result from failure to retain suppository in rectum for a full hour.

Half-life¾Elimination: Average, about 4.5 hours; subject to substantial intersubject variability, possibly because of differences in enterohepatic circulation and subsequent reabsorption.

Onset of action¾Gout: 2-4 hours.

Time to peak effect¾Gout (capsules or oral suspension): 2-3 days for relief of heat and tenderness; 3-5 days for relief of swelling.

Precautions¾ Pregnancy/reproduction¾ First trimester: Crosses the placenta; fetotoxic, teratogenic, and other adverse effects demonstrated in animal studies.

Third trimester: Has caused closure of the ductus arteriosus, inhibition of platelet function resulting in bleeding, renal function impairment or failure with oligohydramnios, gastrointestinal bleeding or perforation, and myocardial degenerative changes in fetuses when given to pregnant women during the third trimester.

Breast-feeding¾Distributed into breast milk; one report of convulsions in a breast-fed infant exposed to the medication.

Pediatrics¾Recommended only for pediatric patients who are unresponsive to or intolerant of less toxic agents. Only immediate-release oral dosage forms should be used. Also, recommended doses should not be exceeded and the patient carefully monitored.

Geriatrics¾Also, increased risk of adverse CNS effects, especially confusion.

Drug interactions and/or related problems¾ Also, concurrent use with potassium-sparing diuretics may cause hyperkalemia.

Also, may block the increase in plasma renin activity induced by bumetanide, furosemide, or indapamide.

Also, concurrent use with zidovudine not recommended; toxicity of either or both of the medications may be increased.

Caution also recommended with aminoglycosides and digitalis glycosides; indomethacin has caused increased plasma concentrations of these medications in infants.

Laboratory value alterations¾Also, may cause false-negative test results with dexamethasone suppression test for endogenous depression and one test for urinary 5-hydroxyindoleacetic acid (5-HIAA).

Also, may increase or decrease blood glucose concentrations.

Medical considerations/contraindications¾ Higher risk than with most other NSAIDs in patients with renal function impairment.

Also, may aggravate epilepsy, mental depression or other mental disturbances, or parkinsonism.

Patient monitoring¾Routine monitoring of liver function recommended.

Side/adverse effects¾ See Table 3.

Additional Dosing Information

See also General Dosing Information.

Indomethacin should be administered in the lowest dose that provides symptomatic relief. Doses greater than 150 to 200 mg per day may increase the risk of adverse effects without providing additional clinical benefit. If therapy is to be continued after the acute phase of the disease has been controlled, periodic attempts should be made to reduce the dose to the lowest dose providing continuing control of symptoms.

If minor adverse effects occur, dosage should be reduced and the patient carefully monitored. If severe side effects occur, therapy should be discontinued.

For oral dosage forms only

Oral dosage forms of indomethacin should always be administered after meals or with food or an antacid to reduce gastrointestinal irritation. However, the oral suspension should not be mixed with an antacid or other liquid prior to use.

To facilitate dosage adjustment and assessment of patient tolerance of the medication, it is recommended that an immediate-release, rather than the extended-release, dosage form be used for initiation of therapy or to increase the daily dose. If the extended-release dosage form is used for initial therapy, or to increase the daily dose, careful observation of the patient is recommended.

For rectal dosage form only

To ensure maximum absorption, the suppository should be retained for at least one full hour after insertion.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

INDOMETHACIN CAPSULES USP

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, initially 25 or 50 mg two to four times a day; if well tolerated, the dosage per day may be increased by 25 or 50 mg at weekly intervals until a satisfactory response is obtained or up to a maximum dose of 200 mg per day. After a satisfactory response has been achieved, dosage should be reduced to the lowest dose that provides continuing control of symptoms. 175, 176

Note: In acute flare-ups of rheumatoid arthritis, dosage may be increased by 25 or 50 mg daily, as needed and tolerated. 176

For those arthritic patients who have persistent night pain and/or morning stiffness, up to 100 mg of the total daily dose may be given at bedtime. Lower bedtime doses may not provide adequate symptomatic relief. 176

A daily dose of less than 75 mg may not be effective in active inflammatory disease.
A daily dose of more than 150 to 200 mg may increase the risk of adverse effects without providing additional clinical benefit. 175, 176

Antigout agent¾Oral, 100 mg initially, then 50 mg three times a day until pain is relieved, with the dosage then being reduced until medication is discontinued.
Anti-inflammatory (nonsteroidal) *¾75 to 150 mg per day in three or four divided doses. 176

Note: When used to treat conditions not requiring chronic therapy, such as acute bursitis or tendinitis of the shoulder, indomethacin should be discontinued when symptoms of inflammation have been controlled for several days. The usual length of treatment is 7 to 14 days. 176

[Antipyretic] *¾Oral, 25 or 50 mg three or four times a day.

Usual adult prescribing limits

Oral, 200 mg a day. 175, 176

Usual pediatric dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 1.5 to 2.5 mg per kg of body weight per day, administered in three or four divided doses, up to a maximum of 4 mg per kg of body weight per day or 150 to 200 mg per day, whichever is less. After a satisfactory response has been obtained, dosage should be reduced to the lowest dose that provides continuing control of symptoms. 176

Strength(s) usually available

U.S.¾25 mg (Rx)[Indocin 176 (lactose)] [Generic] 161

50 mg (Rx)[Indocin 176 (lactose)] [Generic] 161

Canada¾25 mg (Rx)[Apo-Indomethacin 149] [Indocid 175 (lactose)] [Novo-Methacin 193] [Nu-Indo 200]

50 mg (Rx)[Apo-Indomethacin 149] [Indocid 175 (lactose)] [Novo-Methacin 193] [Nu-Indo 200]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F). Store in a well-closed container.

Auxiliary labeling:

· Take with food or antacids.
· Take with a full glass of water.
· Avoid alcoholic beverages.

INDOMETHACIN EXTENDED-RELEASE CAPSULES USP

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 75 mg once a day, in the morning or at bedtime; may be increased to 75 mg two times a day if necessary. 175, 176

Note: It is generally recommended that the daily maintenance dose be determined using the immediate-release formulation. The extended-release dosage form may then be used, if desired, provided that the required dose can be achieved with the available strength.
Careful observation of the patient for signs of intolerance is recommended if the extended-release capsule is used for initiating indomethacin therapy or for increasing the daily dose. Initiation of therapy with one extended-release capsule daily provides the maximum initial dose recommended by the manufacturer. Use of the extended-release capsule to increase the dose provides a greater-than-recommended increase in daily dosage. 32, 176

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾75 mg (Rx)[Indocin SR 176 (sugar)] [Generic] 161

Canada¾75 mg (Rx)[Indocid SR 175 (sucrose)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container.

Auxiliary labeling:

- Take with food or antacids.
- Take with a full glass of water.
- Avoid alcoholic beverages.

Additional information:

The extended-release capsules are designed to release 25 mg of indomethacin immediately and the remaining 50 mg over a 12-hour period.

INDOMETHACIN ORAL SUSPENSION USP

Usual adult dose

See Indomethacin Capsules USP .

Usual adult prescribing limits

See Indomethacin Capsules USP .

Usual pediatric dose

See Indomethacin Capsules USP .

Strength(s) usually available

U.S.¾25 mg per 5 mL (Rx)[Indocin 176 (alcohol 1%)] [Generic] 161

Canada¾Not commercially available.

Packaging and storage:

Store below 30 °C (86 °F). Store in a tight, light-resistant container. Protect from freezing.

Incompatibilities:

Indomethacin is unstable in an alkaline medium and should not be mixed with antacids or other liquids having an alkaline pH.

Auxiliary labeling:

- Take with food or antacids.
- Shake well.
- Avoid alcoholic beverages.

Rectal Dosage Forms

INDOMETHACIN SUPPOSITORIES USP

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory)
Anti-inflammatory (nonsteroidal) *

Antigout agent or
[Antipyretic] *¾Rectal, 50 mg up to four times a day. 176

Note: A daily dose of less than 75 mg may not be effective in active inflammatory disease.
For those arthritic patients who have persistent night pain and/or morning stiffness, up to 100 mg of the total daily dose may be given at bedtime. Lower bedtime doses may not provide adequate symptomatic relief. 176

A daily dose of more than 150 to 200 mg may increase the risk of adverse effects without providing additional clinical benefit. 175, 176

Usual adult prescribing limits

Rectal or combined oral and rectal, 200 mg per day. 175, 176

Usual pediatric dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Rectal, 1.5 to 2.5 mg per kg of body weight per day, administered in 3 or 4 divided doses, up to a maximum of 4 mg per kg of body weight or 150 to 200 mg per day, whichever is less. 176

Strength(s) usually available

U.S.¾50 mg (Rx)[Indocin 176 (butylated hydroxyanisole) (butylated hydroxytoluene) (edetic acid) (glycerin) (polyethylene glycol 3350) (polyethylene glycol 8000) (sodium chloride)]

Canada¾50 mg (Rx)[Indocid 175]

100 mg (Rx)[Indocid 175]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a well-closed container. Protect from freezing.

Auxiliary labeling:

· For rectal use.
· Avoid alcoholic beverages.

KETOPROFEN

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and psoriatic arthritis; pain; acute gouty arthritis and calcium pyrophosphate deposition disease (pseudogout); and dysmenorrhea. May also be used to relieve pain associated with nonrheumatic inflammatory disorders or vascular headaches.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A propionic acid derivative.

Half-life¾Elimination:

Capsules¾1.6 hours; increased by 26% in geriatric patients; also increased by renal function impairment.

Extended-release capsules¾About 5.4 hours; higher value (relative to immediate-release capsules) represents prolonged absorption; increased by 54% in geriatric patients.

Extended-release tablets¾About 3-4 hours; higher value (relative to immediate-release capsules) represents prolonged absorption.

Elimination¾Dialyzable.

Precautions¾ Pregnancy/reproduction¾Fertility: Decreased number of implantation sites in female rats (but no effect on fertility in male rats); high doses caused abnormal spermatogenesis or impaired spermatogenesis in rats and dogs and decreased testicular weight in dogs and baboons.

First trimester: No teratogenicity demonstrated in animal studies; in rabbits, maternally toxic doses shown to be embryotoxic.

Geriatrics¾Protein binding and clearance reduced in elderly people, leading to increased plasma concentration and prolonged half-life.

Drug interactions and/or related problems¾ Probenecid may greatly increase ketoprofen plasma concentration and the risk of toxicity; concurrent use not recommended.

Studies failed to show that ketoprofen increases digoxin plasma concentration.

Laboratory value alterations¾Interference with determinations of urinary albumin, bile salts, 17-ketosteroids, and 17-hydroxycorticosteroids via test procedures that rely on acid precipitation or on color reaction of carbonyl groups as an end point.

Side/adverse effects¾ See Table 3.

Oral Dosage Forms

KETOPROFEN CAPSULES

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 150 to 300 mg a day in three or four divided doses, usually 75 mg three times a day or 50 mg four times a day, initially, then adjusted according to patient response. 35, 205

Analgesic or

Antidysmenorrheal¾Oral, 25 205 to 50 205, 206 mg every six to eight hours as needed. Dosage may be increased if necessary, but single doses higher than 75 mg have not been shown to provide additional analgesia. 205 In the treatment of dysmenorrhea, 75-mg doses may be more effective than lower doses. 35, 205

Note: In patients with renal function impairment, a 33 to 50% reduction of dosage is recommended. 35

Note: The analgesic dosage for self-medication with ketoprofen using the over-the-counter product is 12.5 mg every four to six hours 312, 313.

Usual adult prescribing limits

Oral, 300 mg a day in three or four divided doses. 205, 206

Note: Risk/benefit must be considered when the maximum dose is prescribed because the incidence of gastrointestinal effects and headache is increased with administration of 300 mg per day (as compared with 200 mg per day). 35, 205

Usual pediatric dose

Safety and efficacy have not been established. 205

Strength(s) usually available

U.S.¾25 mg (Rx)[Orudis 205 (lactose)] [Generic] 161

50 mg (Rx)[Orudis 205 (lactose)] [Generic] 161

75 mg (Rx)[Orudis 205 (lactose)] [Generic] 161

Canada¾50 mg (Rx)[Apo-Keto 150] [Orudis 206] [Rhodis 212]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer.

Auxiliary labeling:

- Take with food.
- Take with a full glass of water.
- Avoid alcoholic beverages.

KETOPROFEN EXTENDED-RELEASE CAPSULES

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 150 or 200 mg once a day, in the morning or evening. 205, 207 Elderly or debilitated patients may require lower doses. 311

Note: The extended-release dosage form is not intended as initial therapy; the daily maintenance dose should be determined using an immediate- or delayed-release formulation. The extended-release dosage form may then be used, if desired, provided that the required dose can be achieved with the available strength(s).

Usual pediatric dose

Safety and efficacy have not been established. 205

Strength(s) usually available

U.S.¾100 mg (Rx)[Oruvail 311]

150 mg (Rx)[Oruvail 311]

200 mg (Rx)[Oruvail 205]

Canada¾150 mg (Rx)[Oruvail 207]

200 mg (Rx)[Oruvail 207]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Swallow capsule whole.
· Take with a full glass of water.
· Avoid alcoholic beverages.

Note: The extended-release capsule is formulated with delayed-release as well as extended-release characteristics. Dissolution of the contents of the capsules (coated pellets) does not occur until the medication reaches the alkaline pH of the small intestine.

KETOPROFEN DELAYED-RELEASE TABLETS

Usual adult dose

See Ketoprofen Capsules .

Usual adult prescribing limits

See Ketoprofen Capsules .

Usual pediatric dose

Safety and efficacy have not been established.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾50 mg (Rx)[Apo-Keto-E 150] [Novo-Keto-EC 192] [Orudis-E 206] [Rhodis-EC 212]

100 mg (Rx)[Apo-Keto-E 150] [Novo-Keto-EC 192] [Orudis-E 206] [Rhodis-EC 212]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with a full glass of water.
· Swallow tablets whole.
· Avoid alcoholic beverages.

KETOPROFEN EXTENDED-RELEASE TABLETS

Usual adult dose

See Ketoprofen Extended-release Capsules .

Usual pediatric dose

Safety and efficacy have not been established.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾200 mg (Rx)[Orudis-SR 206] [Generic]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.

· Swallow tablets whole.
· Avoid alcoholic beverages.

KETOPROFEN TABLETS USP

Usual adult dose

See Ketoprofen Capsules .

Usual adult prescribing limits

See Ketoprofen Capsules .

Usual pediatric dose

Safety and efficacy have not been established 312.

Strength(s) usually available
U.S.¾12.5 mg (OTC)[Orudis KT 312 (tartrazine)] [Actron 313 (lactose)]

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with a full glass of water.
· Avoid alcoholic beverages.

Rectal Dosage Forms

KETOPROFEN SUPPOSITORIES

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Rectal, 50 or 100 mg two times a day, in the morning and evening; or 50 or 100 mg in the evening in conjunction with oral administration during the day. 36, 206

Usual adult prescribing limits

Rectal or combined oral and rectal, 300 mg a day. 206

Usual pediatric dose

Safety and efficacy have not been established. 206

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾50 mg (Rx)[Orudis 206]

100 mg (Rx)[Orudis] [206 Rhodis 212]

Packaging and storage:

Store below 30 °C (86 °F), in a well-closed container, unless otherwise specified by manufacturer. Protect from freezing.

Auxiliary labeling:

· For rectal use.
· Avoid alcoholic beverages.

MECLOFENAMATE

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, psoriatic arthritis, pain, dysmenorrhea, and idiopathic hypermenorrhea. May also be used to relieve acute attacks of gout or calcium pyrophosphate deposition disease (pseudogout) and pain associated with nonrheumatic inflammatory conditions or vascular headaches.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A fenamate derivative.
Other actions/effects¾With usual doses has lesser effect on platelet aggregation than most other NSAIDs.
Biotransformation¾Hydroxymethyl metabolite has anti-inflammatory activity.
Half-life¾Elimination:
Single dose¾2 hours.
Multiple doses¾3.3 hours.
Onset of action¾Pain: 1 hour.
Duration of action¾Pain: 4-6 hours.

Precautions¾ Pregnancy/reproduction¾Fetotoxicity and developmental abnormalities have been demonstrated in animals.
Breast-feeding¾Use not recommended because animal studies have shown this agent to interfere with normal development of the young before weaning.
Surgical¾With recommended doses may be less likely than most other NSAIDs to increase perisurgical bleeding.
Laboratory value alterations¾With usual doses may be less likely than most other NSAIDs to increase bleeding time significantly.
Medical considerations/contraindications¾Caution in patients on a sodium-restricted diet.

Side/adverse effects¾ Reported to cause a serum sickness or influenza-like syndrome.
See also Table 3.

Additional Dosing Information

See also General Dosing Information.

Improvement in condition may occur within a few days, but 2 to 3 weeks of continuous use on a regular basis may be required for maximum effectiveness.
Gastrointestinal side effects may respond to a reduction in dosage; however, if severe adverse reactions occur, therapy should be discontinued.

Oral Dosage Forms

Note: The dosing and strengths of the available dosage form are expressed in terms of meclofenamic acid (not the sodium salt).

MECLOFENAMATE SODIUM CAPSULES USP

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 200 mg (meclofenamic acid) a day, in three or four divided doses, initially. Dosage may be increased to up to 400 mg a day if necessary. After a satisfactory response has been obtained, dosage should be reduced to the lowest maintenance dose that provides continuing control of symptoms. 37, 178

Analgesic¾Oral, 50 mg (meclofenamic acid) every four to six hours. If necessary, dosage may be increased to 100 mg every four to six hours. 127, 178

Antidysmenorrheal and
Antihypermenorrheal¾ Oral, 100 mg (meclofenamic acid) three times a day for up to six days. 178

Usual adult prescribing limits

Antirheumatic (nonsteroidal anti-inflammatory)
and analgesic¾Up to 400 mg daily. 178

Usual pediatric dose

Children up to 14 years of age¾Safety and efficacy have not been established. 178

Strength(s) usually available

U.S.¾50 mg (meclofenamic acid) (Rx)[Meclomen 178 (lactose)] [Generic]

100 mg (meclofenamic acid) (Rx)[Meclomen 178 (lactose)] [Generic] 161

Canada¾Not commercially available.

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight, light-resistant container.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

MEFENAMIC ACID

Summary of Differences

Indications¾ Indicated for short-term use (7 days or less) to relieve pain and dysmenorrhea. May also be used for acute attacks of gout or calcium pyrophosphate deposition disease (pseudogout), for pain associated with nonrheumatic inflammatory conditions or vascular headaches, and to prevent migraines associated with menstruation.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾ Chemical group: A fenamate derivative.

Other actions/effects¾With usual doses has lesser effect on platelet aggregation than most other NSAIDs.

Half-life¾Elimination: 2 hours

Precautions¾ Pregnancy/reproduction¾ Fertility: Decreased fertility demonstrated in rodents.

Pregnancy: Increased number of resorptions and decreased survival to weaning demonstrated in rodents.

Surgical¾With usual doses may be less likely than other NSAIDs to inhibit platelet aggregation significantly, but has been reported to cause hypoprothrombinemia, which may increase the risk of perisurgical bleeding.

Laboratory value alterations¾ Interference with urinary bile determinations via the diazo tablet test.

With usual doses is less likely than most other NSAIDs to increase bleeding time significantly because of lesser effect on platelet aggregation; however, may prolong prothrombin time.

Medical considerations/contraindications¾Also, may exacerbate pre-existing hypoprothrombinemia.

Side/adverse effects¾ See Table 3.

Additional Dosing Information

See also General Dosing Information.

It is recommended that mefenamic acid therapy be discontinued promptly if diarrhea or a skin rash develops. Patients who develop diarrhea during mefenamic acid therapy are usually unable to tolerate the drug thereafter.

Mefenamic acid should not be used for more than 7 days at a time.

Oral Dosage Forms

MEFENAMIC ACID CAPSULES USP

Usual adult dose

Analgesic or
Antidysmenorrheal¾Oral, 500 mg initially, followed by 250 mg every six hours as needed. 208

Note: It is recommended that mefenamic acid be used for no longer than 7 days at a time. 38

Usual pediatric dose

Children up to 14 years of age¾Safety and efficacy have not been established. 208

Strength(s) usually available

U.S.¾250 mg (Rx)[Ponstel 209 (lactose) (sodium benzoate)]

Canada¾250 mg (Rx)[Ponstan 208 (lactose)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F). Store in a tight container.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· May cause drowsiness.
· Avoid alcoholic beverages.

MELOXICAM

Summary of Differences

Indications¾ Indicated for osteoarthritis.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: An oxicam derivative.
Absorption¾Neither rate nor extent affected by food
Half-life¾Elimination: 15 to 20 hours.
Time to peak concentration¾5 to 6 hours.

Precautions¾ Pregnancy/reproduction¾Increased embryolethality and reduced neonatal survival in rats.

Oral Dosage Forms

MELOXICAM TABLETS

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 7.5 mg a day as a single dose. Dosage may be increased to 15 mg a day 320.

Usual adult prescribing limits

The maximum recommended daily dose is 15 mg 320.

Usual pediatric dose

Safety and efficacy have not been established 320

Usual geriatric dose

See Usual adult dose

Strength(s) usually available
U.S.¾7.5 mg (Rx)[Mobic 320]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F) in a dry place 320.

NABUMETONE

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis and osteoarthritis.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾ Chemical group: A naphthylalkanone derivative.
Other characteristics:
Nabumetone (prodrug)¾Nonacidic.
6-MNA (active metabolite)¾Acidic.
Other actions/effects¾With usual doses has lesser effect on platelet aggregation than most other NSAIDs.
Absorption¾Rate and extent increased by food or milk.
Biotransformation¾Metabolite 6-MNA, not nabumetone itself, is active substance.
Half-life (plasma)¾Elimination: 6-MNA¾23±3.7 hours; increased in geriatric patients to 30±8.1 hours (although values as high as 74 hours have been reported) and to 39 hours in patients with renal function impairment (creatinine clearance < 30 mL/minute/1.73 cubic meters of body surface area).

Time to peak plasma concentration¾6-MNA, at steady-state: Decreased by food; significantly delayed by hepatic cirrhosis.

Peak plasma concentration¾6-MNA: Increased by food; may be increased in geriatric patients and substantially decreased in patients with hepatic cirrhosis.

Elimination¾6-MNA: Significantly delayed by moderately severe renal function impairment (creatinine clearance < 30 mL/minute/1.73 cubic meters of body surface area).

Precautions¾ Mutagenicity¾Induced chromosomal aberrations in lymphocytes.

Pregnancy/reproduction¾Fetotoxicity but not teratogenicity demonstrated in rats.

Geriatrics¾Higher plasma concentrations and greater interpatient variability in pharmacokinetics of 6-MNA in geriatric patients.

Surgical¾In doses up to 1000 mg per day may be less likely than most other NSAIDs to increase perisurgical bleeding.

Drug interactions and/or related problems¾May be less likely than other NSAIDs to cause problems in patients receiving anticoagulant or thrombolytic therapy.

Medical considerations/contraindications¾Hepatic function impairment may decrease biotransformation to active metabolite sufficiently to decrease efficacy.

Side/adverse effects¾ Lower incidence of peptic ulceration and bleeding than with other NSAIDs.

See also Table 3.

Oral Dosage Forms

NABUMETONE TABLETS

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, initially 1000 mg a day, as a single dose (usually at night) or in two divided doses (in the morning and evening). Dosage may be increased, if necessary, to 1500 mg or 2000 mg a day in two divided doses. After a satisfactory response has been obtained, dosage should be individualized according to patient tolerance and response. The lowest dose that provides continuing control of symptoms should be used for maintenance. 210, 211

Usual adult prescribing limits

Doses larger than 2000 mg a day have not been studied and are not recommended. 210, 211

Usual pediatric dose

Safety and efficacy have not been established 210.

Usual geriatric dose

See Usual adult dose .

Strength(s) usually available

U.S.¾500 mg (Rx)[Relafen 210, 211]

750 mg (Rx)[Relafen 210, 211]

Canada¾500 mg (Rx)[Relafen 210, 211]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), in a well-closed container, 210 unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

NAPROXEN

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and juvenile arthritis; pain; acute attacks of gout and calcium pyrophosphate deposition disease (pseudogout); bursitis and tendinitis; fever; and dysmenorrhea; and for prophylaxis and treatment of vascular headaches.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A propionic acid derivative.
Absorption¾May be increased by sodium bicarbonate.
Half-life¾Elimination: 13 hours.
Onset of action¾Naproxen sodium: Pain¾1 hour.
Time to peak plasma concentration¾Extended-release tablets: Decreased by food.
Peak plasma concentration¾Extended-release tablets: Increased by food.
Time to peak effect¾Gout: 1-2 days.
Pain: 2-4 hours.
Duration of action¾Pain: Up to 7 hours.

Precautions¾ Pregnancy/reproduction¾Teratogenic effects in animals have not been shown.
Pediatrics¾Higher risk of skin rash and increases in bleeding time than in adults receiving the medication.
Laboratory value alterations¾Interference with some assays for urinary 5-hydroxyindoleacetic acid (5-HIAA) and urinary 17-ketogenic steroids.
Medical considerations/contraindications¾Caution with naproxen sodium and naproxen oral suspension for patients who must restrict their sodium intake.

Side/adverse effects¾ See Table 3.

Additional Dosing Information

See also General Dosing Information.

In arthritis, improvement in condition may occur within 2 weeks, but 2 to 4 weeks of continuous use on a regular basis may be required for maximum effectiveness.
Naproxen should be administered in the lowest effective dose to geriatric patients, patients with hepatic function impairment, or patients with renal function impairment (especially if creatinine clearance is < 20 mL per minute).

Oral Dosage Forms

NAPROXEN ORAL SUSPENSION

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 250, 375, or 500 mg two times a day, morning and evening. 1, 188

Note: During long-term administration, dosage may be adjusted according to patient response; lower doses may suffice. 1, 188

For acute exacerbations of rheumatic disease, dosage may be increased to up to 1.5 grams per day for limited periods. Use of this high dose requires that the clinical benefit be increased sufficiently to offset the potential increased risk of adverse effects. 1, 188

Anti-inflammatory (nonsteroidal) or
Analgesic (mild to moderate pain) or
Antidysmenorrheal¾Oral, 500 mg initially, then 250 mg every six to eight hours as needed. 1, 188

Antigout agent *¾Oral, 750 mg initially, then 250 mg every eight hours until the attack has subsided. 1, 188

Usual adult prescribing limits

For mild to moderate pain and
dysmenorrhea¾ Up to a total dose of 1.25 grams daily. 1, 188

Usual pediatric dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 10 mg per kg of body weight per day, given in two divided doses.

Strength(s) usually available

U.S.¾125 mg per 5 mL (Rx)[Naprosyn 188 (fumaric acid) (imitation orange flavor) (imitation pineapple flavor) (magnesium aluminum silicate) (methylparaben) (sodium 8 mg [<1 mmol] per mL) (sorbitol) (sucrose)]

Canada¾125 mg per 5 mL (Rx)[Naprosyn 189]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a well-closed, light-resistant container, unless otherwise specified by manufacturer. Protect from freezing.

Auxiliary labeling:

· Take with food.
· Shake well.
· Avoid alcoholic beverages.

NAPROXEN TABLETS USP

Usual adult dose

See Naproxen Oral Suspension.

Usual adult prescribing limits

See Naproxen Oral Suspension.

Usual pediatric dose

See Naproxen Oral Suspension.

Strength(s) usually available

U.S.¾250 mg (Rx)[Naprosyn 188] [Generic] 161

375 mg (Rx)[Naprosyn 188] [Generic] 161

500 mg (Rx)[Naprosyn 188] [Generic] 161

Canada¾125 mg (Rx)[Apo-Naproxen 152] [Naprosyn 189 (lactose)] [Naxen 190 (lactose)] [Novo-Naprox 194] [Nu-Naprox 201]

250 mg (Rx)[Apo-Naproxen 152] [Naprosyn 189 (lactose)] [Naxen 190 (lactose)] [Novo-Naprox 194] [Nu-Naprox 201]

375 mg (Rx)[Apo-Naproxen 152 (scored)] [Naprosyn 189 (scored) (lactose)] [Naxen 190 (scored) (lactose)] [Novo-Naprox 194 (scored)] [Nu-Naprox 201 (scored)]

500 mg (Rx)[Apo-Naproxen 152 (scored)] [Naprosyn 186 (scored) (lactose)] [Naxen 190 (scored) (lactose)] [Novo-Naprox 194 (scored)] [Nu-Naprox 201 (scored)]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F). Store in a well-closed container.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· May cause drowsiness.
· Avoid alcoholic beverages.

NAPROXEN DELAYED-RELEASE TABLETS

Usual adult dose

See Naproxen Oral Suspension.

Usual adult prescribing limits

See Naproxen Oral Suspension.

Usual pediatric dose

See Naproxen Oral Suspension.

Strength(s) usually available

U.S.¾375 mg (Rx)[EC-Naprosyn 310 (croscarmellose sodium) (povidone) (magnesium stearate) (methacrylic acid copolymer) (talc) (triethyl citrate) (sodium hydroxide) (simethicone emulsion)]

500 mg (Rx)[EC-Naprosyn 310 (croscarmellose sodium) (povidone) (magnesium stearate) (methacrylic acid copolymer) (talc) (triethyl citrate) (sodium hydroxide) (simethicone emulsion)]

Canada¾250 mg (Rx)[Naprosyn-E 189]

375 mg (Rx)[Naprosyn-E 189]

500 mg (Rx)[Naprosyn-E 189]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise directed by manufacturer.

Auxiliary labeling:

· Swallow tablets whole.
· Take with a full glass of water.
· Avoid alcoholic beverages.

NAPROXEN SODIUM TABLETS USP

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 275 or 550 mg two times a day, morning and evening; or 275 mg in the morning and 550 mg in the evening. 142

Note: During long-term administration, dosage may be adjusted according to patient response; lower doses may suffice.
If necessary, dosage may be increased to up to 1650 mg per day for short periods. The use of this higher dose requires that the clinical benefit be increased sufficiently to offset the potential increased risk. 142

Anti-inflammatory (nonsteroidal) or
Analgesic (mild to moderate pain)¾Oral, 550 mg initially, then 275 mg every six to eight hours as needed. 142

Antigout agent *¾Oral, 825 mg initially, then 275 mg every eight hours until the attack has subsided. 142

Antidysmenorrheal¾Oral, 550 mg initially, then 275 mg every six to eight hours as needed. 142

Note: For patient self-medication (over-the-counter use) for pain, fever, or dysmenorrhea¾Patients 12 years of age and older: Oral, 220 mg every eight to twelve hours while symptoms persist, or
Oral, 440 mg for the first dose only, followed by 220 mg twelve hours later and every eight to twelve hours thereafter as needed. 226

Usual adult prescribing limits

For mild to moderate pain and
dysmenorrhea¾Up to a total dose of 1375 mg daily. 142

Note: For patient self-medication (over-the-counter use) for pain, fever, or dysmenorrhea¾Not to exceed 2 tablets (220 mg each) in twenty-four hours for patients 65 years of age or older or 3 tablets in twenty-four hours for patients 12 to 65 years of age. 226

Usual pediatric dose

Pediatric strength not available. It is recommended that naproxen oral suspension or tablets be administered instead. 39

Strength(s) usually available

U.S.¾220 mg (equivalent to 200 mg of naproxen, with 20 mg of sodium) (OTC)[Aleve 226 (magnesium stearate) (microcrystalline cellulose) (povidone) (talc) (Opadry YS-1-4215)]

275 mg (equivalent to 250 mg of naproxen, with 25 mg [approximately 1.1 mmol] of sodium) (Rx)[Anaprox 142 (lactose)] [Generic] 161

550 mg (equivalent to 500 mg of naproxen, with 50 mg [approximately 2.2 mmol] of sodium) (Rx)[Anaprox DS 142] [Generic] 161

Canada¾275 mg (equivalent to 250 mg of naproxen, with 25 mg [approximately 1.1 mmol] of sodium) (Rx)[Anaprox 143 (lactose)] [Apo-Napro-Na 151] [Novo-Naprox Sodium 195] [Synflex 214]

550 mg (equivalent to 500 mg of naproxen, with 50 mg [approximately 2.2 mmol] of sodium) (Rx)[Anaprox DS 143] [Apo-Napro-Na DS 151] [Novo-Naprox Sodium DS 195] [Synflex DS 214]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F). Store in a well-closed container.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· May cause drowsiness.
· Avoid alcoholic beverages.

NAPROXEN SODIUM EXTENDED-RELEASE TABLETS

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 750 to 1000 mg once a day in the morning or evening. 134, 189, 317

Analgesic or
Antidysmenorrheal or
Anti-inflammatory (nonsteroidal)¾Oral, 1000 mg once a day in the morning or evening 317.

Note: For patients who require greater analgesic benefit, 1500 mg once a day for a limited period may be given. Thereafter, the daily dose should not exceed 1000 mg 317.

Antigout¾Oral, initially 1000 to 1500 mg once a day in the morning or evening, followed by 1000 mg once a day, until attack has subsided 317.

Adult prescribing limits

1500 mg per day 317.

Usual pediatric dose

Safety and efficacy have not been established 317.

Usual geriatric dose

See Usual adult dose 317.

Strength(s) usually available

U.S.¾375 mg (Rx)[Naprelan 317]

500 mg (Rx)[Naprelan 317]

Canada¾750 mg (Rx)[Naprosyn-SR 189]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), in a well-closed container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Swallow tablets whole.
· May cause drowsiness.
· Avoid alcoholic beverages.

Rectal Dosage Forms

NAPROXEN SUPPOSITORIES

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Rectal, 500 mg at bedtime, administered in conjunction with oral administration during the day. 189, 190

Usual adult prescribing limits

Total daily dose administered orally and rectally should not exceed 1.5 grams a day. The 1.5-gram daily dose is recommended only for short-term administration during acute exacerbations of rheumatic disease. Also, use of this high dose requires that the additional clinical benefit be sufficient to offset the potential increased risk of adverse effects. 1

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾500 mg (Rx)[Naprosyn 189] [Naxen 190]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Auxiliary labeling:

· For rectal use.
· Avoid alcoholic beverages.

OXAPROZIN

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis and osteoarthritis.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A propionic acid derivative.
Other actions/effects¾ Is as potent as aspirin as an inhibitor of platelet aggregation.
Also has uricosuric activity.
Half-life¾Elimination:
600 mg per day¾25 hours.
1200 mg per day¾21 hours.
Peak plasma concentration¾Accumulates with chronic dosing.

Precautions¾ Carcinogenicity¾Increased hepatic adenomas and carcinomas in male CD mice, but not in female CD mice or in rats.
Pregnancy/reproduction¾Caused fetal malformations in rabbits with doses within the usual human therapeutic range, but not in mice or rats.
Pediatrics¾Preliminary studies done in patients 3 to 16 years of age; elevated aspartate aminotransferase values occurred more frequently in patients treated for juvenile arthritis than for other forms of arthritis.
Geriatrics¾Dosage adjustment not needed on basis of pharmacokinetic considerations. Studies showed increased occurrence of impaired renal function and of decreased hemoglobin concentration, but not of changes in hepatic function, in patients 60 years of age and older compared to younger adults.
Surgical¾Recommended that oxaprozin be discontinued 1 to 2 weeks before elective surgery; may be more likely than most other NSAIDs to increase risk of perisurgical bleeding because of potent and prolonged inhibitory effect on platelet aggregation.
Laboratory value alterations¾Also, may decrease plasma concentrations and increase urine concentrations of uric acid.

Side/adverse effects¾ See Table 3.

Oral Dosage Forms

OXAPROZIN TABLETS

Usual adult dose

Rheumatoid arthritis¾Oral, 1200 mg per day, initially, then adjusted according to patient tolerance and response. 163

Osteoarthritis¾Oral, 1200 mg per day, initially, although a lower dose of 600 mg per day may be sufficient for mild disease or for patients of low body weight. 163

Note: Initial dosage must be individualized according to the severity of disease and patient variables such as body weight and renal function.
A single 1200-mg or 1800-mg loading dose may be administered to patients with normal renal function if necessary to speed the onset of action. 163

An initial dose of 600 mg per day is recommended for patients with renal function impairment. If this dose is well tolerated, higher doses may be administered if needed. 163

Doses of up to 1200 mg per day are usually administered once a day, but patients who are unable to tolerate a single dose of this size may tolerate divided doses. 163

Very severe arthritis may require doses higher than 1200 mg per day, which should be administered in two or three divided doses. It is recommended that these higher doses be reserved for patients weighing more than 50 kg who have normal hepatic and renal function and a low risk of peptic ulceration and who have not experienced adverse effects with lower doses. 163

After a beneficial response has been achieved, dosage should be reduced to the lowest dose that provides continuing control of symptoms. 163

Usual adult prescribing limits

Oral, 1800 mg per day or 26 mg per kg of body weight per day, whichever is lower, in two or three divided doses. 163

Usual pediatric dose

Safety and efficacy in children have not been established. 163 However, one preliminary study in children 3 to 16 years of age used a starting dose of 10 mg per kg of body weight. The dose was increased to 20 mg per kg of body weight if necessary. 269, 270

Strength(s) usually available

U.S.¾600 mg (Rx)[Daypro 163 (scored)]

Canada¾600 mg (Rx)[Daypro 319 (scored)]

Packaging and storage:

Store below 30 °C (86 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight, light-resistant container, unless otherwise specified by manufacturer. 163

Note: Protect unit-dose packages from light. 163

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

PHENYLBUTAZONE

Summary of Differences

Indications¾ Recommended only for short-term treatment of severe arthritic conditions, gout, or calcium pyrophosphate deposition disease (pseudogout) in patients unresponsive to less toxic NSAIDs. Not recommended as initial therapy for any indication.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A pyrazole derivative.

Other actions/effects¾Also induces hepatic microsomal enzyme activity.

Also has uricosuric activity.

Biotransformation¾Metabolized via hepatic microsomal enzymes. Metabolite oxyphenbutazone is active.

Half-life¾Elimination: 54-99 (average, 77) hours; increased to 105 hours in geriatric patients.

Precautions¾ Mutagenicity¾High concentrations induced chromosome abnormalities in Chinese hamster fibroblast cells in vitro .

Pregnancy/reproduction¾Fetotoxicity, but not teratogenicity, demonstrated in animal studies.

Breast-feeding¾Distributed into breast milk; may cause blood dyscrasias or other adverse effects in nursing infants.

Pediatrics¾Use in children up to 15 years of age not recommended.

Geriatrics¾Also, increased risk of blood dyscrasias. Recommended that duration of treatment be limited to 1 week in patients 60 years of age and older.

Drug interactions and/or related problems¾ Concurrent use with alcohol may also impair psychomotor skills.

Higher risk of bleeding with coumarin- or indanedione-derivative anticoagulants than with other NSAIDs because phenylbutazone inhibits the anticoagulant's metabolism; concurrent use not recommended.

Also, increased risk of toxicity with hydantoin anticonvulsants because phenylbutazone may displace them from protein-binding sites and inhibit their metabolism.

Also, by inducing hepatic microsomal enzymes, phenylbutazone may decrease effects of barbiturates, cortisone and possibly other corticosteroids, estrogen-containing oral contraceptives, and digitalis glycosides.

Also, increased risk of severe dermatologic reactions with other dermatitis-causing medications.

Also, cholestyramine may decrease absorption of phenylbutazone; recommend administering phenylbutazone 1 hour before or 4 to 6 hours after cholestyramine.

Also, increased risk of adverse hematologic effects if used concurrently with colchicine.

Also, other hepatic enzyme inducers may increase phenylbutazone metabolism and decrease its half-life.

Concurrent use with methotrexate may also increase risk of agranulocytosis or bone marrow depression.

Also, methylphenidate may inhibit phenylbutazone metabolism, leading to increased plasma concentration and risk of toxicity.

Also, concurrent use with penicillamine may increase risk of serious hematologic and/or renal adverse effects.

Also, concurrent use with sulfonamides may potentiate effects of either or both medications.

Also, antacids in buffered formulations may interfere with absorption of many other medications.

Laboratory value alterations¾Interference with thyroid function tests, specifically, decreases 24-hour 131I thyroidal uptake and increases resin or red cell triiodothyronine (T 3) uptake.

Also, may decrease blood glucose concentrations.

Also, may decrease plasma concentrations and increase urine concentrations of uric acid.

Medical considerations/contraindications¾Also, not recommended in patients with blood dyscrasias (or history of), bone marrow depression, severe cardiac or cardiopulmonary disease or cardiac failure, severe hepatic or renal disease, or active peptic ulcer disease.

Also, may aggravate polymyalgia rheumatica or temporal arteritis.

Patient monitoring¾Complete physical examinations, including urinalyses, and hematologic examinations recommended at regular intervals.

Side/adverse effects¾ Higher risk of blood dyscrasias than with other NSAIDs, especially in geriatric patients.

Reported to cause a serum sickness- or influenza-like syndrome.

Blood dyscrasias may occur days or weeks after medication is discontinued.

See also Table 3.

Additional Dosing Information

See also General Dosing Information.

Because of its toxicity, phenylbutazone should be used in the minimum effective dosage and for the shortest possible time.

In geriatric patients, therapy should be limited to short periods, preferably not to exceed 1 week, because of the high risk of severe, possibly fatal, toxic reactions.

Phenylbutazone is generally better tolerated when administered with food to lessen gastric irritation.

If therapy is not effective within 1 week, the medication should be discontinued.

Edema may be dose-related and may be prevented in some patients by reducing the dosage.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

PHENYLBUTAZONE CAPSULES USP

Usual adult dose

Rheumatoid arthritis *

or Osteoarthritis, acute attacks *

or Ankylosing spondylitis
[or Psoriatic arthritis]¾Oral, 300 to 600 mg a day in three or four divided doses. 224

Antigout agent¾Oral, initially 400 mg as a single dose; then 100 mg every four hours for approximately four days or until a satisfactory response is obtained, with the duration of therapy not exceeding one week. 224

Note: Some clinicians use a dose of 200 mg every four hours for approximately four days or until a satisfactory response is obtained, with the duration of therapy not exceeding two weeks.

Usual pediatric dose

Children up to 15 years of age¾Use is not recommended. 224

Strength(s) usually available

U.S.¾100 mg (Rx)[Cotylbutazone 161] [Generic] 161

Canada¾Not commercially available.

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

PHENYLBUTAZONE TABLETS USP

Usual adult dose

See Phenylbutazone Capsules USP .

Usual pediatric dose

Children up to 15 years of age¾Use is not recommended. 224

Strength(s) usually available

U.S.¾100 mg (Rx) [Generic] 161

Canada¾100 mg (Rx)[Apo-Phenylbutazone 153] [Butazolidin 224]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Store in a tight container.

Auxiliary labeling:

· Take with food.
· Swallow tablets whole.
· Take with a full glass of water.
· Avoid alcoholic beverages.

PHENYLBUTAZONE TABLETS BUFFERED

Usual adult dose

See Phenylbutazone Capsules USP .

Usual pediatric dose

Children up to 15 years of age¾Use is not recommended. 224

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾100 mg of phenylbutazone, with 150 mg of magnesium trisilicate and 100 mg of dried aluminum hydroxide gel (Rx)[Alka Butazolidin 141]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), in a tight container, unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Swallow tablets whole.
· Take with a full glass of water.
· Avoid alcoholic beverages.

PIROXICAM

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute attacks of gout or calcium pyrophosphate deposition disease (pseudogout), and dysmenorrhea.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: An oxicam derivative.

Half-life¾Elimination: 50 hours, although values ranging from 14 to 158 hours have been reported. Increased in patients with renal function impairment. May also be increased in elderly patients, especially females.

Onset of action¾Gout: 2-4 hours.

Peak effect time¾Gout: 3-5 days.

Duration of action¾Gout: 24 hours.

Precautions¾ Pregnancy/reproduction¾Teratogenic effects not demonstrated in animal studies.

Breast-feeding¾Distributed into breast milk; use by breast-feeding mothers not recommended because piroxicam inhibits lactation in animals.

Geriatrics¾Tendency toward increased half-life and steady-state concentrations, especially in females.

Drug interactions and/or related problems¾Studies failed to show that piroxicam increases digoxin plasma concentrations.

Laboratory value alterations¾Also, may increase or decrease blood glucose concentrations.

Medical considerations/contraindications¾Higher risk than with most other NSAIDs in patients with renal function impairment.

Side/adverse effects¾ Reported to cause a serum sickness- or influenza-like syndrome.

See also Table 3.

Additional Dosing Information

See also General Dosing Information.

Because steady-state plasma concentrations are not reached for 7 to 12 days following initiation of therapy, the effectiveness of therapy with piroxicam should not be assessed for 2 weeks.

Oral Dosage Forms

Note: Bracketed uses in the Dosage Forms section refer to categories of use and/or indications that are not included in U.S. product labeling.

PIROXICAM CAPSULES USP

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 20 mg once a day or 10 mg two times a day. 167, 168

[Antidysmenorrheal]¾Oral, 40 mg at the onset of symptoms on the first day only, then 20 mg once a day thereafter if necessary. 168

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾10 mg (Rx)[Feldene 167 (lactose)] [Generic] 161

20 mg (Rx)[Feldene 167 (lactose)] [Generic] 161

Canada¾10 mg (Rx)[Apo-Piroxicam 154] [Feldene 168 (lactose)] [Novo-Pirocam 196] [Nu-Pirox 202] [PMS-Piroxicam 156]

20 mg (Rx)[Apo-Piroxicam 168] [Feldene 168 (lactose)] [Novo-Pirocam 196] [Nu-Pirox 202] [PMS-Piroxicam 156]

Packaging and storage:

Store below 30 °C (86 °F). Store in a tight, light-resistant container.

Auxiliary labeling:

· Take after meals.
· Take with a full glass of water.
· Avoid alcoholic beverages.

Rectal Dosage Forms

PIROXICAM SUPPOSITORIES

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Rectal, 20 mg once a day or 10 mg two times a day. 168

Usual adult prescribing limits

Rectal or combined oral and rectal¾20 mg a day. 168

Usual pediatric dose

Dosage has not been established.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾10 mg (Rx)[Feldene 168]

20 mg (Rx)[Feldene 168]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer. Protect from freezing.

Auxiliary labeling:

· For rectal use.
· Avoid alcoholic beverages.

SULINDAC

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute attacks of gout or calcium pyrophosphate deposition disease (pseudogout), bursitis, and tendinitis.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A pyrroleacetic acid derivative.
Biotransformation¾Hepatic; sulfide metabolite, not sulindac itself, is active substance.
Half-life¾Elimination:
Sulindac¾7.8 hours.
Sulindac sulfide¾16.4 hours.
Time to peak plasma concentration¾Sulindac sulfide: Substantially delayed in patients with alcoholic hepatic disease.
Elimination: Less than 1% of a sulindac dose excreted via the kidneys as the active sulfide metabolite.

Precautions¾ Pregnancy/reproduction¾Fetotoxicity, and, in some studies, a low incidence of teratogenicity, have been demonstrated in animals.
Drug interactions and/or related problems¾ Concurrent chronic use of antacids significantly decreases sulindac plasma concentration.
Decreased concentration of active sulfide metabolite of sulindac and peripheral neuropathy reported with concurrent (topical) use of dimethyl sulfoxide.
Laboratory value alterations¾Also, may increase blood glucose concentrations.
Medical considerations/contraindications¾ Hepatic function impairment may slow metabolism to, but also decrease biliary elimination of, the active sulfide metabolite; net result is increased and prolonged plasma concentration and higher risk of toxicity.
Also, caution and adequate fluid intake recommended for patients with renal calculi (or history of) because renal calculi containing sulindac metabolites have occurred in a few patients.

Side/adverse effects¾ May be less likely than most other NSAIDs to cause renal toxicity.
Reported to cause biliary obstruction.
Reported to cause a characteristic hypersensitivity syndrome.
See also Table 3.

Additional Dosing Information

See also General Dosing Information.

In the treatment of arthritis, improvement in condition may occur within 7 days, but 2 to 3 weeks of continuous use on a regular basis may be required for maximum effectiveness.
Patients with impaired renal function may require lower doses.
Therapy for 7 days in acute gouty arthritis and for 7 to 14 days in acute painful shoulder is usually sufficient.

Oral Dosage Forms

SULINDAC TABLETS USP

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 150 or 200 mg two times a day; may be increased or decreased, depending on patient response. 160, 223

Note: Although some patients have received doses higher than 400 mg per day, such doses have not been fully evaluated and are not recommended.
Antigout agent¾Oral, 200 mg two times a day; dosage to be decreased according to patient response. 160, 223

Anti-inflammatory (acute painful shoulder) ¾Oral, 200 mg two times a day; dosage to be decreased according to patient response. 160, 223

Usual pediatric dose

Safety and efficacy have not been established. 223

Strength(s) usually available

U.S.¾150 mg (Rx)[Clinoril 159] [Generic] 223

200 mg (Rx)[Clinoril 159 (scored)] [Generic] (may be scored) 223

Canada¾150 mg (Rx)[Apo-Sulin 155 (scored)] [Clinoril 160] [Novo-Sundac 198 (scored)]

200 mg (Rx)[Apo-Sulin 155 (scored)] [Clinoril 159 (scored)] [Novo-Sundac 198 (scored)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F). Store in a well-closed container.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

TENOXICAM

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, bursitis, tendinitis, and periarthritis.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: An oxicam derivative.
Half-life¾Elimination: 72±26 (range, 32-110) hours.

Precautions¾ Pregnancy/reproduction¾ Fertility: Decreased number of corpora lutea and implantations in female rats, but no impairment of fertility in male rats, demonstrated in animal studies.
First trimester: Maternotoxicity (panperitonitis, gastric lesions, and uterine hemorrhage) and embryotoxicity, but not teratogenicity, demonstrated in animal studies.
Geriatrics¾Also, risk of hyperkalemia may be increased in geriatric patients.
Drug interactions and/or related problems¾ Studies failed to show that tenoxicam increases digoxin concentrations.
Also, cholestyramine administered in conjunction with intravenously administered tenoxicam shown to decrease half-life of tenoxicam from 67.4 to 31.9 hours and increase tenoxicam clearance by 105%.

Side/adverse effects¾ See Table 3.

Oral Dosage Forms

TENOXICAM TABLETS

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory)
and Anti-inflammatory (nonsteroidal) ¾Oral, 20 mg once a day, at the same time each day. For some patients, 10 mg once a day may be sufficient. The smallest effective dose should be used. 180

Usual adult prescribing limits

20 mg per day. Higher doses may increase the risk of adverse effects without providing a significantly greater therapeutic response. 180

Usual pediatric dose

Children up to 16 years of age¾Dosage has not been established. 180

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾20 mg (Rx)[Apo-Tenoxicam 321 (colloidal silicon dioxide) (croscarmellose sodium) (hydroxypropyl methylcellulose) (lactose monohydrate) (magnesium stearate) (microcrystalline cellulose polydextrose) (polyethylene glycol) (titanium dioxide) (yellow ferric oxide)] [Generic]

20 mg (Rx)[Novo-Tenoxicam 322 (carnauba wax) (comstarch) (dibutyl sebacate) (ethylcellulose) (hydroxypropyl methylcellulose) (lactose) (magnesium stearate) (polydextrose) (pregelatinized starch) (sodium lauryl sulfate) (synthetic yellow oxide) (talc) (titanium dioxide) (triacetin)] [Generic]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

TIAPROFENIC ACID

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis and osteoarthritis.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A propionic acid derivative.
Half-life¾Elimination:
Single dose¾Tablets: 1.7 hours; increased to 2.5 hours in geriatric patients.
At steady-state¾Extended-release capsules (600 mg once a day): 4.2 hours.

Precautions¾ Pregnancy/reproduction¾ Fertility: Decreased number of implantation sites in female rabbits, but no effect on fertility in male or female rats.
First trimester:
Crosses the placenta.
Fetotoxicity, but not teratogenicity, demonstrated in animal studies.
Geriatrics¾Substantially higher frequency of hyperkalemia and/or increased blood urea nitrogen documented in studies.
Drug interactions and/or related problems¾Also, may displace hydantoin anticonvulsants from their protein-binding sites, possibly leading to increased hydantoin half-life and toxicity.

Side/adverse effects¾ See Table 3.

Oral Dosage Forms

TIAPROFENIC ACID EXTENDED-RELEASE CAPSULES

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Oral, 600 mg once a day, at the same time each day.

Usual pediatric dose

Safety and efficacy have not been established.

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾300 mg (Rx)[Surgam SR 213]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Swallow capsules whole.
· Take with a full glass of water.
· Avoid alcoholic beverages.

TIAPROFENIC ACID TABLETS

Usual adult dose

Rheumatoid arthritis¾Oral, 600 mg a day in two or three divided doses. 48, 213

Osteoarthritis¾Oral, 600 mg a day in two or three divided doses, initially. After a satisfactory response has been obtained, dosage may be reduced. Some patients may be maintained on 300 mg a day in divided doses. 48, 213

Usual adult prescribing limits

600 mg a day. 213

Usual pediatric dose

Safety and efficacy have not been established. 213

Strength(s) usually available

U.S.¾Not commercially available.
Canada¾200 mg (Rx)[Albert Tiafen 140 (scored)] [Surgam 213 (scored)]

300 mg (Rx)[Albert Tiafen 140 (scored)] [Surgam 213 (scored)]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F), unless otherwise specified by manufacturer.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

TOLMETIN

Summary of Differences

Indications¾ Indicated for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis, and psoriatic arthritis.

Pharmacology/pharmacokinetics¾ Physicochemical characteristics¾Chemical group: A pyrroleacetic acid derivative.
Absorption¾Extent decreased by food and milk.
Half-life¾Elimination: 5 hours.

Precautions¾ Pregnancy/reproduction¾No teratogenicity or other adverse effects on fetal development demonstrated in animal studies.
Pediatrics¾Studied in pediatric patients 2 years of age and older; no pediatrics-specific problems documented.
Laboratory value alterations¾Interference with sulfosalicylic acid test method for urinary protein.
Medical considerations/contraindications¾Caution in patients who must restrict their sodium intake.

Side/adverse effects¾ Higher incidence of anaphylactic reactions than with other NSAIDs.
Reported to cause a serum sickness- or influenza-like syndrome.
See also Table 3.

Additional Dosing Information

See also General Dosing Information.

Improvement in condition may occur within 7 days, but 1 to 2 weeks of continuous use on a regular basis may be required for maximum effectiveness.

Oral Dosage Forms

Note: The dosing and strengths of the available dosage forms are expressed in terms of the free acid (not the sodium salt).

TOLMETIN SODIUM CAPSULES USP

Usual adult dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Initial: Oral, 400 mg (free acid) three times a day, preferably including a dose in the morning and a dose at bedtime. 216

Maintenance: Rheumatoid arthritis¾Oral, 600 mg to 1.8 grams (free acid) a day in three or four divided doses. 216

Osteoarthritis¾Oral, 600 mg to 1.6 grams (free acid) a day in three or four divided doses. 216

Usual adult prescribing limits

Up to 2 grams (free acid) daily for rheumatoid arthritis or 1.6 grams (free acid) daily for osteoarthritis. 216

Usual pediatric dose

Antirheumatic (nonsteroidal anti-inflammatory) ¾Children up to 2 years of age: Dosage has not been established. 216

Children 2 years of age and over: Initial¾Oral, 20 mg (free acid) per kg of body weight a day in three or four divided doses. 216

Maintenance¾Oral, 15 to 30 mg (free acid) per kg of body weight a day in divided doses. 216

Note: Doses higher than 30 mg (free acid) per kg of body weight per day have not been studied and therefore are not recommended. 216

Strength(s) usually available

U.S.¾400 mg (free acid, with 36 mg [1.568 mmol] of sodium) (Rx)[Tolectin DS 215] [Generic] 161

Canada¾400 mg (free acid, with 36 mg [1.568 mmol] of sodium) (Rx)[Novo-Tolmetin 293] [Tolectin 400 216]

Packaging and storage:

Store below 40 °C (104 °F), preferably between 15 and 30 °C (59 and 86 °F). Store in a tight container.

Auxiliary labeling:

· Take with food.
· Take with a full glass of water.
· Avoid alcoholic beverages.

TOLMETIN SODIUM TABLETS USP

Usual adult dose

See Tolmetin Sodium Capsules USP .

Usual adult prescribing limits

See Tolmetin Sodium Capsules USP .

Usual pediatric dose

See Tolmetin Sodium Capsules USP .

Strength(s) usually available

U.S.¾200 mg (free acid, with 18 mg [0.784 mmol] of sodium) (Rx)[Tolectin 200 215 (scored)] [Generic] 161

600 mg (free acid, with 54 mg [2.352 mmol] of sodium) (Rx)[Tolectin 600] [Generic] 161

Canada¾200 mg (free acid, with 18 mg [0.784 mmol] of sodium) (Rx)[Tolectin 200 215, 216 (scored)]

600 mg (free acid, with 54 mg [2.352 mmol] of sodium) (Rx)[Tolectin 600 216]

Packaging and storage:

Store between 15 and 30 °C (59 and 86 °F). Store in a well-closed container.

Auxiliary labeling:

- Take with food.
- Take with a full glass of water.
- Avoid alcoholic beverages.