

Naproxen (Systemic)

Prototypical NSAIA; propionic acid derivative.

Class: 28:08.04.92 Other Nonsteroidal Anti-inflammatory Agents (AHFS primary)

Brands*: Aleve[®]; Anaprox[®]; Naprelan[®]; Naprosyn[®]; Prevacid[®] NapraPAC[®] (combination)

*also available generically

Boxed Warning

Cardiovascular Risk

- Possible increased risk of serious (sometimes fatal) cardiovascular thrombotic events (e.g., MI, stroke). Risk may increase with duration of use. Individuals with cardiovascular disease or risk factors for cardiovascular disease may be at increased risk. (See Cardiovascular Effects under Cautions.)
- Contraindicated for the treatment of pain in the setting of CABG surgery.

GI Risk

- Increased risk of serious (sometimes fatal) GI events (e.g., bleeding, ulceration, perforation of the stomach or intestine). Serious GI events can occur at any time and may not be preceded by warning signs and symptoms. Geriatric individuals are at greater risk for serious GI events. (See GI Effects under Cautions.)

Uses

- Consider potential benefits and risks of naproxen therapy as well as alternative therapies before initiating therapy with the drug. Use lowest effective dosage and shortest duration of therapy consistent with the patient's treatment goals.

Inflammatory Diseases

- Symptomatic treatment of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. May be used in combination with lansoprazole in patients with these conditions who have a history of documented gastric ulcer and require continued NSAIA use.
- Symptomatic treatment of tendinitis, bursitis, and acute gout.
- Management of juvenile rheumatoid arthritis in children ≥ 2 years of age.

Pain

- Relief of pain.
- NSAIAs considered first-line agents for mild to moderate migraine attacks or for severe attacks that have responded in the past to NSAIA or nonopiate analgesics.
- *Self-medication* in children ≥ 12 years of age and adults for the temporary relief of minor aches and pain associated with the common cold, headache, toothache, muscular aches, backache, and minor pain of arthritis.

Dysmenorrhea

- Symptomatic management of primary dysmenorrhea.
- *Self-medication* for the temporary relief of minor aches and pain associated with menstrual cramps.

Fever

- *Self-medication* for reduction of fever in children ≥ 12 years of age and adults.

Dosage and Administration

General

- Consider potential benefits and risks of naproxen therapy as well as alternative therapies before initiating therapy with the drug.

Administration

Oral Administration

Conventional (immediate-release) tablets, delayed-release tablets, and suspension formulations of naproxen or naproxen sodium usually are administered orally twice daily. When used for the management of osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis, the morning and evening doses may be unequal in size. When used in combination with lansoprazole, the morning dose of naproxen is administered with lansoprazole before eating.

Naproxen sodium extended-release tablets are administered orally once daily.

Do not break, crush, or chew naproxen delayed-release tablets.

Administration with meal, milk, or antacids may minimize adverse GI effects.

Formulation Considerations

Naproxen oral suspension is the preferred dosage form for children because of suitability for providing the calculated dosage.

Naproxen sodium is preferred for management of acute painful conditions when prompt onset of pain relief is desired.

Naproxen delayed-release tablets are not recommended for management of acute gout, tendinitis, bursitis, acute pain, or dysmenorrhea because of slow onset of action.

Dosage

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

If changing from one strength to another or one dosage form to another, be aware that different dose strengths and formulations are not necessarily bioequivalent.

To minimize the potential risk of adverse cardiovascular and/or GI events, use lowest effective dosage and shortest duration of therapy consistent with the patient's treatment goals. Adjust dosage based on individual requirements and response; attempt to titrate to the lowest effective dosage.

Pediatric Patients

Inflammatory Diseases

>Juvenile Rheumatoid Arthritis

Oral: Naproxen 10 mg/kg daily in 2 divided doses.

Pain

Oral: Naproxen sodium *self-medication* in children ≥ 12 years of age: Initially, 440 mg; usual dosage is 220 mg every 8–12 hours.

Fever

Oral: Naproxen sodium *self-medication* in children ≥ 12 years of age: Initially, 440 mg; usual dosage is 220 mg every 8–12 hours.

Adults

Inflammatory Diseases

>Osteoarthritis, Rheumatoid Arthritis, or Ankylosing Spondylitis

Oral:

| Preparation | Dosage |
|---|--|
| Naproxen conventional tablets, delayed-release tablets, or suspension | 250–500 mg twice daily; may increase dosage to 1.5 g daily for up to 6 months |
| Naproxen sodium conventional tablets | 275–550 mg twice daily; may increase dosage to 1.65 g daily for up to 6 months |
| Naproxen sodium extended-release tablets | 825 mg or 1.1 g once daily; may increase dosage to 1.65 g daily for up to 6 months |

When naproxen conventional tablets are used in combination with lansoprazole (15 mg once daily), usual naproxen dosage is 375 or 500 mg twice daily.

>Acute Tendinitis/Bursitis

Oral:

| Preparation | Dosage |
|---|---|
| Naproxen conventional tablets or suspension | 500 mg initially, followed by 500 mg every 12 hours or 250 mg every 6–8 hours as needed |
| Naproxen sodium conventional tablets | 550 mg initially, followed by 550 mg every 12 hours or 275 mg every 6–8 hours as needed |
| Naproxen sodium extended-release tablets | 1.1 g once daily; may increase dosage to 1.65 g once daily for limited period |

>Gout

Oral:

| Preparation | Dosage |
|---|--|
| Naproxen conventional tablets or suspension | 750 mg initially, followed by 250 mg every 8 hours until attack subsides |
| Naproxen sodium conventional tablets | 825 mg initially, followed by 275 mg every 8 hours until attack subsides |
| Naproxen sodium extended-release tablets | 1.1–1.65 g once on first day, followed by 1.1 g once daily until attack subsides |

Pain

Oral:

| Preparation | Dosage |
|---|---|
| Naproxen conventional tablets or suspension | 500 mg initially, followed by 500 mg every 12 hours or 250 mg every 6–8 hours as needed |
| Naproxen sodium conventional tablets | 550 mg initially, followed by 550 mg every 12 hours or 275 mg every 6–8 hours as needed |
| Naproxen sodium extended-release tablets | 1.1 g once daily; may increase dosage to 1.65 g once daily for limited period |

Naproxen sodium for *self-medication* of minor aches and pain: Initially, 440 mg; usual dosage is 220 mg every 8–12 hours.

Dysmenorrhea

Oral:

| Preparation | Dosage |
|---|---|
| Naproxen conventional tablets or suspension | 500 mg initially, followed by 500 mg every 12 hours or 250 mg every 6–8 hours as needed |
| Naproxen sodium conventional tablets | 550 mg initially, followed by 550 mg every 12 hours or 275 mg every 6–8 hours as needed |
| Naproxen sodium extended-release tablets | 1.1 g once daily; may increase dosage to 1.65 g once daily for limited period |

Naproxen sodium *self-medication*: Initially, 440 mg; usual dosage is 220 mg every 8–12 hours.

Fever

Oral: Naproxen sodium *self-medication*: Initially, 440 mg; usual dosage is 220 mg every 8–12 hours.

Prescribing Limits

Pediatric Patients

Pain

Oral: Naproxen sodium *self-medication* in children ≥ 12 years of age: Maximum 440 mg in 8–12 hours; 660 mg in 24 hours. *Self-medication* should not exceed 10 days.

Fever

Oral: Naproxen sodium *self-medication* in children ≥ 12 years of age: Maximum 440 mg in 8–12 hours; 660 mg in 24 hours. *Self-medication* should not exceed 3 days.

Adults

Inflammatory Diseases

>Osteoarthritis, Rheumatoid Arthritis, or Ankylosing Spondylitis

Oral: As naproxen, maximum 1.5 g daily.
As naproxen sodium, maximum 1.65 g daily.

>Acute Tendinitis/Bursitis

Oral: As naproxen, maximum 1.25 g on the first day; thereafter, 1 g daily. Maximum 1.5 g daily for limited period.
As naproxen sodium, maximum 1.375 g on the first day; thereafter, 1.1 g daily. Maximum 1.65 g daily for limited period.

Pain

Oral: As naproxen, maximum 1.25 g on the first day; thereafter, 1 g daily. Maximum 1.5 g daily for limited period.
As naproxen sodium, maximum 1.375 g on the first day; thereafter, 1.1 g daily. Maximum 1.65 g daily for limited period.

Naproxen sodium for *self-medication* of minor aches and pain: Maximum 440 mg in 8–12 hours; 660 mg in 24 hours. *Self-medication* should not exceed 10 days.

Dysmenorrhea

Oral: As naproxen, maximum 1.25 g on the first day; thereafter, 1 g daily.
As naproxen sodium, maximum 1.375 g on the first day; thereafter, 1.1 g daily.

Naproxen sodium *self-medication*: Maximum 440 mg in 8–12 hours; 660 mg in 24 hours.

Fever

Oral: Naproxen sodium *self-medication*: Maximum 440 mg in 8–12 hours; 660 mg in 24 hours. *Self-medication* should not exceed 3 days.

Special Populations

Hepatic Impairment

Dosage adjustment may be needed if high doses required. Consider reduced initial dosage. Use lowest effective dosage.

Renal Impairment

Consider reduced initial dosage.

Not recommended for use in patients with moderate to severe renal impairment ($Cl_{cr} < 30$ mL/minute).

Geriatric Patients

Dosage adjustment may be needed if high doses required. Consider reduced initial dosage. Use lowest effective dosage.

Maximum for *self-medication*, naproxen sodium 220 mg twice daily unless otherwise directed by a clinician.

Cautions

Contraindications

- Known hypersensitivity to naproxen or any ingredient in the formulation.
- History of asthma, urticaria, or other sensitivity reaction precipitated by aspirin or other NSAIDs.
- Treatment of perioperative pain in the setting of CABG surgery.

Warnings/Precautions

Warnings

Cardiovascular Effects

Selective COX-2 inhibitors have been associated with increased risk of cardiovascular events in certain situations. Several prototypical NSAIDs also have been associated with an increased risk of cardiovascular events. Naproxen does not appear to be associated with increased or decreased cardiovascular risk.

Use NSAIDs with caution and careful monitoring (e.g., monitor for development of cardiovascular events), and at the lowest effective dosage for the shortest duration necessary.

Short-term use to relieve acute pain, especially at low dosages, does not appear to be associated with increased risk of serious cardiovascular events (except immediately following CABG surgery).

No consistent evidence that concomitant use of low-dose aspirin mitigates the increased risk of serious adverse cardiovascular events associated with NSAIDs. (See Specific Drugs under Interactions.)

Hypertension and worsening of preexisting hypertension reported; either event may contribute to the increased incidence of cardiovascular events. Use with caution in patients with hypertension; monitor BP. Impaired response to certain diuretics may occur. (See Specific Drugs under Interactions.)

Fluid retention and edema reported. Caution in patients with fluid retention or heart failure.

Each 220-, 275-, 412.5-, or 550-mg naproxen sodium tablet contains about 0.87, 1, 1.5, or 2 mEq of sodium, respectively; each mL of naproxen suspension contains about 0.3 mEq of sodium. Caution in patients with fluid retention, hypertension, or heart failure.

GI Effects

Serious GI toxicity (e.g., bleeding, ulceration, perforation) can occur with or without warning symptoms; increased risk in those with a history of GI bleeding or ulceration, geriatric patients, smokers, those with alcohol dependence, and those in poor general health.

For patients at high risk for complications from NSAID-induced GI ulceration (e.g., bleeding, perforation), consider concomitant use of misoprostol; alternatively, consider concomitant use of a proton-pump inhibitor (e.g., lansoprazole, omeprazole) or use of an NSAID that is a selective inhibitor of COX-2 (e.g., celecoxib).

Renal Effects

Direct renal injury, including renal papillary necrosis, reported in patients receiving long-term NSAID therapy.

Potential for overt renal decompensation. Increased risk of renal toxicity in patients with renal or hepatic impairment or heart failure, in patients with volume depletion, in geriatric patients, and in those receiving a diuretic, ACE inhibitor, or angiotensin II receptor antagonist. (See Renal Impairment under Cautions.)

Sensitivity Reactions

Hypersensitivity Reactions

Anaphylactoid reactions reported.

Immediate medical intervention and discontinuance for anaphylaxis.

Avoid in patients with aspirin triad (aspirin sensitivity, asthma, nasal polyps); caution in patients with asthma.

Dermatologic Reactions

Serious skin reactions (e.g., exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis) reported; can occur without warning. Discontinue at first appearance of rash or any other sign of hypersensitivity (e.g., blisters, fever, pruritus).

General Precautions

Do not use multiple naproxen-containing preparations concomitantly.

Hepatic Effects

Severe reactions including jaundice, fatal fulminant hepatitis, liver necrosis, and hepatic failure (sometimes fatal) reported rarely with NSAIDs.

Elevations of serum ALT or AST reported.

Monitor liver function periodically during long-term therapy. Monitor for symptoms and/or signs suggesting liver dysfunction; monitor abnormal liver function test results. Discontinue if signs or

symptoms of liver disease or systemic manifestations (e.g., eosinophilia, rash) occur or if liver function test abnormalities persist or worsen.

Hematologic Effects

Anemia reported rarely. Periodically determine hemoglobin concentrations during long-term therapy in patients with initial values ≤ 10 g/dL. Determine hemoglobin concentration or hematocrit in patients receiving long-term therapy if signs or symptoms of anemia occur.

May inhibit platelet aggregation and prolong bleeding time.

CNS Effects

Drowsiness and dizziness reported; may impair ability to perform activities requiring mental alertness.

Ocular Effects

Visual disturbances reported; ophthalmic evaluation recommended if visual changes occur.

Other Precautions

Not a substitute for corticosteroid therapy; not effective in the management of adrenal insufficiency.

May mask certain signs of infection.

Obtain CBC and chemistry profile periodically during long-term use.

Use of Fixed Combination

When used in fixed combination with other agents, consider the cautions, precautions, and contraindications associated with the concomitant agents.

Specific Populations

Pregnancy

Category C. Avoid use in third trimester because of possible premature closure of the ductus arteriosus.

Lactation

Distributed into milk; use not recommended.

Pediatric Use

Safety and efficacy not established in children < 2 years of age.

Should not be used for *self-medication* in children < 12 years of age unless otherwise directed by a clinician.

Dosing recommendations for juvenile rheumatoid arthritis based on well-controlled studies.

Safety of extended-release naproxen sodium tablets not established in children.

Risk of overdosage and toxicity (including death) in children < 2 years of age receiving 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. Limited evidence of efficacy for these preparations in this age group; appropriate dosages not established. Therefore, FDA recommends not to use such preparations in children < 2 years of age; safety and efficacy in older children currently under evaluation. 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 agreed to voluntarily revise the product labeling to state that such preparations should not be used in children < 4 years of age. During the transition period, some preparations on pharmacy shelves will have the new recommendation (“do not use in children < 4 years of age”), while others will have the previous recommendation (“do not use in children < 2 years of age”). FDA recommends that parents and caregivers adhere to dosage instructions and warnings on the product labeling that accompanies the preparation and consult a clinician about any concerns.

Geriatric Use

Geriatric patients appear to tolerate GI ulceration and bleeding less well than other individuals. Fatal adverse GI effects reported more frequently in geriatric patients than younger adults.

Select dosage with caution because of age-related decreases in renal function. May be useful to monitor renal function.

Caution advised if high dosages required.

Hepatic Impairment

Caution advised if high dosages required.

Renal Impairment

Use not recommended in patients with moderate to severe renal impairment ($Cl_{cr} < 30$ mL/minute); close monitoring of renal function advised if used.

Metabolites eliminated principally via the kidney.

Common Adverse Effects

Abdominal pain, constipation, dizziness, drowsiness, dyspnea, edema, ecchymoses, headache, heartburn, nausea, pruritus, skin eruptions, tinnitus.

Drug Interactions

Does not induce drug-metabolizing enzymes.

Protein-bound Drugs

Pharmacokinetic interaction possible; caution advised. Observe for adverse effects if used with other protein-bound drugs.

Drugs Affecting Gastric pH

Concomitant administration of delayed-release naproxen tablets with drugs that increase gastric pH not recommended; possible pharmacokinetic interaction.

Specific Drugs

| Drug | Interaction | Comments |
|--|---|--|
| ACE inhibitors | Reduced BP response to ACE inhibitor Possible deterioration of renal function in individuals with renal impairment | Monitor BP |
| Alcohol | Increased risk of GI bleeding | |
| Angiotensin II receptor antagonists | Reduced BP response to angiotensin II receptor antagonist Possible deterioration of renal function in individuals with renal impairment | Monitor BP |
| Antacids | Delayed absorption of naproxen | Concomitant use of intensive antacid therapy with delayed-release naproxen tablets not recommended |
| Anticoagulants (warfarin) | Possible bleeding complications | Caution advised |
| Aspirin | Increased risk of GI ulceration and other complications No consistent evidence that low-dose aspirin mitigates the increased risk of serious cardiovascular events associated with NSAIDs Concomitant administration may interfere with the antiplatelet effect of low-dose aspirin | Manufacturers state that concomitant use not recommended |
| β-Adrenergic blocking agents | Reduced BP response | Monitor BP |
| Cholestyramine | Delayed absorption of naproxen | |
| Diuretics (furosemide, thiazides) | Reduced natriuretic effects | Monitor for diuretic efficacy and renal failure |
| Lithium | Increased plasma lithium concentrations | Monitor for lithium toxicity |
| Methotrexate | Possible toxicity associated with increased plasma methotrexate concentrations | Caution advised |
| Probenecid | Increased plasma concentrations and half-life of naproxen | |
| Sucralfate | Delayed absorption of naproxen | Concomitant use with delayed-release naproxen tablets not recommended |

Pharmacokinetics

Absorption

Bioavailability

Well absorbed following oral administration; bioavailability is about 95%.

Extent of absorption and peak plasma concentrations similar for commercially available formulations; rate of absorption varies depending on formulation used. Peak plasma concentration usually attained within about 1–2 hours (naproxen sodium conventional tablets), 2–4 hours (naproxen conventional tablets), 1–4 hours (naproxen suspension), 3–5 hours (naproxen sodium extended-release tablets), or 4–6 hours (naproxen delayed-release tablets).

Onset

Naproxen sodium conventional tablets and extended-release tablets provide pain relief within 30 minutes; naproxen conventional tablets provide pain relief within 1 hour.

Duration

Analgesic effect lasts up to 12 hours.

Food

Food delays time to peak plasma concentration by about 6–8 hours following administration as naproxen delayed-release tablets.

Distribution

Plasma Protein Binding

>99%.

Elimination

Metabolism

Metabolized in the liver to 6-desmethylnaproxen.

Elimination Route

Excreted in urine (95%) mainly as conjugates of naproxen or 6-desmethylnaproxen.

Half-life

12–17 hours.

Special Populations

In patients with renal impairment, possible accumulation of naproxen metabolites.

Stability

Storage

Oral

Conventional and Delayed-release Tablets

15–30°C.

Extended-release Tablets

20–25°C.

Suspension

15–30°C in light-resistant container.

Actions

- Inhibits cyclooxygenase-1 (COX-1) and COX-2.
- Pharmacologic actions similar to those of other prototypical NSAIDs; exhibits anti-inflammatory, analgesic, and antipyretic activity.

Advice to Patients

- Importance of reading the medication guide for NSAIDs that is provided each time the drug is dispensed.
- When used for *self-medication*, importance of reading the product labeling.
- When used for *self-medication*, importance of using the lowest effective dosage and of not exceeding the recommended dosage or duration of therapy.
- When used for *self-medication*, importance of reviewing the warning information provided by the manufacturer.
- Risk of serious cardiovascular events with long-term use.
- Risk of GI bleeding and ulceration.
- Risk of serious skin reactions. Risk of anaphylactoid and other sensitivity reactions.
- Risk of hepatotoxicity.
- Importance of notifying clinician if signs and symptoms of a cardiovascular event (chest pain, dyspnea, weakness, slurred speech) occur.
- Importance of notifying clinician if signs and symptoms of GI ulceration or bleeding, unexplained weight gain, or edema develops.
- Importance of discontinuing naproxen and contacting clinician if rash or other signs of hypersensitivity (blisters, fever, pruritus) develop. Importance of seeking immediate medical attention if an anaphylactic reaction occurs.
- Importance of discontinuing therapy and contacting clinician immediately if signs and symptoms of hepatotoxicity (nausea, fatigue, lethargy, pruritus, jaundice, upper right quadrant tenderness, flu-like symptoms) occur.
- Important of not engaging in activities requiring alertness if adverse CNS effects (drowsiness, dizziness, vertigo, depression) occur.

- Importance of women informing clinicians if they are or plan to become pregnant or plan to breast-feed. Importance of avoiding naproxen in late pregnancy (third trimester).
- Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs.
- Importance of informing patients of other important precautionary information. (See Cautions.)

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

Naprosyn[®], Roche

Tablets

250 mg*

Naprosyn[®] (Naproxen Tablets), Roche

375 mg*

Naprosyn[®] (Naproxen Tablets), Roche

500 mg*

Naprosyn[®] (Naproxen Tablets), Roche

Tablets, delayed-release (enteric-coated)

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

Naproxen Sodium

220 mg (equivalent to
naproxen 200 mg)*

Aleve® Caplets®,
(Naproxen Sodium
Tablets), Bayer

Aleve® Tablets, Bayer

Tablets, extended-release*

412.5 mg (equivalent to
375 mg naproxen)

Naprelan®, Carrick

550 mg (equivalent to 500
mg naproxen)

Naprelan® ((Naproxen
Sodium Film Coated
Tablets), Carrick

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
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