HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS safely and effectively. See full prescribing information for NAPROSYN, EC-NAPROSYN and ANAPROX DS.

NAPROSYN® (naproxen) tablets,
EC-NAPROSYN® (naproxen delayed-release tablets),
ANAPROX® DS (naproxen sodium tablets), for oral use
Initial U.S. Approval: 1976

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. (5.1)**
- **NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS are contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)**
- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)**

----------RECENT MAJOR CHANGES----------

Boxed Warning	05/2016
Warnings and Precautions (5.1, 5.5)	05/2016

----------INDICATIONS AND USAGE----------

NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS are non-steroidal anti-inflammatory drugs indicated for:

the relief of the signs and symptoms of:
- rheumatoid arthritis
- osteoarthritis
- ankylosing spondylitis
- polyarticular juvenile idiopathic arthritis

NAPROSYN Tablets and ANAPROX DS are also indicated for:

the relief of signs and symptoms of:
- tendonitis
- bursitis
- acute gout

the management of:
- pain
- primary dysmenorrhea

----------DOSAGE AND ADMINISTRATION----------

Use the lowest effective dosage for shortest duration consistent with individual patient treatment goals. (2.1)

Rheumatoid Arthritis, Osteoarthritis, and Ankylosing Spondylitis

NAPROSYN Tablets	250 mg (one-half tablet) 500 mg	twice daily
ANAPROX DS	275 mg (one-half tablet) 550 mg	twice daily
EC-NAPROSYN	375 mg or 500 mg	twice daily

To maintain the integrity of the enteric coating, the EC-NAPROSYN tablet should not be broken, crushed or chewed during ingestion.

The dose may be adjusted up or down depending on the clinical response of the patient.
In patients who tolerate lower doses well, the dose may be increased to naproxen 1500 mg/day for up to 6 months.

Polyarticular Juvenile Idiopathic Arthritis
NAPROSYN Tablets may not allow for the flexible dose titration needed in pediatric patients with polyarticular juvenile idiopathic arthritis. A liquid formulation may be more appropriate. Recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses. Dosing with NAPROSYN Tablets is not appropriate for children weighing less than 50 kilograms.

Management of Pain, Primary Dysmenorrhea, and Acute Tendonitis and Bursitis
Recommended starting dose 550 mg of naproxen sodium as ANAPROX DS followed by 550 mg every 12 hours or 275 mg every 6 to 8 hours as required. The initial total daily dose should not exceed 1375 mg of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium. ANAPROX DS is recommended for the management of acute painful conditions when prompt onset of pain relief is desired.

Acute Gout
Recommended starting dose 750 mg of NAPROSYN Tablets followed by 250 mg every 8 hours until the attack has subsided. ANAPROX DS may also be used at a starting dose of 825 mg followed by 275 mg every 8 hours. EC-NAPROSYN is not recommended because of the delay in absorption.

----------DOSAGE FORMS AND STRENGTHS----------

NAPROSYN® (naproxen) tablets: 500 mg
EC-NAPROSYN® (naproxen) delayed-release tablets: 375 mg and 500 mg
ANAPROX® DS (naproxen sodium) tablets: 550 mg (contains 50 mg of sodium)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to naproxen or any components of the drug product (4)
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs (4)
- In the setting of CABG surgery (4)

----------WARNINGS AND PRECAUTIONS----------

Hepatotoxicity: Inform patients of warning signs and symptoms of hepatotoxicity. Discontinue if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (5.3)
Hypertension: Patients taking some antihypertensive medications may have impaired response to these therapies when taking NSAIDs. Monitor blood pressure. (5.4,7)
Heart Failure and Edema: Avoid use of NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS in patients with severe heart failure unless benefits are expected to outweigh risk of worsening heart failure. (5.5)
Renal Toxicity: Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia. Avoid use of NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS in patients with advanced renal disease unless benefits are expected to outweigh risk of worsening renal function. (5.6)
Anaphylactic Reactions: Seek emergency help if an anaphylactic reaction occurs. (5.7)
Exacerbation of Asthma Related to Aspirin Sensitivity: NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS are contraindicated in patients with aspirin-sensitive asthma. Monitor patients with preexisting asthma (without aspirin sensitivity). (5.8)
Serious Skin Reactions: Discontinue NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS at first appearance of skin rash or other signs of hypersensitivity. (5.9)
Premature Closure of Fetal Ductus Arteriosus: Avoid use in pregnant women starting at 30 weeks gestation. (5.10, 8.1)
Hematologic Toxicity: Monitor hemoglobin or hematocrit in patients with any signs or symptoms of anemia. (5.11,7)

----------ADVERSE REACTIONS----------

Most common adverse reactions to naproxen were dyspepsia, abdominal pain, nausea, headache, rash, ecchymosis, and edema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Canton Laboratories LLC.at1-844-302-5227 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs):
Monitor patients for bleeding who are concomitantly taking NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS with drugs that interfere with hemostasis. Concomitant use of NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS and analgesic doses of aspirin is not generally recommended. (7)
ACE inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS may diminish the antihypertensive effect of these drugs. Monitor blood pressure. (7)
ACE Inhibitors and ARBs: Concomitant use with NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function. (7)
Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects. (7)
Digoxin: Concomitant use with NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels. (7)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Use of NSAIDs during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs in pregnant women starting at 30 weeks gestation. (5.10, 8.1)
Infertility: NSAIDs are associated with reversible infertility. Consider withdrawal of NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS in women who have difficulties conceiving. (8.3)
Renal Impairment: Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: [03/2017]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [*see Warnings and Precautions (5.1)*].**
- **NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [*see Contraindications (4), Warnings and Precautions (5.1)*].**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events [*see Warnings and Precautions* (*5.2*)].**

1 INDICATIONS AND USAGE

NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS are indicated for:

the relief of the signs and symptoms of:

- rheumatoid arthritis
- osteoarthritis
- ankylosing spondylitis
- Polyarticular Juvenile Idiopathic Arthritis

NAPROSYN Tablets and ANAPROX DS are also indicated for:

the relief of signs and symptoms of:

- tendonitis
- bursitis
- acute gout

the management of:

- pain
- primary dysmenorrhea

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Instructions

Carefully consider the potential benefits and risks of NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS and other treatment options before deciding to use NAPROSYN Tablets, EC-NAPROSYN and ANAPROX DS. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals [*see Warnings and Precautions (5)*].

After observing the response to initial therapy with NAPROSYN Tablets, EC-NAPROSYN or ANAPROX DS, the dose and frequency should be adjusted to suit an individual patient's needs.

To maintain the integrity of the enteric coating, the EC-NAPROSYN tablet should not be broken, crushed or chewed during ingestion.

Naproxen-containing products such as NAPROSYN, EC-NAPROSYN and ANAPROX DS, and other naproxen products should not be used concomitantly since they all circulate in the plasma as the naproxen anion.

2.2 Rheumatoid Arthritis, Osteoarthritis and Ankylosing Spondylitis

The recommended dosages of NAPROSYN Tablets, ANAPROX DS, and EC-NAPROSYN are shown in Table 1.

Table 1: Recommended dosages for NAPROSYN Tablets, ANAPROX DS, and EC-NAPROSYN

NAPROSYN	250 mg (one half tablet) 500 mg	twice daily
ANAPROX DS	275 mg (one half tablet) 550 mg (naproxen 500 mg with 50 mg sodium)	twice daily
EC-NAPROSYN	375 mg or 500 mg	twice daily twice daily

During long-term administration, the dose of naproxen may be adjusted up or down depending on the clinical response of the patient. A lower daily dose may suffice for long-term administration. The morning and evening doses do not have to be equal in size and the administration of the drug more frequently than twice daily is not necessary.

The morning and evening doses do not have to be equal in size and administration of the drug more frequently than twice daily does not generally make a difference in response.

In patients who tolerate lower doses well, the dose may be increased to naproxen 1500 mg/day for limited periods of up to 6 months when a higher level of anti-inflammatory/analgesic activity is required. When treating such patients with naproxen 1500 mg/day, the physician should observe sufficient increased clinical benefits to offset the potential increased risk.

2.3 Polyarticular Juvenile Idiopathic Arthritis

Naproxen solid-oral dosage forms may not allow for the flexible dose titration needed in pediatric patients with polyarticular juvenile idiopathic arthritis. A liquid formulation may be more appropriate for weight-based dosing and due to the need for dose flexibility in children.

In pediatric patients, doses of 5 mg/kg/day produced plasma levels of naproxen similar to those seen in adults taking 500 mg of naproxen [*see Clinical Pharmacology (12)*]. The recommended total daily dose of naproxen is approximately 10 mg/kg given in 2 divided doses. Dosing with NAPROSYN Tablets is not appropriate for children weighing less than 50 kilograms.

2.4 Management of Pain, Primary Dysmenorrhea, and Acute Tendonitis and Bursitis

The recommended starting dose of ANAPROX DS (naproxen sodium) tablets is 550 mg followed by 550 mg every 12 hours or 275 mg (one half of a 550 mg tablet) every 6 to 8 hours as required. The initial total daily dose should not exceed 1375 mg (two and one-half tablets) of naproxen sodium. Thereafter, the total daily dose should not exceed 1100 mg of naproxen sodium. Because the sodium salt of naproxen is more rapidly absorbed, ANAPROX DS is recommended for the management of acute painful conditions when prompt onset of pain relief is desired. NAPROSYN Tablets may also be used. The recommended starting dose of NAPROSYN Tablets is 500 mg followed by 250 mg (one half of a 500 mg NAPROSYN tablet) every 6-8 hours as required.. The total daily dose should not exceed 1250 mg of naproxen.

EC-NAPROSYN is not recommended for initial treatment of acute pain because absorption of naproxen is delayed compared to other naproxen-containing products [*see Clinical Pharmacology (12)*].

2.5 Acute Gout

The recommended starting dose is 750 mg (one and one-half tablets) of NAPROSYN Tablets followed by 250 mg (one-half tablet) every 8 hours until the attack has subsided. ANAPROX DS may also be used at a starting dose of 825 mg (one and one-half tablets) followed by 275 mg (one-half tablet) every 8 hours. EC-NAPROSYN is not recommended because of the delay in absorption.

2.6 Non-Interchangeability with Other Formulations of Naproxen

Different dose strengths and formulations (e.g., tablets, suspension) of naproxen are not interchangeable. This difference should be taken into consideration when changing strengths or formulations.

3 DOSAGE FORMS AND STRENGTHS

NAPROSYN® (naproxen) tablets: 500 mg: yellow, capsule-shaped, engraved with NPR LE 500 on one side and scored on the other.

EC-NAPROSYN® (naproxen) delayed-release tablets: 375 mg: white, oval biconvex coated tablets imprinted with NPR EC 375 on one side.

EC-NAPROSYN® (naproxen) delayed-release tablets: 500 mg: white, oblong coated tablets imprinted with NPR EC 500 on one side.

ANAPROX® DS (naproxen sodium) tablets: 550 mg: dark blue, oblong-shaped, engraved with NPS 550 on one side and scored on both sides.

4 CONTRAINDICATIONS

NAPROSYN Tablets, EC-NAPROSYN, and ANAPROX DS are contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to naproxen or any components of the drug product [*see Warnings and Precautions (5.7, 5.9)*]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [*see Warnings and Precautions (5.7, 5.8)*]
- In the setting of coronary artery bypass graft (CABG) surgery [*see Warnings and Precautions (5.1)*]

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as naproxen, increases the risk of serious gastrointestinal (GI) events [*see Warnings and Precautions (5.2)*].

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications (4)*].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated

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