
Naproxen

28:08.04.92 Other Nonsteroidal Anti-inflammatory Agents (AHFS

primary); ms120 (VA primary)

Naproxen Sodium

28:08.04.92 Other Nonsteroidal Anti-inflammatory Agents (AHFS

primary); ms120 (VA primary)

- Naproxen and naproxen sodium are prototypical anti-inflammatory agents (NSAIA) that also exhibit analgesic and antipyretic activity.

Uses

Naproxen and naproxen sodium are used to relieve mild to moderately severe pain. Conventional (immediate-release) and delayed-release (enteric-coated) tablets and suspension formulations of naproxen or naproxen sodium are used for anti-inflammatory and analgesic effects in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis. Conventional (immediate-release) tablets and suspension formulations of naproxen or naproxen sodium also are used for the symptomatic treatment of tendinitis, bursitis, acute gout, pain, and primary dysmenorrhea. Suspension formulations of naproxen are preferred for the management of juvenile arthritis since this formulation provides maximum dosage flexibility. Because of the delayed-release properties of enteric-coated naproxen tablets, this formulation is not recommended for the management of acute pain. Extended-release naproxen sodium tablets are used for the symptomatic treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis, acute gout, mild to moderately severe pain, and primary dysmenorrhea. (Naproxen 250 mg is approximately equivalent to naproxen sodium 275 mg.) Naproxen sodium also may be used for *self-medication* for anti-inflammatory and analgesic effects to provide temporary relief of *minor* aches and pains, including those associated with arthritis, and of dysmenorrhea and for its antipyretic effect to reduce fever.

The potential benefits and risks of naproxen therapy as well as alternative therapies should be considered prior to initiating naproxen therapy. The lowest possible effective dosage and shortest duration of therapy consistent with treatment goals of the patient should be employed.

■ Inflammatory Diseases

Naproxen and naproxen sodium are used for anti-inflammatory and analgesic effects in the symptomatic treatment of rheumatoid arthritis, osteoarthritis, juvenile rheumatoid arthritis, and ankylosing spondylitis. Naproxen also is used in combination with lansoprazole for the symptomatic treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis in patients with a history of documented gastric ulcer who require continued use of an NSAIA. For information on the combined use of naproxen and lansoprazole, see Prevention under Uses: NSAIA-induced Ulcers, in Lansoprazole 56:28.36.

Rheumatoid Arthritis, Juvenile Arthritis, and Osteoarthritis

When used in the treatment of rheumatoid arthritis or juvenile rheumatoid arthritis, naproxen has relieved pain and stiffness, reduced swelling, and improved mobility and grip strength. In the treatment of osteoarthritis, naproxen has relieved pain and stiffness and improved knee joint function. Naproxen appears to be only palliative in these conditions and has not been shown to permanently arrest or reverse the underlying disease process. Naproxen sodium also may be used for *self-medication* to provide temporary relief of minor aches and pains associated with arthritis.

Most clinical evaluations of naproxen in the management of rheumatoid arthritis or osteoarthritis have shown that the anti-inflammatory and analgesic effects of usual dosages of naproxen are greater than those of placebo and about equal to those of usual dosages of salicylates, indomethacin, fenoprofen, or ibuprofen. The results of a study in patients with osteoarthritis suggested that naproxen (500 mg twice daily) was less effective than tolmetin (800 mg twice daily) in some measures of pain relief, although improvements in functional ability did not differ. In controlled studies in patients with juvenile rheumatoid arthritis, the anti-inflammatory and analgesic effects of usual dosages of naproxen were comparable to those of usual dosages of aspirin, indomethacin, or piroxicam. Patient response to oral NSAIA is variable; patients who do not respond to or cannot tolerate one NSAIA might be successfully treated with a different agent. However, NSAIA are generally contraindicated in patients in whom sensitivity reactions (e.g., urticaria, bronchospasm, severe rhinitis) are precipitated by aspirin or other NSAIA. (See Cautions: Precautions and Contraindications.)

In the management of rheumatoid arthritis in adults, NSAIA may be useful for initial symptomatic treatment; however, NSAIA do not alter the course of the disease or prevent joint destruction. Disease modifying antirheumatic drugs (DMARDs) (e.g., azathioprine, cyclosporine, etanercept, oral or injectable gold compounds,

hydroxychloroquine, infliximab, leflunomide, methotrexate, minocycline, penicillamine, sulfasalazine) have the potential to reduce or prevent joint damage, preserve joint integrity and function, and reduce total health care costs, and all patients with rheumatoid arthritis are candidates for DMARD therapy. DMARDs should be initiated early in the disease course and should not be delayed beyond 3 months in patients with active disease (i.e., ongoing joint pain, substantial morning stiffness, fatigue, active synovitis, persistent elevation of erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP], radiographic evidence of joint damage) despite an adequate regimen of NSAIA. NSAIA therapy may be continued in conjunction with DMARD therapy or, depending on patient response, may be discontinued. For further information on the treatment of rheumatoid arthritis, see Uses: Rheumatoid Arthritis in Methotrexate 10:00.

The manufacturers state that naproxen and its salt may be used safely in conjunction with gold compounds and/or corticosteroids in the treatment of rheumatoid arthritis. The manufacturers state that combined use of naproxen or its salt and corticosteroids has not resulted in greater improvement than with steroids alone, although addition of naproxen or its salt to a regimen of gold compounds has resulted in greater improvement than with gold salts alone.

Use of naproxen or its salt with aspirin is not recommended by the manufacturers. There is inadequate proof that the combination is more efficacious than either drug alone, and the potential for adverse reactions may be increased. (See Drug Interactions: Nonsteroidal Anti-inflammatory Agents.)

Ankylosing Spondylitis

When used in patients with ankylosing spondylitis, naproxen has relieved night pain, morning stiffness, and pain at rest. In a limited number of controlled studies, the anti-inflammatory and analgesic effects of usual dosages of naproxen in the symptomatic treatment of ankylosing spondylitis were greater than those of placebo and comparable to those of usual dosages of aspirin or phenylbutazone (no longer commercially available in the US).

Other Inflammatory Conditions

Naproxen has been used effectively to relieve pain, fever, redness, swelling, and tenderness in patients with acute gouty arthritis.

When used in the treatment of acute painful shoulder, the anti-inflammatory and analgesic effects of naproxen sodium are greater than those of placebo and about equal to those of indomethacin. When used in the treatment of tendinitis and bursitis, the anti-inflammatory and analgesic effects of usual dosages of naproxen sodium are comparable to those of usual dosages of oxyphenbutazone (no longer commercially available in the US).

■ Pain

Naproxen and its salt are used to relieve postoperative pain (including that associated with dental surgery), postpartum pain, primary dysmenorrhea, pain following insertion of an intrauterine contraceptive device, orthopedic pain, headache (including migraine), and visceral pain associated with cancer. Naproxen sodium also may be used for *self-medication* to provide temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, and backache.

There are few published studies comparing the effectiveness of naproxen and its salt with other analgesics in the relief of nonarthritic pain. In one study, a single 275-mg oral dose of naproxen sodium was as effective as a single 650-mg oral dose of aspirin in the relief of postpartum uterine pain. In another study, when used to relieve postoperative or orthopedic pain, 550 mg of oral naproxen sodium followed by 275 mg every 6 hours was at least as effective as 650 mg of acetaminophen orally every 6 hours or 50 mg of pentazocine orally every 6 hours; in this study, the onset of action appeared to be more rapid for naproxen sodium than for acetaminophen or pentazocine. In another study of patients with postoperative pain, the analgesic effects of 550 mg of oral naproxen sodium and 60 mg of oral codeine sulfate were additive (the combination was more effective than either drug alone).

Some experts state that an NSAIA (e.g., naproxen or its salt) is a reasonable first-line therapy for mild to moderate migraine attacks or for severe attacks that have responded in the past to similar NSAIA or non-opiate analgesics. When used for prophylaxis† of migraine headache, naproxen and its salt appear to have a modest effect on headache frequency, intensity, and/or duration. For further information on management and classification of migraine headache, see Vascular Headaches: General Principles in Migraine Therapy, under Uses in Sumatriptan 28:32.28.

■ Dysmenorrhea

When used to relieve dysmenorrhea, including that which develops after insertion of an intrauterine contraceptive device, an oral dosage of 500 mg of naproxen or 550 mg of naproxen sodium followed by 250 mg of naproxen or 275 mg of naproxen sodium every 6 hours, respectively, has been reported to be more effective than placebo or aspirin (650 mg 4 times daily). In a placebo-controlled study of women with primary menorrhagia† or menorrhagia associated with intrauterine contraceptive devices†, administration of naproxen (750 mg daily for the first 2 days of menstrual bleeding followed by 500 mg daily thereafter for up to 7 days) resulted in a reduction of blood loss. In one controlled study in patients with postpartum pain, a single oral dose of 550 mg of naproxen sodium appeared to provide greater pain relief after 4 and 5 hours than 500 mg of naproxen; however, there was no difference in onset of analgesia. Naproxen sodium also may be used for *self-medication* to provide temporary relief of manifestations of dysmenorrhea (e.g., menstrual cramps).

■ Other Uses

Naproxen sodium has been used in adults for *self-medication* as an antipyretic. The drug also has been used as an antipyretic in children; one study indicates that a single oral dose of naproxen (2.5 or 7.5 mg/kg) was at least as effective as a single oral dose of aspirin (15 mg/kg) in the reduction of fever in children. The results of one study suggested that the combination of naproxen sodium and ampicillin was more effective than ampicillin alone in alleviating fever, dyspnea, and coughing associated with acute respiratory infections in children†.

Naproxen has been used in the symptomatic management of osteitis deformans† (Paget's disease of bone) and Bartter's syndrome†.

Results from a large, prospective, population-based cohort study in geriatric individuals indicate a lower prevalence of Alzheimer's disease† among patients who received an NSAIA for 2 years or longer. Similar findings have been reported from some other, but not all, observational studies.

Dosage and Administration

■ Administration

The potential benefits and risks of naproxen therapy as well as alternative therapies should be considered prior to initiating naproxen therapy.

Naproxen and naproxen sodium are administered orally. Enteric-coated tablets of naproxen should not be broken, crushed, or chewed, so that the delayed-release properties of this formulation are maintained. Adverse GI effects may be minimized by administering the drugs with meals, milk, or a magnesium and aluminum hydroxides antacid. When used for *self-medication*, the manufacturer recommends that each dose of naproxen sodium be taken with a full glass of water. Because of the delayed-release properties of enteric-coated naproxen tablets, this formulation is not recommended for the management of acute pain. Also, the manufacturer states that because naproxen sodium is absorbed more rapidly than naproxen, the sodium salt conventional tablet formulation is recommended for the management of acute painful conditions when prompt onset of pain relief is desired.

■ Dosage

The lowest possible effective dosage and shortest duration of therapy consistent with treatment goals of the patient should be employed. Dosage of naproxen must be carefully adjusted according to individual requirements and response, using the lowest possible effective dosage. Lower dosages of the drug should be considered in patients with renal or hepatic impairment or in geriatric patients. Use of naproxen or naproxen sodium in patients with moderate to severe renal impairment (creatinine clearance less than 30 mL/minute) is not recommended.

Patients receiving naproxen for *self-medication* should be advised to use the lowest effective dosage and not to exceed the recommended dosage or duration of therapy.

Patients should be warned that the risk of GI bleeding is increased when recommended durations of *self-medication* are exceeded and when more than one NSAIA are used concomitantly.

Each 220, 275, 412.5, or 550 mg of naproxen sodium is approximately equivalent to 200, 250, 375, or 500 mg of naproxen, respectively.

Different dose strengths and formulations are not necessarily bioequivalent, and this should be considered when changing from one strength to another or from one formulation to another.

Inflammatory Diseases

Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis.

For the symptomatic treatment of osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis, but excluding acute gouty arthritis), the usual adult dosage of naproxen is 250–500 mg (275–550 mg of naproxen sodium) twice daily in the morning and evening. Alternatively, 250 mg of naproxen (275 mg of naproxen sodium) may be given in the morning, and 500 mg (550 mg of the sodium salt) may be given in the evening. It is not necessary to administer either drug more often than twice daily, and morning and evening doses do not have to be equal in size.

The usual adult dosage of extended-release naproxen tablets is 750 mg or 1 g (825 mg or 1.1 g of naproxen sodium) administered once daily. Patients receiving other naproxen dosage forms twice daily may be switched to the extended-release naproxen sodium tablets by replacing their total daily dosage with an equal dosage of the extended-release formulation and then administered once daily.

Subsequent dosage of naproxen or naproxen sodium should be adjusted according to the patient's response and tolerance. In patients who tolerate lower dosages well, the dosage of naproxen may be increased to 1.5 g (1.65 g of naproxen sodium) daily for limited periods of time (up to 6 months) when a greater level of anti-inflammatory and/or analgesic activity is necessary; when a dosage of 1.5 g (1.65 g of the sodium salt) daily is administered, an adequate increase in clinical benefit should be evident to justify potential increased risks associated with this dosage. Symptomatic improvement usually begins within 2 weeks after beginning therapy. If improvement does not occur within 2 weeks, an additional 2 weeks of therapy may be tried.

When naproxen is used in combination with lansoprazole (15 mg once daily) for the symptomatic treatment of rheumatoid arthritis, osteoarthritis, or ankylosing spondylitis, the usual adult dosage of naproxen is 375 or 500 mg twice daily. One dose of naproxen is administered with the daily dose of lansoprazole in the morning before eating, and a second dose of naproxen is administered in the evening.

For *self-medication* to provide temporary relief of pain associated with arthritis, adults 65 years of age and younger can receive 200 mg of naproxen (220 mg of naproxen sodium) every 8–12 hours or 400 mg (440 mg of the sodium salt) initially and

200 mg (220 mg of the sodium salt) 12 hours later; dosage should not exceed 600 mg of naproxen (660 mg of naproxen sodium) daily for *self-medication* in these adults unless otherwise directed by a clinician. In older adults, dosage for *self-medication* should not exceed 200 mg of naproxen (220 mg of naproxen sodium) every 12 hours unless otherwise directed by a clinician. Such *self-medication* should not exceed 10 days unless otherwise directed.

Juvenile Arthritis.

For the symptomatic treatment of juvenile rheumatoid arthritis, the recommended dosage of naproxen is approximately 10 mg/kg daily given in 2 divided doses. Because naproxen and naproxen sodium tablets are not well suited for providing the calculated pediatric dosage of the drug, naproxen oral suspension preferably should be used in this age group. (See Cautions: Pediatric Precautions.)

Other Inflammatory Conditions.

For the symptomatic treatment of acute gouty arthritis, the usual adult dosage of naproxen is 750 mg (825 mg of naproxen sodium) initially followed by 250 mg (275 mg of naproxen sodium) every 8 hours; therapy is continued until the attack subsides. Alternatively, in the management of acute gout, an initial dosage of 1–1.5 g of naproxen (using extended-release naproxen sodium tablets) may be used (as a single dose) on the first day, followed by 1 g given once daily until the attack subsides. The manufacturer states that delayed-release (enteric-coated) naproxen tablets are not recommended for treatment of acute gout because of the delayed absorption of the drug from this preparation. Relief of pain and tenderness and decreases in heat and swelling have been reported to occur within 24–48 hours.

For the relief of tendinitis or bursitis, the usual initial adult dose of naproxen is 500 mg (550 mg of naproxen sodium), followed by 500 mg (550 mg of the sodium salt) every 12 hours or 250 mg (275 mg of the sodium salt) every 6–8 hours as necessary. Total initial daily dose should not exceed 1.25 g of naproxen (1.375 g of naproxen sodium). Alternatively, the usual adult oral dosage of naproxen from extended-release tablets is 1 g (1.1 g of naproxen sodium) administered once daily. If adequate response does not occur, dosage of the extended-release tablets may be increased to 1.5 g of naproxen daily; however, such dosages should be used for a limited period only. Thereafter, the total daily dose should not exceed 1 g of naproxen (1.1 g of naproxen sodium).

Pain and Dysmenorrhea

For relief of mild to moderate pain or dysmenorrhea, the usual initial adult dose of naproxen is 500 mg (550 mg of naproxen sodium), followed by 500 mg (550 mg of the sodium salt) every 12 hours or 250 mg (275 mg of the sodium salt) every 6–8 hours as necessary. Total initial daily dose should not exceed 1.25 g of naproxen (1.375 g of naproxen sodium). Alternatively, the usual adult oral dosage of naproxen from extended-release tablets is 1 g (1.1 g of naproxen sodium) administered once daily. If adequate response does not occur, dosage of the extended-release tablets may be increased to 1.5 g of naproxen daily; however, such dosages should be used for a limited period only. Thereafter, the total daily dose should not exceed 1 g of naproxen (1.1 g of naproxen sodium).

Alternatively, for *self-medication* of these conditions in adults 65 years of age and younger, a naproxen dosage of 200 mg (220 mg of naproxen sodium) every 8–12 hours can be used. Some patients may experience greater relief with an initial dose of 400 mg (440 mg of the sodium salt) and then 200 mg (220 mg of the sodium salt) 12 hours later. Regardless of the regimen employed, dosage for *self-medication* should not exceed 600 mg of naproxen (660 mg of naproxen sodium) daily unless otherwise directed by a clinician. For adults older than 65 years of age, dosage for *self-medication* should not exceed 200 mg (220 mg of the sodium salt) every 12 hours unless otherwise directed by a clinician. *Self-medication* of pain should not exceed 10 days unless otherwise directed.

Fever

For *self-medication* of fever, the usual dosage recommended for *self-medication* of pain can be used. (See Dosage: Pain and Dysmenorrhea, in Dosage and Administration.) Antipyretic therapy with naproxen sodium should not exceed 3 days for *self-medication* unless otherwise directed by a clinician.

Cautions

■ Cardiovascular Effects

Peripheral edema has occurred in patients receiving naproxen; congestive heart failure, palpitations, vasculitis, tachycardia, and dyspnea have occurred less frequently. Increases in blood pressure have been reported in patients receiving naproxen. Long-term use may be associated with an increased risk of cardiovascular and cerebrovascular events.

The association between cardiovascular complications and use of nonsteroidal anti-inflammatory agents (NSAIA), including selective cyclooxygenase-2 (COX-2) inhibitors and prototypical NSAIA, is an area of ongoing concern and study. Selective COX-2 inhibitors have been associated with increased risk of cardiovascular events in certain situations. Several prototypical NSAIA also have been associated with an increased risk of cardiovascular events. Data from some long-term controlled studies that have included both a prototypical NSAIA and a COX-2 inhibitor have not clearly demonstrated that the risk of serious adverse cardiovascular events is greater with use of a COX-2 inhibitor than with use of a prototypical NSAIA. Findings from a recent systematic review of controlled observational studies and a meta-analysis of published and unpublished data from randomized studies of these agents suggest that use of celecoxib (dosage exceeding 200 mg daily), diclofenac, or indomethacin is associated

with an increased risk of cardiovascular events. The possibility exists that meloxicam and ibuprofen also are associated with increased cardiovascular risk. Naproxen does not appear to be associated with increased or decreased cardiovascular risk. Data were insufficient to assess risk associated with use of other prototypical NSAIDs. (See Cautions: Cardiovascular Effects, in Celecoxib 28:08.04.08.)

Short-term use of NSAIDs to relieve acute pain, especially at low dosages, does not appear to be associated with an increased risk of serious cardiovascular events (except immediately following coronary artery bypass graft [CABG] surgery). Therefore, in early 2005, the US Food and Drug Administration (FDA) concluded that preparations of NSAIDs (including naproxen) that currently were available without a prescription had a favorable benefit-to-risk ratio when used according to labeled instructions, and determined that these preparations should remain available without a prescription despite the addition of a boxed warning to the professional labeling of prescription-only preparations of these drugs.

There is no consistent evidence that use of low-dose aspirin mitigates the increased risk of serious cardiovascular events associated with NSAIDs.

■ GI Effects

Adverse reactions to naproxen mainly involve the GI tract. Constipation, heartburn, abdominal pain, and nausea occur in about 3–9% of patients receiving the drug. Less frequently, dyspepsia, diarrhea, stomatitis, vomiting, anorexia, colitis, peptic ulcer, GI bleeding/perforation, hematemesis, and flatulence occur. In patients with rheumatoid arthritis, adverse GI effects appear to be more frequent and more severe at a naproxen dosage of 1.5 g (1.65 g of naproxen sodium) daily than at 750 mg (825 mg of naproxen sodium) daily. The frequency of adverse GI effects in children appears to be similar to that in adults. Adverse GI effects may be minimized by administering naproxen with meals, milk, or an aluminum and magnesium hydroxides antacid.

Naproxen may reactivate latent peptic ulcer and may cause peptic ulcers in patients with no previous history of ulcers. Hemorrhage and perforation of ulcers may occur, occasionally causing fatalities. Hematemesis, GI bleeding without obvious ulcer formation, and melena also have occurred. Prodromal symptoms do not always precede GI bleeding. Ulcerative stomatitis, esophagitis, and nonpeptic GI ulceration have been reported during postmarketing experience. Although a causal relationship has not been directly determined, one case-control analysis suggests that NSAIDs may contribute to the formation of esophageal stricture in patients with gastroesophageal reflux.

The risk of GI bleeding is increased in geriatric patients older than 60 years of age and in patients with a history of GI ulcers or bleeding, those receiving an anticoagulant or taking multiple NSAIDs concomitantly, those consuming 3 or more alcohol-containing beverages daily, and those receiving prolonged therapy.

Clinical studies of conventional versus delayed-release (enteric-coated) naproxen tablets demonstrated similar prevalence of minor GI complaints; however, individual patients may prefer one formulation over the other. In a dosage of 500 mg daily, naproxen has been reported to produce fewer adverse GI effects than 3.6–4.8 g of aspirin daily. In one study, a single dose of 550 mg of naproxen sodium produced fewer adverse GI effects than a single dose of 650 mg of aspirin. It is not known whether naproxen causes less peptic ulceration than does aspirin. In one study, the amount of GI bleeding as determined by fecal blood loss and gastroscopic evaluation in healthy adults was reported to be less with 1 g of naproxen or 1.1 g of naproxen sodium daily than with 3.25 g of aspirin daily. In another study in patients with rheumatoid arthritis, fecal blood loss following 750 mg of naproxen daily was less than that following 3.6 g of aspirin daily and no different than that during the control period. The frequency of adverse GI effects in patients receiving 500 mg of naproxen or 550 mg of naproxen sodium daily is reportedly similar to that in patients receiving 1.2 g of ibuprofen daily and less than that in patients receiving 100 mg of indomethacin daily or 2.4 g of fenoprofen daily.

Serious adverse GI effects (e.g., bleeding, ulceration, perforation) can occur at any time in patients receiving NSAID therapy, and such effects may *not* be preceded by warning signs or symptoms. Only 1 in 5 patients who develop a serious upper GI adverse event while receiving an NSAID is symptomatic. Therefore, clinicians should remain alert to the possible development of serious GI effects (e.g., bleeding, ulceration) in any patient receiving NSAID therapy, and such patients should be followed chronically for the development of manifestations of such effects and advised of the importance of this follow-up. In addition, patients should be advised about the signs and symptoms of serious NSAID-induced GI toxicity and what action to take if they occur. If signs and symptoms of a serious GI event develop, additional evaluation and treatment should be initiated promptly; the NSAID should be discontinued until appropriate diagnostic studies have ruled out a serious GI event.

Results of studies to date are inconclusive concerning the relative risk of various prototypical NSAIDs in causing serious GI effects. In patients receiving NSAIDs and observed in clinical studies of several months' to 2 years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appeared to occur in approximately 1% of patients treated for 3–6 months and in about 2–4% of those treated for 1 year. Longer duration of therapy with an NSAID increases the likelihood of a serious GI event. However, short-term therapy is not without risk. High dosages of any NSAID probably are associated with increased risk of such effects, although controlled studies documenting this probable association are lacking for most NSAIDs. Therefore, whenever use of relatively high dosages (within the recommended dosage range) is considered, sufficient benefit to offset the potential increased risk of GI toxicity should be anticipated.

Studies have shown that patients with a history of peptic ulcer disease and/or GI bleeding who are receiving NSAIDs have a substantially higher risk of developing

GI bleeding than patients without these risk factors. In addition to a history of ulcer disease, pharmacoepidemiologic studies have identified several comorbid conditions and concomitant therapies that may increase the risk for GI bleeding, including concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status. Patients with rheumatoid arthritis are more likely to experience serious GI complications from NSAID therapy than are patients with osteoarthritis. In addition, geriatric or debilitated patients appear to tolerate GI ulceration and bleeding less well than other individuals, and most spontaneous reports of fatal GI effects have been in such patients.

For patients at high risk for complications from NSAID-induced GI ulceration (e.g., bleeding, perforation), concomitant use of misoprostol can be considered for preventive therapy (See Misoprostol 56:28.28.) Alternatively, some clinicians suggest that a proton-pump inhibitor (e.g., lansoprazole, omeprazole) may be used concomitantly to decrease the incidence of serious GI toxicity associated with NSAID therapy. (See Lansoprazole 56:28.36.) In one study, therapy with high dosages of famotidine (40 mg twice daily) was more effective than placebo in preventing peptic ulcers in NSAID-treated patients; however, the effect of the drug was modest. In addition, efficacy of usual dosages of H₂-receptor antagonists for the prevention of NSAID-induced gastric and duodenal ulcers has not been established. Therefore, most clinicians do not recommend use of H₂-receptor antagonists for the prevention of NSAID-associated ulcers. Another approach in high-risk patients who would benefit from NSAID therapy is use of an NSAID that is a selective inhibitor of cyclooxygenase-2 (COX-2) (e.g., celecoxib), since these agents are associated with a lower incidence of serious GI bleeding than are prototypical NSAIDs. However, while celecoxib (200 mg twice daily) was comparably effective to diclofenac sodium (75 mg twice daily) plus omeprazole (20 mg daily) in preventing recurrent ulcer bleeding (recurrent ulcer bleeding probabilities of 4.9 versus 6.4%, respectively, during the 6-month study) in *H. pylori*-negative arthritis (principally osteoarthritis) patients with a recent history of ulcer bleeding, the protective efficacy was unexpectedly low for both regimens and it appeared that neither could completely protect patients at high risk. Additional study is necessary to elucidate optimal therapy for preventing GI complications associated with NSAID therapy in high-risk patients.

■ Nervous System Effects

Adverse nervous system effects of naproxen include headache, drowsiness, and dizziness, which occur in about 3–9% of patients. Vertigo, lightheadedness, inability to concentrate, mental depression, nervousness, irritability, fatigue, malaise, insomnia, sleep disorders, dream abnormalities, and aseptic meningitis may also occur. Although a causal relationship to naproxen has not been definitely established, reversible peripheral neuropathy, cognitive dysfunction, and seizures have occurred rarely in patients receiving the drug. The frequency of adverse nervous system effects in children appears to be similar to that in adults.

■ Otic and Ocular Effects

Patients receiving naproxen have experienced tinnitus and, less frequently, other hearing or visual disturbances (e.g., hearing impairment). Corneal opacity, papillitis, papilledema, and retrobulbar optic neuritis have been reported during postmarketing experience.

■ Hematologic Effects

Adverse hematologic effects of naproxen include thrombocytopenia, leukopenia, granulocytopenia, and eosinophilia. Although a causal relationship to naproxen has not been established, agranulocytosis, aplastic anemia, and hemolytic anemia have occurred in patients receiving the drug. Naproxen can inhibit platelet aggregation and may prolong bleeding time. The frequency of prolonged bleeding time may be greater in children than in adults.

■ Renal and Electrolyte Effects

Renal disease, glomerulonephritis, interstitial nephritis, nephrotic syndrome, renal failure, renal papillary necrosis, dysuria, and hyperkalemia have been reported in patients receiving naproxen. Abnormal laboratory findings include hematuria and asymptomatic increases in BUN and serum creatinine. In one patient who developed increased serum creatinine concentration and decreased creatinine clearance during naproxen therapy, these measurements returned to pretreatment values following discontinuance of the drug and remained within normal limits after sulindac therapy was started. Chronic high doses of naproxen have caused nephritis and cortical and papillary necrosis in animals.

■ Hepatic Effects

Jaundice (including cholestatic jaundice which cleared promptly when naproxen was discontinued) and fatal hepatitis have been reported rarely in patients receiving the drug. Abnormal liver function test results, including mild and generally transient increases in serum alkaline phosphatase, have occurred in some patients.

Borderline elevations of one or more liver function test results may occur in up to 15% of patients treated with NSAIDs; meaningful (3 times the upper limit of normal) elevations of serum ALT (SGPT) or AST (SGOT) concentration have occurred in less than 1% of patients receiving NSAIDs in controlled clinical studies. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Naproxen or naproxen sodium should be discontinued if signs or symptoms of a severe hepatic reaction occur. (See Cautions: Precautions and Contraindications.)

■ Dermatologic Effects

Pruritus, skin eruptions or rashes, and ecchymoses occur frequently during naproxen administration. Sweating, photosensitive dermatitis, photosensitivity reactions

resembling porphyria cutanea tarda and epidermolysis bullosa, and purpura have also occurred occasionally. The frequency of rash may be greater in children than in adults. Toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome, urticaria, alopecia, erythema nodosum, fixed drug eruption, lichen planus, and pustular reaction have been reported during postmarketing experience.

■ Other Adverse Effects

Thirst, myalgia, muscle weakness and cramps, pyrexia, sore throat, eosinophilic pneumonitis or colitis, anaphylactoid reactions, pancreatitis, and menstrual disturbances also have been reported during naproxen therapy. Hypoglycemia, hyperglycemia, angioedema, systemic lupus erythematosus, vasculitis, asthma, pulmonary edema, and female infertility have been reported during postmarketing experience. In a patient receiving naproxen in combination with aspirin, infective symptoms associated with an empyema appeared to be suppressed.

■ Precautions and Contraindications

With the exception of precautions related to the sodium content of naproxen sodium, the cautions associated with naproxen sodium use are the same as those for naproxen use. Each 220-, 275-, 412.5, or 550-mg naproxen sodium tablet contains about 0.87, 1, 1.5, or 2 mEq of sodium, respectively, and each mL of the commercially available naproxen suspension contains about 0.3 mEq of sodium; this should be considered in patients whose sodium intake must be restricted. Multiple naproxen-containing preparations (e.g., naproxen conventional and delayed-release [enteric-coated] tablets, naproxen suspension, naproxen sodium conventional and extended-release tablets) should not be used concomitantly, as all of these products circulate in the plasma as naproxen anion and may result in naproxen toxicity.

Patients should be advised that naproxen, like other NSAIDs, is not free of potential adverse effects, including some that can cause discomfort, and that, rarely, more serious effects (e.g., myocardial infarction, stroke, GI bleeding), which may require hospitalization and may even be fatal, can occur. Patients also should be informed that, while NSAIDs may be commonly employed for conditions that are less serious, NSAID therapy often is considered essential for the management of some diseases (e.g., rheumatoid arthritis), and the drugs have a major role in the management of pain. Clinicians may wish to discuss with their patients the potential risks and likely benefits of NSAID therapy, particularly when consideration is being given to use of these drugs in less serious conditions for which therapy without an NSAID may represent an acceptable alternative to both the patient and clinician.

Patients should be advised to read the medication guide for NSAIDs that is provided to the patient each time the drug is dispensed.

NSAIDs (i.e., certain prototypical NSAIDs, selective COX-2 inhibitors) may increase the risk of serious adverse cardiovascular thrombotic events. (See Cautions: Cardiovascular Effects.) Patients with known cardiovascular disease or risk factors for cardiovascular disease may be at increased risk for NSAID-associated cardiovascular events. To minimize the potential risk of adverse cardiovascular events, the lowest effective dosage and shortest possible duration of therapy should be employed. Clinicians and patients receiving NSAIDs (including those without previous symptoms of cardiovascular disease) should remain alert to the possible development of cardiovascular events. Patients should be informed about the signs and symptoms of serious cardiovascular toxicity (chest pain, dyspnea, weakness, slurring of speech) and instructed on action to take should such toxicity occur.

There is no consistent evidence that concomitant use of low-dose aspirin mitigates the increased risk of serious cardiovascular events associated with NSAIDs. Concomitant use of aspirin and an NSAID increases the risk for serious GI events. Because of the potential for increased adverse effects, patients receiving an NSAID should be advised not to take aspirin.

Use of NSAIDs can result in the onset of hypertension or worsening of preexisting hypertension; either of these occurrences may contribute to the increased incidence of cardiovascular events. Patients receiving NSAIDs and diuretics (i.e., thiazide or loop diuretics) may have an impaired response to the diuretic. NSAIDs should be used with caution in patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID therapy and throughout therapy.

NSAIDs should be used with caution in patients with fluid retention or heart failure, since fluid retention and edema have been observed in some patients receiving these drugs.

The risk of potentially serious adverse GI effects should be considered in patients receiving naproxen, particularly in patients receiving chronic therapy with the drug. (See Cautions: GI Effects.) Naproxen should be used with caution and under close supervision in patients with a history of GI disease. Since peptic ulceration and/or GI bleeding have been reported in patients receiving the drug, patients should be advised to promptly report signs or symptoms of GI ulceration or bleeding to their clinician.

Naproxen should be used with extreme caution and under close supervision in patients with a history of GI bleeding or peptic ulceration, and such patients should receive an appropriate ulcer preventive regimen. All patients considered at increased risk of potentially serious adverse GI effects (e.g., geriatric patients, those receiving high therapeutic dosages of NSAIDs, those with a history of peptic ulcer disease, those receiving anticoagulants or corticosteroids concomitantly) should be monitored closely for signs and symptoms of ulcer perforation or GI bleeding. To minimize the potential risk of adverse GI effects, the lowest effective dosage and shortest possible duration of therapy should be employed. For patients who are at high risk, therapy other than an NSAID should be considered.

Elevations in serum ALT may be the most sensitive indicator of NSAID-induced liver dysfunction. Patients who experience signs and/or symptoms suggestive of liver dysfunction or an abnormal liver function test result while receiving naproxen should be evaluated for evidence of the development of a severe hepatic reaction. Severe reactions, including jaundice and/or fatal hepatitis, have occurred during therapy with naproxen. Although such reactions are rare, naproxen should be discontinued if abnormal liver function test results persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash).

Since naproxen can inhibit platelet aggregation, patients who may be adversely affected by a prolongation of bleeding time should be carefully observed during naproxen therapy. If signs and/or symptoms of anemia occur during therapy with naproxen, hemoglobin concentration and hematocrit should be determined.

Because renal prostaglandins may have a supportive role in maintaining renal perfusion in patients with prerenal conditions, administration of an NSAID to such patients may cause a dose-dependent reduction in prostaglandin formation and thereby precipitate overt renal decompensation. Patients at greatest risk of this reaction include those with impaired renal function, heart failure, or hepatic dysfunction; those with extracellular fluid depletion (e.g., patients receiving diuretics); those taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor antagonist concomitantly; and geriatric patients. Patients should be advised to consult their clinician promptly if unexplained weight gain or edema occurs. Recovery of renal function to pretreatment levels usually occurs following discontinuance of NSAID therapy. Some clinicians recommend that renal function be monitored periodically in patients receiving long-term NSAID therapy.

Naproxen has not been evaluated in patients with renal impairment, and the manufacturer states that use of the drug is not recommended in patients with moderate to severe renal impairment (creatinine clearance less than 30 mL/minute). If NSAIDs are used in patients with advanced renal disease, close monitoring is recommended.

Lower dosages of naproxen should be considered in patients with renal or hepatic impairment and in geriatric patients.

Anaphylactoid reactions have been reported in patients receiving naproxen. Patients receiving naproxen should be informed of the signs and symptoms of an anaphylactoid reaction (e.g., difficulty breathing, swelling of the face or throat) and advised to seek immediate medical attention if an anaphylactoid reaction develops.

Serious skin reactions (e.g., exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis) can occur in patients receiving NSAIDs. These serious skin reactions may occur without warning; patients should be advised to consult their clinician if skin rash and blisters, fever, or other signs of hypersensitivity reaction (e.g., pruritus) occur. NSAIDs should be discontinued at the first appearance of rash or any other sign of hypersensitivity.

Patients receiving long-term NSAID therapy should have a complete blood cell count and chemistry profile performed periodically.

Patients receiving naproxen for self-medication should be advised to use the lowest effective dosage and not to exceed the recommended dosage or duration of therapy. Unless otherwise directed by a clinician, patients receiving naproxen for *self-medication* should be advised to discontinue the drug and consult a clinician if pain persists for more than 10 days or fever persists for longer than 3 days. Patients should not use naproxen for *self-medication* immediately before or after cardiac surgery or if they have experienced an allergic reaction to any analgesic or antipyretic. Patients receiving the drug for *self-medication* also should be advised to consult a clinician before initiating naproxen if they have experienced adverse effects associated with any analgesic or antipyretic; if they have a GI disorder, coagulation disorder, hypertension, cardiac disease, or renal disease; if they are receiving therapy with a diuretic; or if they are 60 years of age or older. Patients receiving the drug for *self-medication* should consult a clinician or pharmacist before initiating naproxen if they are under a clinician's care for any continuing serious medical condition; they are receiving an anticoagulant, a corticosteroid, or any other NSAID-containing preparation; or they are taking any other drugs on a regular basis. They also should be advised to stop taking the drug and to report to their clinician symptoms of GI bleeding (faintness, vomiting blood, bloody or black stools); any new, unusual, or unexpected symptoms that occur during *self-medication* with the drug; if pain or fever gets worse during therapy; or if stomach pain intensifies or persists with use of the drug. Patients should be advised that the risk of GI bleeding is increased if they are 60 years of age or older, have a GI disorder (e.g., history of GI bleeding or peptic ulceration), are receiving an anticoagulant or corticosteroid, are receiving another NSAID (including aspirin) concomitantly, if they generally consume 3 or more alcohol-containing drinks per day, or if they exceed the recommended dosage or duration of naproxen therapy. In addition, patients should be advised that taking naproxen for longer than 10 days or exceeding the recommended dosage may increase the risk of a cardiovascular event.

The possibility exists that naproxen can interfere with the antiplatelet effect of low-dose aspirin. (See Drug Interactions: Nonsteroidal Anti-inflammatory Agents.)

Patients should be warned that naproxen may impair their ability to perform activities requiring mental alertness or physical coordination (e.g., operating machinery, driving a motor vehicle).

Because NSAIDs have caused adverse ocular effects, patients who experience visual disturbances or changes during naproxen therapy should have an ophthalmologic examination.

Naproxen is not a substitute for corticosteroids. If corticosteroid dosage is decreased during naproxen therapy, it should be done gradually and patients should be observed

for adverse effects, including adrenocortical insufficiency or symptomatic exacerbation of the inflammatory condition being treated.

The possibility that the antipyretic and anti-inflammatory effects of NSAIDs may mask the usual signs and symptoms of infection or other diseases should be considered.

Naproxen is contraindicated in patients with known hypersensitivity to the drug. In addition, NSAIDs, including naproxen, generally are contraindicated in patients in whom asthma, urticaria, or other sensitivity reactions are precipitated by aspirin or other NSAIDs, since there is potential for cross-sensitivity between NSAIDs and aspirin, and severe, rarely fatal, anaphylactic reactions to NSAIDs have been reported in these patients. Although NSAIDs generally are contraindicated in these patients, the drugs have occasionally been used in NSAID-sensitive patients who have undergone desensitization. Because patients with asthma may have aspirin-sensitivity asthma, naproxen should be used with caution in patients with asthma. In patients with asthma, aspirin sensitivity is manifested principally as bronchospasm and usually is associated with nasal polyps; the association of aspirin sensitivity, asthma, and nasal polyps is known as the aspirin triad. Patients who are considering use of naproxen for *self-medication* should be advised that naproxen is contraindicated in patients who have experienced asthma, urticaria, or other sensitivity reaction to other analgesics or antipyretics. For a further discussion of cross-sensitivity of NSAIDs, see Cautions: Sensitivity Reactions, in the Salicylates General Statement 28:08.04.24.

NSAIDs are contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.

■ Pediatric Precautions

Safety and efficacy of naproxen in children younger than 2 years of age have not been established. Pediatric dosage recommendations for juvenile rheumatoid arthritis are based on well-controlled studies. There are no adequate efficacy or dose-response data for other pediatric conditions, but clinical experience in juvenile rheumatoid arthritis and other use experience indicate that single doses of 2.5–5 mg/kg with a total daily dose not exceeding 15 mg/kg are safe in children older than 2 years of age. The manufacturers of delayed-release naproxen tablets and extended-release naproxen sodium tablets state that studies using such tablets in pediatric patients have not been performed and therefore, the safety of these formulations in children has not been established. Naproxen sodium should not be used for *self-medication* in children younger than 12 years of age unless otherwise directed by a clinician.

Overdosage and toxicity (including death) have been reported in children younger than 2 years of age receiving nonprescription (over-the-counter, OTC) preparations containing antihistamines, cough suppressants, expectorants, and nasal decongestants alone or in combination for relief of symptoms of upper respiratory tract infection. Such preparations also may contain analgesics and antipyretics (e.g., naproxen). There is limited evidence of efficacy for these preparations in this age group, and appropriate dosages (i.e., approved by the US Food and Drug Administration [FDA]) have not been established. Therefore, FDA stated that nonprescription cough and cold preparations should not be used in children younger than 2 years of age; the agency continues to assess safety and efficacy of these preparations in older children. Meanwhile, because children 2–3 years of age also are at increased risk of overdosage and toxicity, some manufacturers of oral nonprescription cough and cold preparations recently have agreed to voluntarily revise the product labeling to state that such preparations should not be used in children younger than 4 years of age. Because FDA does not typically request removal of products with previous labeling from pharmacy shelves during a voluntary label change, some preparations will have the new recommendation (“do not use in children younger than 4 years of age”), while others will have the previous recommendation (“do not use in children younger than 2 years of age”). FDA recommends that parents and caregivers adhere to the dosage instructions and warnings on the product labeling that accompanies the preparation if administering to children and consult with their clinician about any concerns. Clinicians should ask caregivers about use of nonprescription cough and cold preparations to avoid overdosage. For additional information on precautions associated with the use of cough and cold preparations in pediatric patients, see Cautions: Pediatric Precautions in Pseudoephedrine 12:12.12.

■ Geriatric Precautions

Although the total plasma concentrations of naproxen in geriatric patients are similar to those attained in younger adults, the unbound plasma fraction of the drug is increased in geriatric patients when compared with that in younger adults. Therefore, consideration should be given for reduced dosage of naproxen or naproxen sodium in geriatric patients, and the lowest possible effective dose should be used. Naproxen and naproxen sodium should be used with caution in geriatric patients when high dosages are required and some adjustment of dosage may be needed. Geriatric individuals appear to tolerate GI ulceration and bleeding less well than other individuals, and many of the spontaneous reports of fatal adverse GI effects in patients receiving NSAIDs involve geriatric individuals. Naproxen is eliminated substantially by the kidneys, and individuals with renal impairment may be at increased risk of toxic reactions to the drug. Because geriatric patients frequently have decreased renal function, particular attention should be paid to naproxen dosage, and it may be useful to monitor renal function in these patients.

■ Carcinogenicity

A 2-year study in rats was performed to evaluate the carcinogenic potential of naproxen at 8, 16, or 24 mg/kg daily (50, 100, or 150 mg/m², respectively); the maximum dose used was 0.28 times the human systemic exposure at the recommended dose. There was no evidence of carcinogenicity.

■ Pregnancy, Fertility, and Lactation

Pregnancy

Reproduction studies of naproxen in rats at 20 mg/kg daily (125 mg/m², 0.23 times the human systemic exposure), rabbits at 20 mg/kg daily (220 mg/m², 0.27 times the human systemic exposure), and mice at 170 mg/kg daily (510 mg/m², 0.28 times the human systemic exposure) have not revealed evidence of harm to the fetus. Naproxen inhibits prostaglandin synthesis which may result in prolongation of gestation and interference with labor if the drug is given late in pregnancy. Inhibitors of prostaglandin synthesis may have adverse effects on the fetal cardiovascular system (e.g., premature closure of the ductus arteriosus) and are associated with an increased risk of neonatal complications such as necrotizing enterocolitis or intracranial hemorrhage. Severe hypoxemia due to persistent pulmonary hypertension has occurred in infants whose mothers received naproxen to delay parturition. Neonatal death also has been reported when the drug was used to prevent preterm labor; autopsy of a neonate showed brain hemorrhage, multiple gastric ulcers, extensive GI bleeding, and an adverse cardiovascular effect known to be associated with use of NSAIDs. In addition, severe hyponatremia, water retention, cerebral irritation, and paralytic ileus was reported in a neonate whose mother ingested 5 g of naproxen 8 hours before delivery; it has been suggested that naproxen adversely affected renal function. Renal dysfunction and abnormal prostaglandin E concentrations in premature infants also have been reported. There are no adequate and controlled studies to date using naproxen in pregnant women. The drug should be used during the first and second trimesters of pregnancy only when the potential benefits justify the potential risks to the fetus; use of the drug in the third trimester should be avoided. Women who are pregnant or nursing should seek the advice of a health professional before using naproxen sodium for *self-medication*. It is especially important not to *self-administer* naproxen sodium during the last 3 months of pregnancy unless specifically directed to do so by a physician, because it may cause problems in the unborn child or complications during delivery.

Fertility

Reproduction studies of naproxen in rats at 20 mg/kg daily (125 mg/m², 0.23 times the human systemic exposure), rabbits at 20 mg/kg daily (220 mg/m², 0.27 times the human systemic exposure), and mice at 170 mg/kg daily (510 mg/m², 0.28 times the human systemic exposure) have not revealed evidence of impaired fertility. Information on the effects of naproxen on fertility in humans is lacking. At least one human case was reported in which ejaculatory dysfunction occurred during naproxen therapy and was reversed upon discontinuing the drug; a definite causal relationship was not established.

Lactation

Naproxen is distributed into milk. Because of the potential for adverse effects from naproxen or naproxen sodium in infants, use of the drug in nursing women should be avoided.

Drug Interactions

■ Protein-bound Drugs

Because naproxen is highly protein bound, it theoretically could be displaced from binding sites by, or it could displace from binding sites, other protein-bound drugs such as oral anticoagulants, hydantoins, other nonsteroidal anti-inflammatory agents (NSAIDs; including aspirin), sulfonamides, and sulfonylureas. Patients receiving naproxen with any of these drugs should be observed for adverse effects.

■ Angiotensin-converting Enzyme Inhibitors and Angiotensin II Receptor Antagonists

There is some evidence that concomitant use of NSAIDs with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists may reduce the blood pressure response to the antihypertensive agent.

■ Anticoagulants and Thrombolytic Agents

The effects of warfarin and NSAIDs on GI bleeding are synergistic. Concomitant use of naproxen and warfarin is associated with a higher risk of GI bleeding compared with use of either agent alone.

Administration of naproxen with warfarin results in a slight increase in free warfarin in serum, but does not affect the hypoprothrombinemic effect of warfarin. Naproxen should be used with caution in patients receiving any anticoagulant or thrombolytic agent (e.g., streptokinase).

■ Antidiabetic Agents

Results of a study in patients with diabetes mellitus showed no interference by naproxen on the effect of tolbutamide on plasma glucose concentrations.

■ Diuretics

NSAIDs can reduce the natriuretic effects of furosemide or thiazide diuretics. This effect may be related to inhibition of renal prostaglandin synthesis. Patients receiving concomitant NSAID and diuretic therapy should be monitored for signs of renal failure and efficacy of the diuretic.

■ Nonsteroidal Anti-inflammatory Agents

Concomitant use of aspirin and an NSAID increases the risk for serious GI events. Because of the potential for increased adverse effects, patients receiving naproxen should be advised not to take aspirin. There is no consistent evidence that use of low-

dose aspirin mitigates the increased risk of serious cardiovascular events associated with NSAIDs.

Administration of aspirin with naproxen may decrease protein binding of naproxen, but clearance of free (unbound) naproxen does not appear to be altered. The clinical importance of this pharmacokinetic interaction has not been established.

Ibuprofen can interfere with the antiplatelet effect of low-dose aspirin (81 mg daily; immediate-release preparation) when the drugs are administered concomitantly. The interaction can be minimized by appropriate timing of ibuprofen administration relative to that of immediate-release, low-dose aspirin. (See Drug Interactions: Nonsteroidal Anti-inflammatory Agents in Ibuprofen 28:08.04.92.) The US Food and Drug Administration (FDA) states that other NSAIDs that are used for *self-medication* (i.e., ketoprofen, naproxen) should be viewed as having the potential to interfere with the antiplatelet effect of low-dose aspirin unless data are available that indicate otherwise. In one study, concomitant administration of naproxen (500 mg) and low-dose aspirin (100 mg) interfered with the antiplatelet effect of aspirin.

■ Probenecid

Administration of probenecid with naproxen substantially increases the plasma half-life of naproxen and plasma naproxen concentrations. In one study, the plasma half-life of naproxen increased to an average of 37 hours and plasma naproxen concentrations increased by an average of 50% when the drugs were administered concomitantly. It was suggested that probenecid interfered with the plasma clearance of naproxen by inhibiting the formation of glucuronide conjugates of naproxen, as well as inhibiting its renal clearance.

■ Methotrexate

Severe, sometimes fatal, toxicity has occurred following administration of an NSAIA concomitantly with methotrexate (principally high-dose therapy) in patients with various malignant neoplasms or rheumatoid arthritis. The toxicity was associated with elevated and prolonged blood concentrations of methotrexate. The exact mechanism of the interaction remains to be established, but it has been suggested that NSAIDs may inhibit renal elimination of methotrexate, possibly by decreasing renal perfusion via inhibition of renal prostaglandin synthesis or by competing for renal elimination. Naproxen and methotrexate should be administered concomitantly with caution. (See Drug Interactions: Nonsteroidal Anti-inflammatory Agents, in Methotrexate 10:00.)

■ Lithium

Naproxen may increase serum lithium concentrations and reduce renal lithium clearance. If naproxen and lithium are administered concurrently, the patient should be observed closely for signs of lithium toxicity, and serum lithium concentrations should be monitored carefully during the initial stages of combined therapy or subsequent dosage adjustment. In addition, appropriate adjustment of lithium dosage may be required when therapy with naproxen is discontinued.

■ Drugs Affecting Gastric pH

Concomitant administration of naproxen and aluminum hydroxide or magnesium oxide antacids may result in delayed absorption of naproxen. Because delayed-release (enteric-coated) naproxen tablets are formulated to release the drug at relatively nonacidic pH (i.e., in the small intestine), concomitant use of this formulation with intensive antacid therapy or histamine H₂-receptor antagonists is not recommended.

In a controlled study in healthy adults, concomitant oral administration of naproxen and cimetidine did not appear to alter the pharmacokinetics of either drug and did not affect the inhibition of gastric acid output by cimetidine.

■ Cholestyramine

Concomitant administration of naproxen and cholestyramine may result in delayed absorption of naproxen.

■ Sucralfate

Concomitant administration of naproxen and sucralfate may result in delayed absorption of naproxen. Concomitant use of sucralfate with naproxen delayed-release tablets is not recommended.

■ Other Drugs

Naproxen should be used cautiously, if at all, with other drugs that might potentiate the adverse GI effects.

Naproxen may interfere with the antihypertensive effects of β -adrenergic blocking agents, including propranolol.

Laboratory Test Interferences

Naproxen or its metabolites may cause falsely elevated urinary 17-ketogenic steroid concentrations by interfering with the *m*-dinitrobenzene reagent used in the test. Although 17-hydroxycorticosteroid measurements (Porter-Silber method) are not significantly altered, withdrawal of naproxen for 72 hours before testing has been recommended.

Naproxen may also interfere with some urinary assays of 5-hydroxyindoleacetic acid (5-HIAA).

Acute Toxicity

Limited information is available on the acute toxicity of naproxen or naproxen sodium.

■ Pathogenesis

The acute dose of naproxen or naproxen sodium associated with life-threatening toxicity in humans is not known. The oral LD₅₀ of naproxen is 4110, 1234, more than 1000, and 543 mg/kg in hamsters, mice, dogs, and rats, respectively.

■ Manifestations

There have been several cases of naproxen overdose in children which have resulted in acute toxicity. Acute renal failure and hyperkalemia were reported in a 2-year-old child with juvenile arthritis who received a naproxen sodium dosage of 20 mg/kg daily for 1 month. Death occurred in an 8-month-old child following administration of 110–440 mg of naproxen sodium for 5 days for fever and upper respiratory infection. A 2-year-old child recovered after ingesting up to 2 g of naproxen, hydrogen peroxide, and eucalyptus oil and who developed drowsiness, ataxia, and prolonged bleeding time. Another 2-year-old child developed dyspepsia after ingesting 625 mg of naproxen. In addition, seizures were reported in a 5-year-old child who ingested an unknown amount of naproxen sodium.

Most cases of naproxen overdose have been reported in adults. Adverse GI effects (e.g., heartburn, vomiting) and seizures usually occur in these patients; drowsiness and prolongation of clotting time also may occur. The incidence of adverse effects in adults may differ from those in children since rash and prolonged bleeding time appear to occur more frequently in children while other reactions occur more frequently in adults; the incidence of adverse GI and CNS effects are similar.

One patient who ingested 25 g of naproxen experienced mild nausea and indigestion. Life-threatening adverse effects are uncommon; however, seizures, apnea, metabolic acidosis, and impaired renal function have been reported following overdose of naproxen. One death due to CNS depression has been attributed to naproxen overdose.

■ Treatment

In acute naproxen overdose, general measures should include immediately emptying the stomach by inducing emesis or by gastric lavage, followed by initiation of supportive and symptomatic treatment. If the patient is comatose, having seizures, or lacks the gag reflex, gastric lavage may be performed if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents. Hemodialysis appears to be of no value in enhancing elimination of naproxen.

Pharmacology

Naproxen has pharmacologic actions similar to those of other prototypical NSAIDs. The drug exhibits anti-inflammatory, analgesic, and antipyretic activity. The exact mechanisms have not been clearly established, but many of the actions appear to be associated principally with the inhibition of prostaglandin synthesis. Naproxen inhibits the synthesis of prostaglandins in body tissues by inhibiting cyclooxygenase; at least 2 isoenzymes, cyclooxygenase-1 (COX-1) and -2 (COX-2) (also referred to as prostaglandin G/H synthase-1 [PGHS-1] and -2 [PGHS-2], respectively), have been identified that catalyze the formation of prostaglandins in the arachidonic acid pathway. Naproxen, like other prototypical NSAIDs, inhibits both COX-1 and COX-2. Although the exact mechanisms have not been clearly established, NSAIDs appear to exert anti-inflammatory, analgesic, and antipyretic activity principally through inhibition of the COX-2 isoenzyme; COX-1 inhibition presumably is responsible for the drugs' unwanted effects on GI mucosa and platelet aggregation.

■ Anti-inflammatory, Analgesic, and Antipyretic Effects

The anti-inflammatory, analgesic, and antipyretic effects of naproxen and other NSAIDs, including selective inhibitors of COX-2 (e.g., celecoxib, rofecoxib), appear to result from inhibition of prostaglandin synthesis. While the precise mechanism of the anti-inflammatory and analgesic effects of NSAIDs continues to be investigated, these effects appear to be mediated principally through inhibition of the COX-2 isoenzyme at sites of inflammation with subsequent reduction in the synthesis of certain prostaglandins from their arachidonic acid precursors.

Naproxen stabilizes lysosomal membranes and inhibits the response of neutrophils to chemotactic stimuli. The drug does not possess glucocorticoid or adrenocorticoid-stimulating properties.

There is no evidence that long-term therapy with naproxen results in tolerance to or physical dependence on the drug. The drug probably cannot suppress the abstinence syndrome in opiate-dependent patients.

Naproxen lowers body temperature in patients with fever. Although the mechanism of the antipyretic effect of NSAIDs is not known, it has been suggested that suppression of prostaglandin synthesis in the CNS (probably in the hypothalamus) may be involved.

■ Genitourinary and Renal Effects

Naproxen-induced inhibition of prostaglandin synthesis may result in decreased frequency and intensity of uterine contractility. Prostaglandins E₂ and F_{2 α} increase the amplitude and frequency of uterine contractions in pregnant women; current evidence suggests that primary dysmenorrhea is also mediated by these prostaglandins. Whether the increased production of prostaglandins associated with primary dysmenorrhea is mediated by COX-1 or COX-2 remains to be determined. Blood concentrations of a metabolite of prostaglandin F_{2 α} have been found to decrease in women with dysmenorrhea who were receiving naproxen. Therapy with naproxen has been effective in relieving menstrual pain and has reduced blood loss in women with menorrhagia, probably by inhibiting the formation of these prostaglandins. Administration of naproxen during late pregnancy may prolong gestation by inhibiting uterine contractions.

Naproxen has been reported to adversely affect renal function. (See Cautions: Renal Effects.) The mechanisms of adverse renal effects of naproxen have not been determined, but may involve inhibition of renal synthesis of prostaglandins.

Naproxen does not appear to have uricosuric activity.

■ GI Effects

Naproxen can cause gastric mucosal damage which may result in ulceration and/or bleeding. (See Cautions: GI Effects.) These gastric effects have been attributed to inhibition of the synthesis of prostaglandins produced by COX-1. Other factors possibly involved in NSAIA-induced gastropathy include local irritation, promotion of acid back-diffusion into gastric mucosa, uncoupling of oxidative phosphorylation, and enterohepatic recirculation of the drugs.

Epidemiologic and laboratory studies suggest that NSAIA may reduce the risk of colon cancer. Although the exact mechanism by which NSAIA may inhibit colon carcinogenesis remains to be determined, it has been suggested that inhibition of prostaglandin synthesis may be involved.

■ Hematologic Effects

Although naproxen can inhibit platelet aggregation and may prolong bleeding time, it does not affect prothrombin or whole blood clotting time. (See Cautions: Hematologic Effects.) In one study, the drug inhibited the second phase of platelet aggregation induced by adenosine diphosphate or epinephrine. Like aspirin and other prototypical NSAIA, the effects of naproxen on platelets appear to be associated with the inhibition of the synthesis of prostaglandins produced by COX-1.

Pharmacokinetics

Naproxen pharmacokinetics have not been determined in individuals with renal or hepatic impairment, nor in children younger than 5 years of age. Pharmacokinetics of the drug in the delayed-release (enteric-coated) formulation have not been determined in individuals younger than 18 years of age.

■ Absorption

Preparations of naproxen differ in their pattern of absorption, owing to the chemical form of naproxen (i.e., the base or sodium salt) and the formulation used. When administered as the acid or the sodium salt, naproxen is completely absorbed from the GI tract; the sodium salt is absorbed more rapidly than the acid. Oral bioavailability of naproxen is 95%. There appears to be no difference in bioavailability between a single 500-mg conventional tablet and two 250-mg conventional tablets of naproxen. Commercially available formulations of naproxen (i.e., conventional tablets, delayed-release tablets, oral suspension) are bioequivalent in terms of extent of absorption (i.e., area under the curve) and peak plasma concentrations; however, the rate of absorption varies depending on the formulation used. When naproxen (either as conventional or delayed-release tablets) or naproxen sodium (either as conventional or extended-release tablets) is taken with food, the rate but not the extent of absorption of the drug is decreased. Studies to date indicate that antacids may have variable, but probably clinically insignificant, effects on absorption of naproxen (either as conventional or delayed-release tablets) or naproxen sodium.

The manufacturers state that peak plasma concentrations of the drug occur in 2–4 hours following oral administration of naproxen as conventional tablets; peak plasma concentration occurs 1–4 hours following administration of the oral suspension. In several studies, following oral administration of a single 500-mg dose of naproxen (as one 500-mg or two 250-mg conventional tablets) to fasting, healthy adults, mean peak plasma concentrations of the drug ranged from 62–96 mcg/mL and occurred at 1.5–2 hours. The manufacturers state that peak plasma concentrations of the drug occur in 1–2 hours following oral administration of naproxen sodium as conventional tablets. Following oral administration of a single 550-mg dose of naproxen sodium as a conventional tablet (equivalent to 500 mg of naproxen) to a group of fasting, healthy adults, mean peak plasma concentrations of the drug were 70 mcg/mL and occurred at about 1 hour. In children 5–16 years of age, plasma naproxen concentrations following a single 5- to 10-mg/kg dose of the suspension are similar to those attained in healthy adults following a 500-mg dose. Steady-state plasma concentrations of naproxen are achieved within 4–5 days.

Commercially available delayed-release (enteric-coated) tablets of naproxen (EC-Naprosyn[®]) contain the drug within a copolymer coating dispersion. Dissolution of the coating is pH-dependent, with the most rapid dissolution occurring at pH above 6; no dissolution occurs below pH 4. The coating is designed to release the drug in the higher pH environment of the small intestine, avoiding dissolution in the more acidic environment of the stomach. Naproxen is well-absorbed from the enteric-coated formulation. Peak plasma concentration usually is reached about 4–6 (range: 2–12) hours following oral administration of the first dose of the enteric-coated formulation. A crossover study of oral administration of naproxen as conventional or delayed-release tablets in a dosage of 500 mg twice daily in fasted, healthy individuals demonstrated that after one week, only time to peak plasma concentration differed between the two formulations (1.9 versus 4 hours for conventional versus delayed-release tablets, respectively); there were no differences in peak plasma concentration or extent of absorption (i.e., area under the curve).

Commercially available extended-release tablets of naproxen sodium (Naprelan[®]) contain an immediate-release component (about 30% of the total dose) and an extended-release component comprised of microparticles that slowly release the drug. The tablet matrix rapidly disintegrates in the stomach, and the microparticles are dispersed

throughout the small intestine and into the proximal large intestine allowing absorption of the drug throughout the GI tract. Naproxen is well absorbed from naproxen sodium extended-release tablets, with a reported bioavailability of about 95%; peak steady-state plasma naproxen concentrations usually are reached in about 3–5 hours following oral administration. The absorption rate from extended-release naproxen sodium tablets is slower than from conventional tablets. Prolonged drug absorption from extended-release tablets allows for once-daily dosing with this formulation.

Plasma naproxen concentrations of 30–90 mcg/mL reportedly are required for anti-inflammatory or analgesic effect. In a group of patients with rheumatoid arthritis, the anti-inflammatory effect of naproxen was positively correlated with serum naproxen concentrations, although no such relationship was found for adverse effects. Onset of pain relief can begin within 1 hour in patients receiving naproxen (as conventional tablets) and within 30 minutes in patients receiving naproxen sodium (as conventional tablets), as evidenced by reduction in pain intensity scores, increase in pain relief scores, decrease in the number of patients requiring additional analgesic medication, and delay in time to remedication. In a comparative study in patients with postpartum uterine cramping, there was no difference between the drugs in onset of analgesia; both drugs provided pain relief within 1 hour. Peak analgesia occurs within 1 hour with naproxen sodium and within 2 hours with naproxen. The duration of action of both drugs is generally 7–12 hours. Because of the delayed absorption of enteric-coated naproxen tablets, onset of analgesia may be delayed.

■ Distribution

The volume of distribution of naproxen is 0.16 L/kg. In one study, the apparent volume of distribution of naproxen averaged about 8.3 L in healthy adults and about 11.9 L in patients with severe renal failure (serum creatinine 5.4–12.5 mg/dL).

After therapeutic doses, naproxen is more than 99% bound to plasma proteins. When naproxen binding sites become saturated (at twice daily doses of 500 mg or more), plasma free drug concentrations increase and may result in increased urinary clearance rates. Therefore, plasma naproxen concentrations tend to plateau when dosage exceeds 500 mg twice daily. In a study in patients with severe renal failure, binding of naproxen to serum proteins was decreased compared to healthy adults; the decreased binding may have accounted for an increase in metabolism and apparent volume of distribution of the drug observed in these patients. In patients with chronic alcoholic liver disease, total plasma concentrations of naproxen are decreased while concentrations of the unbound drug are increased.

Naproxen crosses the placenta. Naproxen is also distributed into milk in concentrations of about 1% of simultaneous maternal plasma drug concentrations.

■ Elimination

In healthy adults, the plasma half-life of naproxen reportedly ranges from 10–20 hours. The manufacturers state that the plasma half-life of naproxen is about 13 hours. The plasma half-life and elimination of the drug appear to be similar in children and adults. Clearance of naproxen is 0.13 mL/minute per kg.

Naproxen is extensively metabolized in the liver to 6-desmethylnaproxen. Approximately 95% of the drug is excreted in urine as unchanged naproxen (less than 1%) and 6-desmethylnaproxen (less than 1%) and their glucuronide or other conjugates (66–92%). Some data suggest that renal excretion of unchanged naproxen may be negligible or absent; previously reported concentrations of unchanged drug may reflect rapid hydrolysis of conjugates during collection, storage, and handling of urine samples. The half-life of naproxen metabolites and conjugates is shorter than 12 hours.

Naproxen metabolites may accumulate in patients with renal impairment. Elimination of naproxen is reduced in patients with severe renal impairment. A small amount (less than 5%) of the drug is excreted in feces.

Chemistry and Stability

■ Chemistry

Naproxen, a propionic acid derivative, is a prototypical anti-inflammatory agent (NSAIA). The drug is structurally and pharmacologically related to fenoprofen and ibuprofen.

Naproxen is commercially available as the acid and as the sodium salt. Each 275 mg of naproxen sodium is approximately equivalent to 250 mg of naproxen and each 220 mg of naproxen sodium is approximately equivalent to 200 mg of naproxen. The acid occurs as a white to off-white, practically odorless, crystalline powder and is practically insoluble in water at low pH, freely soluble in water at high pH, and freely soluble in alcohol. Naproxen sodium occurs as a white to creamy white, crystalline powder and is freely soluble in water at neutral pH and sparingly soluble in alcohol. The apparent pK_a of naproxen is 4.15. Each 220-, 275-, 412.5-, or 550-mg tablet of naproxen sodium contains about 0.87, 1, 1.5, or 2 mEq of sodium, respectively, and each 5 mL of the commercially available naproxen suspension contains about 1.5 mEq each of sodium and chloride. Naproxen sodium is commercially available as conventional tablets and as extended-release tablets. Extended-release tablets of naproxen sodium (Naprelan[®]) contain an immediate-release component (about 30% of the total dose) and an extended-release component comprised of microparticles that slowly release the drug.

■ Stability

Commercially available naproxen and naproxen sodium conventional tablets and naproxen delayed-release (enteric-coated) tablets should be stored in well-closed containers at 15–30°C; the containers for the delayed-release tablets also should be light resistant. Extended-release naproxen sodium tablets should be stored in well-closed

containers at 20–25°C. Naproxen oral suspension should be stored in light-resistant containers at 15–30°C, and temperatures exceeding 40°C should be avoided. Naproxen conventional and delayed-release (enteric-coated) tablets should be stored in well-closed, light-resistant containers. Naproxen sodium tablets should be stored in well-closed containers.

Naproxen and naproxen sodium preparations containing the equivalent of 250 mg of naproxen or more per retail package should be stored in child-resistant containers in order to limit the potential toxicity associated with accidental ingestion in children.

Preparations

Excipients in commercially available drug preparations may have clinically important effects in some individuals; consult specific product labeling for details.

Naproxen

Oral Suspension	125 mg/5 mL*	Naproxen Suspension , Roxane
Tablets		Naprosyn [®] , Roche
	250 mg*	Naprosyn [®] , Roche
	375 mg*	Naprosyn [®] , Roche
	500 mg*	Naprosyn [®] , Roche
Tablets, delayed-release (enteric-coated)		Naprosyn [®] , Roche
	375 mg*	EC-Naprosyn [®] , Roche
		Naproxen Delayed-release Tablets ,
	500 mg*	EC-Naprosyn [®] (scored), Roche
		Naproxen Delayed-release Tablets ,

Naproxen Combinations

Oral Kit	14 tablets, Naproxen 375 mg (Naprosyn [®])	
	7 capsules delayed-release (containing enteric-coated granules), Lansoprazole, 15 mg (Prevacid [®])	Prevacid[®] NapraPAC[®] 375 , TAP Pharmaceuticals
	14 tablets, Naproxen 500 mg (Naprosyn [®])	
	7 capsules delayed-release (containing enteric-coated granules), Lansoprazole, 15 mg (Prevacid [®])	Prevacid[®] NapraPAC[®] 500 , TAP Pharmaceuticals

Naproxen Sodium

Oral Tablets	220 mg (equivalent to naproxen 200 mg)*	Aleve[®] Caplets[®] , Bayer
Tablets, extended-release*		Aleve[®] Tablets , Bayer

Naproxen Sodium

	412.5 mg (equivalent to 375 mg naproxen)	Naprelan[®] , Carnrick
	550 mg (equivalent to 500 mg naproxen)	Naprelan[®] , Carnrick
Tablets, film-coated	275 mg (equivalent to naproxen 250 mg)*	Anaprox[®] , Roche
	550 mg (equivalent to naproxen 500 mg)*	Anaprox[®] DS (scored), Roche

Naproxen Sodium Combinations

Oral Tablets, extended release	220 mg (equivalent to 200 mg naproxen) with Pseudoephedrine Hydrochloride 120 mg	Aleve[®] Cold and Sinus , Roche
---------------------------------------	--	---

*available from one or more manufacturer, distributor, and/or repackager by generic (nonproprietary) name

† Use is not currently included in the labeling approved by the US Food and Drug Administration.

Selected Revisions January 2009, © Copyright, April 1983, American Society of Health-System Pharmacists, Inc.