Brand Names

Aflaxen, Aleve, Aleve Arthritis, All Day Pain Relief, All Day Relief, Anaprox, Anaprox DS, EC-Naprosyn, Midol Extended Relief, Naprelan, Naprelan Dose Card, Naprosyn

Indication Specific Dosing

For the treatment of ankylosing spondylitis, osteoarthritis, or rheumatoid arthritis

Oral dosage (naproxen tablets or suspension)

Adults

250 or 500 mg PO twice daily. May adjust the dose based on clinical response. Max: 1,500 mg/day for limited periods of up to 6 months.

Oral dosage (naproxen sodium tablets)

Adults

275 or 550 mg PO twice daily. May adjust the dose based on clinical response. Max: 1,500 mg/day for limited periods of up to 6 months.

Oral dosage (naproxen delayed-release tablets)

Adults

375 or 500 mg PO twice daily. May adjust the dose based on clinical response. Max: 1,500 mg/day for limited periods of up to 6 months.

Oral dosage (naproxen sodium controlled-release tablets)

Adults

750 or 1,000 mg PO once daily. May adjust the dose based on clinical response. Max: 1,500 mg/day for limited periods.

For the treatment of juvenile rheumatoid arthritis (JRA)/juvenile idiopathic arthritis (JIA)

Oral dosage (naproxen tablets)

Children and Adolescents 2 to 17 years and weighing 50 kg or more

5 mg/kg/dose (Max: 500 mg/dose) PO twice daily.

Oral dosage (naproxen suspension)

Children and Adolescents 2 to 17 years

5 mg/kg/dose (Max: 500 mg/dose) PO twice daily.

For the treatment of acute gout

Oral dosage (naproxen tablets or suspension)

Adults

750 mg PO once, then 250 mg PO every 8 hours as needed until the attack has subsided.

Oral dosage (naproxen sodium tablets)

Adults

825 mg PO once, then 275 mg PO every 8 hours as needed until the attack has subsided.

Oral dosage (naproxen controlled-release tablets)

Adults

1,000 to 1,500 mg PO once, then 1,000 mg PO once daily as needed until the attack has subsided.

For the treatment of mild pain to moderate pain, including minor aches and pains associated with arthralgia, dental pain, headache, musculoskeletal pain (including backache), and/or the common cold

For the treatment of mild to moderate pain

Oral dosage (naproxen tablets or suspension)

Adults

500 mg PO once, then 250 mg PO every 6 to 8 hours as needed. Max: 1,250 mg/day.

Oral dosage (naproxen sodium tablets)

Adults

550 mg PO once, then 550 mg PO every 12 hours or 275 mg PO every 6 to 8 hours as needed. Max: 1,375 mg on day 1, then 1,100 mg/day.

Oral dosage (naproxen sodium controlled-release tablets)

Adults

1,000 or 1,500 mg PO once daily. Usual Max: 1,000 mg/day.

For the treatment of minor aches and pains associated with arthralgia, dental pain, headache, musculoskeletal pain (including backache), and/or the common cold

Oral dosage (OTC naproxen sodium capsules or tablets)

Adults

440 mg PO once, then 220 mg PO every 8 to 12 hours. Max: 660 mg/day.

Children and Adolescents 12 to 17 years

440 mg PO once, then 220 mg PO every 8 to 12 hours. Max: 660 mg/day.

For the treatment of dysmenorrhea

Oral dosage (naproxen tablets or suspension)

Adults

500 mg PO once, then 250 mg PO every 6 to 8 hours as needed. Max: 1,250 mg/day.

Oral dosage (naproxen sodium tablets)

Adults

550 mg PO once, then 550 mg PO every 12 hours as needed. The FDA-approved dosage is 550 mg PO once, then 550 mg PO every 12 hours or 275 mg PO every 6 to 8 hours as needed. Max: 1,375 mg on day 1, then 1,100 mg/day.

Adolescents†

550 mg PO once, then 550 mg PO every 12 hours as needed.

Oral dosage (naproxen sodium controlled-release tablets)

Adults

1,000 or 1,500 mg PO once daily. Usual Max: 1,000 mg/day.

Oral dosage (OTC naproxen sodium capsules or tablets)

Adults

440 mg PO once, then 220 mg PO every 8 to 12 hours as needed. Max: 660 mg/day. Discontinue use if pain gets worse or lasts for more than 10 days.

Children and Adolescents 12 to 17 years

440 mg PO once, then 220 mg PO every 8 to 12 hours. Max: 660 mg/day. Discontinue use if pain gets worse or lasts for more than 10 days.

For the treatment of fever

Oral dosage (OTC naproxen sodium capsules or tablets)

Adults

440 mg PO once, then 220 mg PO every 8 to 12 hours. Max: 660 mg/day. Discontinue use if fever gets worse or lasts for more than 3 days.

Children and Adolescents 12 to 17 years

440 mg PO once, then 220 mg PO every 8 to 12 hours. Max: 660 mg/day. Discontinue use if fever gets worse or lasts for more than 3 days.

For the treatment of bursitis and tendinitis

Oral dosage (naproxen tablets or suspension)

Adults

500 mg PO once, then 250 mg PO every 6 to 8 hours as needed. Max: 1,250 mg/day.

Oral dosage (naproxen sodium tablets)

Adults

550 mg PO once, then 550 mg PO every 12 hours or 275 mg PO every 6 to 8 hours as needed. Max: 1,375 mg on day 1, then 1,100 mg/day.

Oral dosage (naproxen sodium controlled-release tablets)

Adults

1,000 or 1,500 mg PO once daily. Usual Max: 1,000 mg/day.

For the acute treatment of migraine†

Oral dosage (naproxen)

Adults

500 mg PO as a single dose. Guidelines classify naproxen as having established efficacy for the treatment of acute migraine.

Oral dosage (naproxen sodium)

Adults

550 mg PO as a single dose. Guidelines classify naproxen as having established efficacy for the treatment of acute migraine.

For menstrual migraine prophylaxis†

Oral dosage (naproxen sodium tablets)

Adults

500 or 550 mg PO once or twice daily for 6 days starting 2 to 7 days before the expected onset of menses and repeated monthly with each menstrual cycle.

For the prevention of heterotopic ossification†

Oral dosage (naproxen tablets or oral suspension)

Adults

250 mg PO 3 times daily for 6 weeks or 500 mg PO twice daily for 7 days after total hip arthroplasty.

For the treatment of acute or recurrent pericarditis†

For the treatment of acute pericarditis†

Oral dosage (naproxen tablets or suspension)

Adults

250 to 500 mg PO every 12 hours, initially; may increase dose up to 1,500 mg/day if tolerated and needed and continue for 1 to 2 weeks, then decrease dose by 125 to 250 mg/day every 1 to 2 weeks in combination with colchicine.

Children and Adolescents 2 to 17 years

5 mg/kg/dose PO every 12 hours for 1 to 4 weeks; up to 15 mg/kg/day has been tolerated. Consider tapering dose gradually every 1 to 2 weeks.

For the treatment of recurrent pericarditis†

Oral dosage (naproxen tablets or suspension)

Adults

250 to 500 mg PO every 12 hours, initially; may increase dose up to 1,500 mg/day if tolerated and needed and continue for at least 2 to 4 weeks, then decrease dose by 125 to 250 mg/day every 1 to 2 weeks in combination with colchicine.

Children and Adolescents 2 to 17 years

5 mg/kg/dose PO every 12 hours for at least 2 to 4 weeks in combination with colchicine; up to 15 mg/kg/day has been tolerated. Consider tapering dose gradually every 1 to 2 weeks.

For the treatment of uveitis†

Oral dosage (naproxen tablets or suspension)

Adults

250 to 500 mg PO 2 times daily.

Children and Adolescents

5 to 7.5 mg/kg/dose (Max: 500 mg/dose) PO 2 times daily.

For the treatment of rheumatic arthritis†

Oral dosage (naproxen tablets or suspension)

Adults

250 to 500 mg PO twice daily, initially. May increase the dose up to 1,250 mg/day based on clinical response and tolerability. Treat for 1 month or until inflammation has subsided.

Infants, Children, and Adolescents

5 to 10 mg/kg/dose (Max: 500 mg/dose) PO 2 times daily, initially. May increase the dose up to 1,250 mg/day based on clinical response and tolerability. Treat for 1 month or until inflammation has subsided.

Contraindications And Precaution

Drug Interactions

The coadministration of certain medications may lead to harm and require avoidance or therapy modification; review all drug interactions prior to concomitant use of other medications.

Hypersensitivity

This medication is contraindicated in patients with a history of hypersensitivity to it or any of its components.

cardiovascular disease, coronary artery bypass graft surgery (CABG), serious cardiovascular events

Naproxen is contraindicated in the setting of coronary artery bypass graft surgery (CABG). An increased incidence of myocardial infarction and stroke was found in clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10 to 14 days after CABG surgery. NSAIDs may increase the risk of serious cardiovascular events, which can be fatal. Guidelines recommend against NSAID use in individuals presenting with and hospitalized for ST-elevation myocardial infarction (STEMI) due to increased risk of mortality and cardiovascular (CV) complications associated with their use. Avoid NSAID use in individuals with a recent myocardial infarction unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If an NSAID is used in individuals

with a recent myocardial infarction, monitor for signs of cardiac ischemia. Observational data from a national registry demonstrated that individuals treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning the first week of treatment. An increased relative risk of death in NSAID users continued during the follow-up period of 4 years. Data demonstrate that individuals treated with NSAIDs were more likely to die in the first year after a myocardial infarction compared to those not treated with 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, individuals with known cardiovascular 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 with an NSAID; the increase in CV thrombotic risk has been observed most consistently at higher doses. Current evidence is insufficient to determine if the risk of an event is higher or lower for any particular NSAID compared to other NSAIDs. There is no consistent evidence that concomitant use of aspirin mitigates the increased risk for CV thrombotic events. To minimize the potential risk for an adverse CV event in NSAID-treated individuals, use the lowest effective dose for the shortest duration possible; remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. NSAIDs may worsen pre-existing hypertension, which may contribute to the increased incidence of CV events. Monitor blood pressure during NSAID treatment initiation and throughout therapy. Avoid NSAID use in individuals with severe heart failure, unless the benefits of treatment are expected to outweigh the risks. Monitor for signs of worsening heart failure if an NSAID is used in individuals with severe heart failure. Monitor renal function in individuals with heart failure during use of an NSAID. Data demonstrate an increased risk for myocardial infarction, hospitalization for heart failure, and death with NSAID use in individuals with heart failure.

aspirin exacerbated respiratory disease, asthma

Naproxen is contraindicated in individuals with aspirin exacerbated respiratory disease, which may include chronic rhinosinusitis complicated by nasal polyps, severe and potentially fatal acute bronchospasm, and/or intolerance to aspirin and other NSAIDs. When an NSAID is used in individuals with pre-existing asthma without known aspirin sensitivity, monitor for changes in the signs and symptoms of asthma.

bleeding disorder, ethanol ingestion, GI bleeding, peptic ulcer disease, serious gastrointestinal events, tobacco smoking

Individuals with a prior history of GI bleeding and/or peptic ulcer disease who use NSAIDs had a more than 10-fold increased risk of developing a GI bleed compared to individuals without these risk factors. Individuals with advanced hepatic disease or bleeding disorder are also at increased risk for GI bleeding. Other risk factors for GI bleeding in individuals receiving NSAIDs include longer duration of NSAID therapy, concomitant use of oral corticosteroids, aspirin, anticoagulants, or SSRIs, tobacco smoking, ethanol ingestion, older age, and poor general health status. Coadministration with certain medications, specifically aspirin or other NSAIDs, is contraindicated due to the cumulative risk of inducing serious NSAID-related adverse events; concomitant use of ketorolac with aspirin or other NSAIDs increases the risk of GI toxicity, with little or no increase in efficacy. Serious gastrointestinal events, including bleeding, inflammation, perforation, and ulceration, can occur at any time and without warning symptoms in individuals receiving NSAIDs. To minimize the risk of an adverse GI event in NSAID-treated individuals, use the lowest effective NSAID dose for the shortest possible duration. Avoid concurrent administration of other NSAIDs; in the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor more closely for evidence of GI bleeding. Avoid NSAID use in individuals at higher risk for GI adverse events unless benefits are expected to outweigh the increased bleeding risk, and consider alternate therapies other than NSAIDs for those individuals and individuals with active GI bleeding. Monitor individuals for signs and symptoms of GI bleeding and ulceration during NSAID therapy.

hepatic disease

Use caution when high doses of naproxen are used in individuals with hepatic impairment or hepatic failure; dosage adjustment may be necessary in these individuals. Use the lowest effective naproxen dose. Monitor renal function in individuals with hepatic impairment during use of an NSAID. NSAID use in individuals with hepatic failure in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion may precipitate renal decompensation. Advanced hepatic disease is also a risk factor for GI bleeding in individuals who use NSAIDs.

hypovolemia, renal disease

Naproxen is not recommended for use in individuals with moderate to severe and severe renal impairment or renal failure (CrCl less than 30 mL/minute). Avoid NSAID use in individuals with advanced renal disease, unless the benefits are expected to outweigh the risks of worsening renal function. If an NSAID is used in individuals with advanced renal disease, monitor for signs and symptoms of worsening renal function. Correct volume status in individuals with dehydration or hypovolemia prior to starting an NSAID.

Monitor renal function in individuals with renal impairment, dehydration, or hypovolemia during use of an NSAID. NSAID use in individuals with renal impairment, dehydration, or hypovolemia in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion may precipitate renal decompensation. The renal effects of NSAIDs may hasten the progression of renal dysfunction in individuals with pre-existing renal disease.

geriatric

Geriatric adults, compared to younger individuals, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the older adult outweighs these potential risks, start NSAID dosing at the low end of the dosing range, and monitor for adverse effects. According to the Beers Criteria, NSAIDs are considered potentially inappropriate medications (PIMs) in geriatric adults. There is an increased risk of GI bleeding and peptic ulcer disease in high-risk groups including those older than 75 years, or those taking systemic corticosteroids, anticoagulants, or antiplatelet medications. The risk of GI ulcers, gross bleeding, or perforation is cumulative with continued use. Avoid the chronic use of NSAIDs in high-risk individuals, including those with a history of gastric or duodenal ulcers, unless other alternatives are not effective, and the individual can take a gastroprotective agent. The use of a gastroprotective agent, like a proton pump inhibitor or misoprostol, reduces but does not eliminate GI risks. NSAIDs may also increase blood pressure and induce kidney injury. Avoid use of NSAIDs in geriatric adults with the following conditions due to the potential for symptom exacerbation or adverse effects: symptomatic heart failure (fluid retention, symptom exacerbation) or chronic kidney disease Stage 4 or higher (CrCl less than 30 mL/minute) (acute kidney injury, further decline of renal function). Use with caution in individuals with asymptomatic heart failure.

pregnancy

Avoid the use of NSAIDs, such as naproxen, during pregnancy starting at 30 weeks gestation due to the risk of premature closure of the fetal ductus arteriosus. When use is necessary between 20 and 30 weeks gestation, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if treatment exceeds 48 hours. Discontinue the NSAID if oligohydramnios develops, and follow up according to clinical practice. Use of NSAIDs around 20 weeks gestation and later may also cause fetal renal dysfunction, leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always,

reversible with treatment discontinuation. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some cases, invasive neonatal procedures such as exchange transfusion or dialysis have been required. Observational data regarding other potential embryo-fetal risks of NSAID use during the first or second trimesters are inconclusive. Animal studies indicate that prostaglandins play an important role in endometrial blood flow, embryo implantation, and fetal kidney development. Inhibiting prostaglandin synthesis has been associated with increased pre- and post-implantation loss and impaired kidney development in animals at NSAID doses relevant to clinical use. The effects of naproxen on labor and obstetric delivery are unknown. In animal studies, NSAIDs inhibit prostaglandin synthesis, delay parturition, and increase the incidence of still birth.

people who may become pregnant, reproductive risk

Counsel people who may become pregnant about the reproductive risk associated with naproxen. NSAIDs may delay or prevent prostaglandin-mediated rupture of ovarian follicles, which has been associated with reversible infertility. Small studies with NSAIDs demonstrated a reversible delay in ovulation. Consider withdrawal of NSAIDs in people who may become pregnant who have difficulties conceiving or who are undergoing infertility evaluation.

breast-feeding

Use naproxen with caution during breast-feeding. Limited data indicate naproxen is present in human milk in low concentrations (less than 1% of maternal serum levels), and that adverse effects in breastfed children are uncommon. There has been a report of naproxen possibly causing prolonged bleeding time, thrombocytopenia, and acute anemia in a 7-day-old infant exposed to the drug through the milk of a lactating individual also taking bacampicillin. Based on this report and the long half-life of naproxen, other agents may be preferred. Alternative analgesic and antiinflammatory drugs considered to be usually compatible with breast-feeding include acetaminophen and ibuprofen.

Pregnancy And Lactation

Avoid the use of NSAIDs, such as naproxen, during pregnancy starting at 30 weeks gestation due to the risk of premature closure of the fetal ductus arteriosus. When use is necessary between 20 and 30 weeks gestation, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if treatment exceeds 48 hours. Discontinue the NSAID if oligohydramnios develops, and

follow up according to clinical practice. Use of NSAIDs around 20 weeks gestation and later may also cause fetal renal dysfunction, leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some cases, invasive neonatal procedures such as exchange transfusion or dialysis have been required. Observational data regarding other potential embryo-fetal risks of NSAID use during the first or second trimesters are inconclusive. Animal studies indicate that prostaglandins play an important role in endometrial blood flow, embryo implantation, and fetal kidney development. Inhibiting prostaglandin synthesis has been associated with increased pre- and post-implantation loss and impaired kidney development in animals at NSAID doses relevant to clinical use. The effects of naproxen on labor and obstetric delivery are unknown. In animal studies, NSAIDs inhibit prostaglandin synthesis, delay parturition, and increase the incidence of still birth.

Interactions

Acebutolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Acetaminophen; Aspirin, ASA; Caffeine: (Major) Concomitant use of analgesic doses of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before

naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%). Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular protection.

Acetaminophen; Aspirin: (Major) Concomitant use of analgesic doses of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%). Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular protection.

Acetaminophen; Aspirin; diphenhydrAMINE: (Major) Concomitant use of analgesic doses

of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%). Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular protection.
Acetaminophen; Ibuprofen: (Major) Avoid concomitant use of ibuprofen with any other NSAID due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Acyclovir: (Moderate) Monitor patients for signs of worsening renal function during coadministration of acyclovir and nonsteroidal antiinflammatory drugs. Coadministration may increase the risk for drug-induced nephrotoxicity.
Adefovir: (Moderate) Chronic coadministration of adefovir with nephrotoxic drugs, such as nonsteroidal antiinflammatory drugs may increase the risk of developing nephrotoxicity even in patients who have normal renal function. The use of adefovir with NSAIDs may be done cautiously. As stated in the current adefovir prescribing information, 'Ibuprofen (800 mg PO three times daily), when given concomitantly with adefovir dipivoxil, increased the adefovir Cmax by 33% and AUC by 23%, as well as

urinary recovery. The increase appears to be due to higher oral bioavailability, not a reduction in renal clearance of adefovir.' In an in vitro investigation, the antiviral effect of adefovir was unaltered and the renal proximal tubule accumulation of adefovir was inhibited by the presence of a NSAID. Adefovir is efficiently transported by the human renal organic anion transporter 1, and the presence of this transporter appears to mediate the accumulation of the drug in renal proximal tubules. The in vitro study suggests that the use of a NSAID with adefovir may potentially reduce the nephrotoxic potential of adefovir. Of course, NSAIDs are associated with nephrotoxicity of their own; therefore, further data on the interaction between NSAIDs and adefovir in humans are needed.
Albuterol; Budesonide: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Aldesleukin, IL-2: (Major) Aldesleukin, IL-2 may cause nephrotoxicity. Concurrent administration of drugs possessing nephrotoxic effects, such as nonsteroidal antiinflammatory agents (NSAIDs), with Aldesleukin, IL-2 may increase the risk of kidney dysfunction. In addition, reduced kidney function secondary to Aldesleukin, IL-2 treatment may delay elimination of concomitant medications and increase the risk of adverse events from those drugs.
Alendronate: (Minor) Monitor for gastrointestinal adverse events during concurrent use of alendronate and nonsteroidal antiinflammatory drugs. Both medications have been associated with gastrointestinal irritation although data suggest concomitant use introduces little additional risk for adverse effects for most patients.
Alendronate; Cholecalciferol: (Minor) Monitor for gastrointestinal adverse events during concurrent use of alendronate and nonsteroidal antiinflammatory drugs. Both medications have been associated with gastrointestinal irritation although data suggest concomitant use introduces little additional risk for adverse effects for most patients.
Aliskiren: (Moderate) NSAIDs may attenuate the antihypertensive effects of aliskiren by inhibiting the synthesis of vasodilatory prostaglandins. In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function who are being treated with NSAIDs, the coadministration of aliskiren may result in a further deterioration of renal function, including acute renal failure. These effects are usually reversible. Therefore, blood pressure and renal function should be monitored closely when an NSAID is administered to a patient taking aliskiren.
Aliskiren; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the

natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics. (Moderate) NSAIDs may attenuate the antihypertensive effects of aliskiren by inhibiting the synthesis of vasodilatory prostaglandins. In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function who are being treated with NSAIDs, the coadministration of aliskiren may result in a further deterioration of renal function, including acute renal failure. These effects are usually reversible. Therefore, blood pressure and renal function should be monitored closely when an NSAID is administered to a patient taking aliskiren.
Alpha-blockers: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Alteplase: (Moderate) NSAIDs can cause GI bleeding, inhibit platelet aggregation, prolong bleeding time; these pharmacodynamic effects may be increased when administered to patients receiving thrombolytic agents. Patients receiving these drugs concurrently should be monitored closely for bleeding.
Aluminum Hydroxide: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Aluminum Hydroxide; Magnesium Carbonate: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Aluminum Hydroxide; Magnesium Hydroxide: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Aluminum Hydroxide; Magnesium Hydroxide; Simethicone: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use

should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Aluminum Hydroxide; Magnesium Trisilicate: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Amikacin: (Moderate) It is possible that additive nephrotoxicity may occur in patients who receive nonsteroidal antiinflammatory drugs (NSAIDs) concurrently with other nephrotoxic agents, such as amikacin.
aMILoride: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the natriuretic effect of diuretics in some patients. NSAIDS have been associated with an inhibition of prostaglandin synthesis, which may result in reduced renal blood flow leading to renal insufficiency and increases in blood pressure that are often accompanied by peripheral edema and weight gain. Patients taking diuretics and NSAIDS concurrently are at higher risk of developing renal insufficiency. If an NSAID and a diuretic are used concurrently, carefully monitor the patient for signs and symptoms of decreased renal function and diuretic efficacy.
aMILoride; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics. (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the natriuretic effect of diuretics in some patients. NSAIDS have been associated with an inhibition of prostaglandin synthesis, which may result in reduced renal blood flow leading to renal insufficiency and increases in blood pressure that are often accompanied by peripheral edema and weight gain. Patients taking diuretics and NSAIDS concurrently are at higher risk of developing renal insufficiency. If an NSAID and a diuretic are used concurrently, carefully monitor the patient for signs and symptoms of decreased renal function and diuretic efficacy.
Aminolevulinic Acid: (Moderate) Agents that inhibit prostaglandin synthesis such as nonsteroidal antiinflammatory drugs (NSAIDs), could decrease the efficacy of photosensitizing agents used in photodynamic therapy. Avoidance of NSAIDs before and during photodynamic therapy may be advisable.
Aminosalicylate sodium, Aminosalicylic acid: (Major) Avoid concomitant use of naproxen with aminosalicylic acid due to an increased risk of gastrointestinal toxicity and renal impairment, with little or no increase in efficacy.
amLODIPine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an

antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. amLODIPine; Atorvastatin: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. amLODIPine; Benazepril: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related

decreases in renal function and an increased risk of stroke and coronary artery disease. (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
amLODIPine; Celecoxib: (Major) Avoid concomitant use of celecoxib with any other NSAID due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers. (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
amLODIPine; Olmesartan: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The

antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. amLODIPine; Valsartan: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. amLODIPine; Valsartan; hydroCHLOROthiazide, HCTZ: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-

inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Amphotericin B lipid complex (ABLC): (Moderate) Concurrent use of amphotericin B and other nephrotoxic medications, including nonsteroidal antiinflammatory drugs (NSAIDs), may enhance the potential for drug-induced renal toxicity. Monitor renal function carefully during concurrent therapy. Amphotericin B dosage reduction may be necessary if renal impairment occurs.
Amphotericin B liposomal (LAmB): (Moderate) Concurrent use of amphotericin B and other nephrotoxic medications, including nonsteroidal antiinflammatory drugs (NSAIDs), may enhance the potential for drug-induced renal toxicity. Monitor renal function carefully during concurrent therapy. Amphotericin B dosage reduction may be necessary if renal impairment occurs.
Amphotericin B: (Moderate) Concurrent use of amphotericin B and other nephrotoxic medications, including nonsteroidal antiinflammatory drugs (NSAIDs), may enhance the potential for drug-induced renal toxicity. Monitor renal function carefully during concurrent therapy. Amphotericin B dosage reduction may be necessary if renal impairment occurs.
Anagrelide: (Moderate) Monitor for signs and symptoms of bleeding during concomitant platelet inhibitor and chronic nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of bleeding.
Angiotensin II receptor antagonists: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Angiotensin-converting enzyme inhibitors: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE

inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Antacids: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Antithrombin III: (Moderate) An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal anti-inflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.
Apixaban: (Major) An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal antiinflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.
Aprepitant, Fosaprepitant: (Minor) Use caution if naproxen and aprepitant are used concurrently and monitor for a possible decrease in the efficacy of naproxen. After administration, fosaprepitant is rapidly converted to aprepitant and shares the same drug interactions. Naproxen is a CYP2C9 substrate and aprepitant is a CYP2C9 inducer. Administration of a CYP2C9 substrate, tolbutamide, on days 1, 4, 8, and 15 with a 3-day regimen of oral aprepitant (125 mg/80 mg/80 mg) decreased the tolbutamide AUC by 23% on day 4, 28% on day 8, and 15% on day 15. The AUC of tolbutamide was decreased by 8% on day 2, 16% on day 4, 15% on day 8, and 10% on day 15 when given prior to oral administration of aprepitant 40 mg on day 1, and on days 2, 4, 8, and 15. The effects of aprepitant on tolbutamide were not considered significant. When a 3-day regimen of aprepitant (125 mg/80 mg/80 mg) given to healthy patients on stabilized chronic warfarin therapy (another CYP2C9 substrate), a 34% decrease in S-warfarin trough concentrations was noted, accompanied by a 14% decrease in the INR at five days after completion of aprepitant.
Argatroban: (Moderate) An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal anti-inflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.
Aspirin, ASA: (Major) Concomitant use of analgesic doses of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A

pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%). Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular protection. Aspirin, ASA; Butalbital; Caffeine: (Major) Concomitant use of analgesic doses of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before

naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%). Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular protection.

Aspirin, ASA; Caffeine: (Major) Concomitant use of analgesic doses of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%). Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular protection.

Aspirin, ASA; Caffeine; Orphenadrine: (Major) Concomitant use of analgesic doses of

aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%). Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular protection.

Aspirin, ASA; Carisoprodol; Codeine: (Major) Concomitant use of analgesic doses of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the

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Aspirin, ASA; Citric Acid; Sodium Bicarbonate: (Major) Concomitant use of analgesic doses of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%).

Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular protection. (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Aspirin, ASA; Dipyridamole: (Major) Concomitant use of analgesic doses of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%).
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Aspirin, ASA; Omeprazole: (Major) Concomitant use of analgesic doses of aspirin and

naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%). Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular protection.

Aspirin, ASA; oxyCODONE: (Major) Concomitant use of analgesic doses of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the

peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%). Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular protection.

Atazanavir: (Minor) Caution is warranted when atazanavir is administered with naproxen as there is a potential for elevated naproxen concentrations. In vitro data suggest naproxen is a substrate for CYP2C8; atazanavir is a weak inhibitor of this enzyme.

Atazanavir; Cobicistat: (Minor) Caution is warranted when atazanavir is administered with naproxen as there is a potential for elevated naproxen concentrations. In vitro data suggest naproxen is a substrate for CYP2C8; atazanavir is a weak inhibitor of this enzyme.

Atenolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.

Atenolol; Chlorthalidone: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics. (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.

Auranofin: (Moderate) Due to the inhibition of renal prostaglandins by NSAIDs, concurrent use with other nephrotoxic agents, such as gold compounds, may lead to additive nephrotoxicity. Monitor renal function carefully during concurrent therapy.

azaTHIOprine: (Moderate) NSAIDs should be used with caution in patients receiving immunosuppressives as they may mask fever, pain, swelling and other signs and symptoms of an infection.
Azelastine; Fluticasone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Azilsartan: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Azilsartan; Chlorthalidone: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Bacitracin: (Major) Avoid concurrent use of bacitracin with nonsteroidal antiinflammatory drugs. Coadministration may increase the risk for drug-induced nephrotoxicity.
Beclomethasone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Benazepril: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Benazepril; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal

function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Benzgalantamine: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.
Benzoic Acid; Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate: (Major) Avoid concomitant use of naproxen with phenyl salicylate due to an increased risk of gastrointestinal toxicity and renal impairment, with little or no increase in efficacy.
Beta-blockers: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Betamethasone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Betaxolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Bictegravir; Emtricitabine; Tenofovir Alafenamide: (Moderate) Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and tenofovir alafenamide may result in additive nephrotoxicity. Monitor for renal toxicity if concomitant use is required. (Moderate) Monitor for nonsteroidal antiinflammatory drug (NSAID) or emtricitabine-related adverse events during concomitant use. Concomitant use may increase NSAID or emtricitabine concentrations. Coadministration of drugs that reduce renal function or compete for active tubular secretion, such as NSAIDs and emtricitabine, may increase

the risk of adverse reactions.
Bismuth Subsalicylate: (Major) Avoid concomitant use of naproxen with bismuth subsalicylate due to an increased risk of gastrointestinal toxicity and renal impairment, with little or no increase in efficacy.
Bismuth Subsalicylate; metroNIDAZOLE; Tetracycline: (Major) Avoid concomitant use of naproxen with bismuth subsalicylate due to an increased risk of gastrointestinal toxicity and renal impairment, with little or no increase in efficacy.
Bisoprolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Bisoprolol; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics. (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Bivalirudin: (Moderate) An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal anti-inflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.
Brimonidine; Timolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Budesonide: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Budesonide; Formoterol: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Budesonide; Glycopyrrolate; Formoterol: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Bumetanide: (Moderate) If a nonsteroidal anti-inflammatory drug (NSAID) and a diuretic are used concurrently, carefully monitor the patient for signs and symptoms of decreased renal function and diuretic efficacy. Patients taking diuretics and NSAIDs concurrently are at higher risk of developing renal insufficiency. NSAIDs may reduce the

natriuretic effect of diuretics in some patients. NSAIDs have been associated with an inhibition of prostaglandin synthesis, which may result in reduced renal blood flow leading to renal insufficiency and increases in blood pressure that are often accompanied by peripheral edema and weight gain.
BUPivacaine; Meloxicam: (Major) Avoid concomitant use of meloxicam with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Busulfan: (Major) Due to the thrombocytopenic effects of busulfan, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, ASA, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Butalbital; Aspirin; Caffeine; Codeine: (Major) Concomitant use of analgesic doses of aspirin and naproxen is generally not recommended due to the increased risk of bleeding and renal impairment. Because there may be an increased risk of cardiovascular events after discontinuation of naproxen due to the interference with the antiplatelet effect of aspirin during the washout period, for patients taking low-dose aspirin for cardioprotection who require intermittent analgesics, consider use of an NSAID that does not interfere with the antiplatelet effect of aspirin, or non-NSAID analgesics as appropriate. A pharmacodynamic study demonstrated that lower dose naproxen (220mg/day or 220mg twice daily) interfered with the antiplatelet effect of low-dose immediate-release aspirin, with the interaction most marked during the washout period of naproxen. There is reason to expect that the interaction would be present with prescription doses of naproxen or with enteric-coated low-dose aspirin; however, the peak interference with aspirin function may be later than observed in the study due to the longer washout period. A decrease in antiplatelet activity was observed at 24 hours after 10 days of naproxen 220 mg/day with low-dose immediate-release aspirin 81 mg/day (93.1%) vs. aspirin alone (98.7%). The interaction was observed even after discontinuation of naproxen on day 11 while aspirin therapy continued but normalized by day 13. The interaction was greater when naproxen was given 30 minutes before aspirin (87.7% vs. 98.7%) and minimal when aspirin was administered 30 minutes before naproxen (95.4% vs. 98.7%). The interaction was minimal at 24 hours after day 10 when naproxen 220 mg twice daily was given 30 minutes before low-dose immediate-release aspirin (95.7% vs. 98.7%); however, the interaction was greater on day 11 after naproxen discontinuation (84.3% vs. 98.7%) and did not normalize by day 13 (90.7% vs. 98.5%). Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone. Naproxen is not a substitute for low dose aspirin for cardiovascular

protection.
Calcium Carbonate; Famotidine; Magnesium Hydroxide: (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Calcium Chloride: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Calcium Phosphate, Supersaturated: (Moderate) Concomitant use of medicines with potential to alter renal perfusion or function such as nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of acute phosphate nephropathy in patients taking sodium phosphate monobasic monohydrate; sodium phosphate dibasic anhydrous.
Calcium-channel blockers: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Candesartan: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Candesartan; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including

antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Capreomycin: (Major) Because capreomycin is primarily eliminated by the kidney, coadministration with other potentially nephrotoxic drugs, including nonsteroidal antiinflammatory drugs (NSAIDs), may increase serum concentrations of either drug. Theoretically, the chronic coadministration of these drugs may increase the risk of developing nephrotoxicity, even in patients who have normal renal function. Monitor patients for changes in renal function if these drugs are coadministered.
Captopril: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Captopril; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Carmustine, BCNU: (Major) Due to the thrombocytopenic effects of carmustine, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, ASA, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding. These additive effects may not occur for at least 6 weeks after the administration of carmustine due to the delayed myelosuppressive effects of carmustine.

Carteolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Carvedilol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Cefotaxime: (Minor) Cefotaxime's product label states that cephalosporins may potentiate the adverse renal effects of nephrotoxic agents, such as aminoglycosides, nonsteroidal antiinflammatory drugs (NSAIDs), and loop diuretics. Carefully monitor renal function, especially during prolonged therapy or use of high aminoglycoside doses. The majority of reported cases involve the combination of aminoglycosides and cephalothin or cephaloridine, which are associated with dose-related nephrotoxicity as singular agents. Limited but conflicting data with other cephalosporins have been noted.
Celecoxib: (Major) Avoid concomitant use of celecoxib with any other NSAID due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Celecoxib; Tramadol: (Major) Avoid concomitant use of celecoxib with any other NSAID due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Chlorambucil: (Major) Due to the thrombocytopenic effects of chlorambucil, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, ASA, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Chlorothiazide: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Chlorpheniramine; Ibuprofen; Pseudoephedrine: (Major) Avoid concomitant use of ibuprofen with any other NSAID due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Chlorthalidone: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk

of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Cholestyramine: (Minor) The absorption of NSAIDs can be delayed if cholestyramine is concomitantly administered.
Choline Salicylate; Magnesium Salicylate: (Major) Avoid concomitant use of naproxen with choline salicylate due to an increased risk of gastrointestinal toxicity and renal impairment, with little or no increase in efficacy. (Major) Avoid concomitant use of naproxen with magnesium salicylate due to an increased risk of gastrointestinal toxicity and renal impairment, with little or no increase in efficacy.
Cholinesterase inhibitors: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.
Ciclesonide: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Cidofovir: (Contraindicated) The concomitant administration of cidofovir and nonsteroidal antiinflammatory drugs (NSAIDs) is contraindicated due to the potential for increased nephrotoxicity. NSAIDs should be discontinued 7 days prior to beginning cidofovir.
Cilostazol: (Moderate) Monitor for signs and symptoms of bleeding during concomitant platelet inhibitor and chronic nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of bleeding.
Cimetidine: (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Ciprofloxacin: (Moderate) Use quinolones and nonsteroidal anti-inflammatory drugs (NSAIDs) concomitantly with caution due to potential increased risk of CNS stimulation and convulsive seizures. NSAIDs in combination with very high doses of quinolones have been shown to provoke convulsions in preclinical studies and postmarketing.
Citalopram: (Moderate) Monitor for signs and symptoms of bleeding during concomitant selective serotonin reuptake inhibitor (SSRI) and nonsteroidal antiinflammatory drug (NSAID) use due to increased risk for bleeding. Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the

occurrence of upper gastrointestinal bleeding.
Citric Acid; Potassium Citrate; Sodium Citrate: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.
Cladribine: (Major) Due to the thrombocytopenic effects of cladribine, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Clevidipine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Clofarabine: (Major) Due to the thrombocytopenic effects of clofarabine, an additive risk of bleeding may be seen in patients receiving concomitant NSAIDs. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Clopidogrel: (Moderate) Monitor for signs and symptoms of bleeding during concomitant platelet inhibitor and chronic nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of bleeding.
Colistimethate, Colistin, Polymyxin E: (Major) The administration of colistimethate sodium may increase the risk of developing nephrotoxicity, even in patients who have normal renal function. Nonsteroidal antiinflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when used concurrently. Monitor patients for changes in renal function if these drugs are coadministered. Since colistimethate sodium is eliminated by the kidney, coadministration with other potentially nephrotoxic drugs, including nonsteroidal antiinflammatory drugs (NSAIDs), may theoretically increase serum concentrations of either drug.
Colistin: (Major) The administration of colistimethate sodium may increase the risk of

developing nephrotoxicity, even in patients who have normal renal function. Nonsteroidal antiinflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when used concurrently. Monitor patients for changes in renal function if these drugs are coadministered. Since colistimethate sodium is eliminated by the kidney, coadministration with other potentially nephrotoxic drugs, including nonsteroidal antiinflammatory drugs (NSAIDs), may theoretically increase serum concentrations of either drug.
Corticosteroids: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Cortisone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
cycloSPORINE: (Moderate) Serum creatinine ,potassium concentrations, and cyclosporine concentrations should be closely monitored when systemic cyclosporine is given with nonsteroidal antiinflammatory drugs (NSAIDs). Renal dysfunction associated with cyclosporine may be potentiated by concurrent usage of NSAIDs. The effects of NSAIDs on the production of renal prostaglandins may cause changes in the elimination of cyclosporine. Potentiation of renal dysfunction may especially occur in a dehydrated patient. Patients should be monitored for signs and symptoms of cyclosporine toxicity and infection, as NSAIDs may mask fever, pain, or swelling. Increased tear production was not seen in patients receiving ophthalmic NSAIDs or using punctual plugs concurrently with cyclosporine ophthalmic emulsion.
Cytarabine, ARA-C: (Major) The main toxic effect of cytarabine, ARA-C is bone marrow suppression with leukopenia, thrombocytopenia and anemia. Due to the thrombocytopenic effects of cytarabine, an additive risk of bleeding may be seen in patients receiving concomitant NSAIDs. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding. Dipyridamole can block membrane transport of cytarabine in tumor cells, therefore decreasing its antineoplastic activity.
Dabigatran: (Major) Educate patients about the signs of increased bleeding and the need to report these signs to a healthcare provider immediately if coadministration of dabigatran and a nonsteroidal antiinflammatory drug (NSAID) is necessary. Dabigatran can cause significant and, sometimes, fatal bleeding. This risk may be increased by concurrent use of chronic NSAID therapy.
Dabrafenib: (Moderate) Use dabrafenib and naproxen together with caution; naproxen exposure may be decreased. Use an alternate agent in place of naproxen if possible. If concomitant use with cannot be avoided, monitor patients for loss of naproxen efficacy. Dabrafenib is a weak CYP29 inducer and naproxen is a CYP2C9 substrate. When a single-dose of a sensitive CYP2C9 substrate was administered after 15 days of dabrafenib 150

mg twice daily, the AUC value of the CYP2C9 substrate was decreased by 37%.
Dacarbazine, DTIC: (Major) Leukopenia and thrombocytopenia are common toxicities of dacarbazine, DTIC. Due to the thrombocytopenic effects of dacarbazine, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, ASA, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Dalteparin: (Moderate) An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal antiinflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.
Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide: (Moderate) Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and tenofovir alafenamide may result in additive nephrotoxicity. Monitor for renal toxicity if concomitant use is required. (Moderate) Monitor for nonsteroidal antiinflammatory drug (NSAID) or emtricitabine-related adverse events during concomitant use. Concomitant use may increase NSAID or emtricitabine concentrations. Coadministration of drugs that reduce renal function or compete for active tubular secretion, such as NSAIDs and emtricitabine, may increase the risk of adverse reactions.
Dasatinib: (Major) Due to the thrombocytopenic and possible platelet inhibiting effects of dasatinib, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors (including aspirin), strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding. Caution should be exercised if patients are required to take medications that inhibit platelet function or anticoagulants concomitantly with dasatinib.
Deferasirox: (Moderate) Because gastric ulceration and GI bleeding have been reported in patients taking deferasirox, use caution when coadministering with other drugs known to increase the risk of peptic ulcers or gastric hemorrhage including NSAIDs. In addition, coadministration of deferasirox with other potentially nephrotoxic drugs, including NSAIDs, may increase the acute renal failure. Monitor serum creatinine and/or creatinine clearance in patients who are receiving deferasirox and nephrotoxic drugs concomitantly.
Deflazacort: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Delafloxacin: (Moderate) Use quinolones and nonsteroidal anti-inflammatory drugs (NSAIDs) concomitantly with caution due to potential increased risk of CNS stimulation and convulsive seizures. NSAIDs in combination with very high doses of quinolones have been shown to provoke convulsions in preclinical studies and postmarketing.

Desmopressin: (Major) Additive hyponatremic effects may be seen in patients treated with desmopressin and drugs associated with hyponatremia including NSAIDs. Use combination with caution, and monitor patients for signs and symptoms of hyponatremia. A woman who took both desmopressin and ibuprofen was found in a comatose state. As her serum sodium concentration was 121 mmol/L, and her plasma osmolality was low in the presence of a high-normal urine osmolality and normal sodium excretion, she was treated with fluid restriction. Her serum sodium concentration was 124 mmol/L within a day and was 135 mmol/L by the second day. The woman had previously received desmopressin without the development of clinical symptoms of hyponatremia.
Desvenlafaxine: (Moderate) Platelet aggregation may be impaired by desvenlafaxine due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving nonsteroidal antiinflammatory drugs (NSAIDs). Patients should be monitored for signs and symptoms of bleeding while taking desvenlafaxine with NSAIDs.
dexAMETHasone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Diclofenac: (Major) Avoid concomitant use of diclofenac with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Diclofenac; miSOPROStol: (Major) Avoid concomitant use of diclofenac with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Diflunisal: (Major) Avoid concomitant use of diflunisal with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers. Additionally, concomitant administration of naproxen and diflunisal significantly decreased the urinary excretion of naproxen and its glucuronide metabolite; naproxen and diflunisal plasma concentrations were unaffected.
Digoxin: (Moderate) Concomitant use of nonsteroidal antiinflammatory drugs (NSAIDs) with digoxin may result in increased serum concentrations of digoxin. NSAIDs may cause a significant deterioration in renal function. A decline in glomerular filtration or tubular secretion may impair the excretion of digoxin. Monitor patients during concomitant treatment for possible digoxin toxicity and reduce digoxin dose as necessary.
dilTIAZem: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs,

to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
diphenhydrAMINE; Ibuprofen: (Major) Avoid concomitant use of ibuprofen with any other NSAID due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Dipyridamole: (Moderate) Monitor for signs and symptoms of bleeding during concomitant platelet inhibitor and chronic nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of bleeding.
DOCEtaxel: (Major) Due to the thrombocytopenic effects of docetaxel, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors (including aspirin), strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Donepezil: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.
Donepezil; Memantine: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.
Doravirine; lamiVUDine; Tenofovir disoproxil fumarate: (Moderate) Avoid administering tenofovir, PMPA concurrently with or recently after a nephrotoxic agent, such as high-dose or multiple nonsteroidal antiinflammatory drugs (NSAIDs). Cases of acute renal

failure, some requiring hospitalization and renal replacement therapy, have been reported after high-dose or multiple NSAIDs were initiated in patients who appeared stable on tenofovir. Consider alternatives to NSAIDs in patients at risk for renal dysfunction. If these drugs must be coadministered, carefully monitor the estimated creatinine creatinine, serum phosphorus, urine glucose, and urine protein prior to, and periodically during, treatment.
Dorzolamide; Timolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Doxazosin: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Drospirenone: (Minor) Drospirenone has antimineralocorticoid effects; the progestin may increase serum potassium. Other drugs that may have additive effects on serum potassium with drospirenone include chronic treatment with NSAIDs, and monitoring of serum potassium in the 1st month of concurrent therapy is recommended.
Drospirenone; Estetrol: (Minor) Drospirenone has antimineralocorticoid effects; the progestin may increase serum potassium. Other drugs that may have additive effects on serum potassium with drospirenone include chronic treatment with NSAIDs, and monitoring of serum potassium in the 1st month of concurrent therapy is recommended.
Drospirenone; Estradiol: (Minor) Drospirenone has antimineralocorticoid effects; the progestin may increase serum potassium. Other drugs that may have additive effects on serum potassium with drospirenone include chronic treatment with NSAIDs, and monitoring of serum potassium in the 1st month of concurrent therapy is recommended.
Drospirenone; Ethinyl Estradiol: (Minor) Drospirenone has antimineralocorticoid effects; the progestin may increase serum potassium. Other drugs that may have additive effects on serum potassium with drospirenone include chronic treatment with NSAIDs,

and monitoring of serum potassium in the 1st month of concurrent therapy is recommended.
Drospirenone; Ethinyl Estradiol; Levomefolate: (Minor) Drospirenone has antimineralocorticoid effects; the progestin may increase serum potassium. Other drugs that may have additive effects on serum potassium with drospirenone include chronic treatment with NSAIDs, and monitoring of serum potassium in the 1st month of concurrent therapy is recommended. (Minor) L-methylfolate should be used cautiously in patients taking high doses of naproxen. Plasma concentrations of L-methylfolate may be reduced when used concomitantly with high doses of naproxen. Monitor patients for decreased efficacy of L-methylfolate if these agents are used together.
DULoxetine: (Moderate) Monitor for signs and symptoms of bleeding during concomitant duloxetine and nonsteroidal antiinflammatory drug (NSAID) use due to increased risk for bleeding. Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding.
Edoxaban: (Major) An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal antiinflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.
Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate: (Moderate) Avoid administering tenofovir, PMPA concurrently with or recently after a nephrotoxic agent, such as high-dose or multiple nonsteroidal antiinflammatory drugs (NSAIDs). Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after high-dose or multiple NSAIDs were initiated in patients who appeared stable on tenofovir. Consider alternatives to NSAIDs in patients at risk for renal dysfunction. If these drugs must be coadministered, carefully monitor the estimated creatinine creatinine, serum phosphorus, urine glucose, and urine protein prior to, and periodically during, treatment. (Moderate) Monitor for nonsteroidal antiinflammatory drug (NSAID) or emtricitabine-related adverse events during concomitant use. Concomitant use may increase NSAID or emtricitabine concentrations. Coadministration of drugs that reduce renal function or compete for active tubular secretion, such as NSAIDs and emtricitabine, may increase the risk of adverse reactions.
Efavirenz; lamiVUDine; Tenofovir Disoproxil Fumarate: (Moderate) Avoid administering tenofovir, PMPA concurrently with or recently after a nephrotoxic agent, such as high-dose or multiple nonsteroidal antiinflammatory drugs (NSAIDs). Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after high-dose or multiple NSAIDs were initiated in patients who appeared stable on tenofovir. Consider alternatives to NSAIDs in patients at risk for renal dysfunction. If these drugs must be coadministered, carefully monitor the estimated

creatinine creatinine, serum phosphorus, urine glucose, and urine protein prior to, and periodically during, treatment.
Elexacaftor; tezacaftor; ivacaftor: (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as naproxen. In vitro studies showed ivacaftor to be a weak inhibitor of CYP2C9. Co-administration may lead to increased exposure to CYP2C9 substrates; however, the clinical impact of this has not yet been determined.
Eltrombopag: (Moderate) Eltrombopag is a UDP-glucuronyltransferase inhibitor. NSAIDs are a substrate of UDP-glucuronyltransferases. The significance or effect of this interaction is not known; however, elevated concentrations of the NSAID are possible. Monitor patients for adverse reactions if eltrombopag is administered with an NSAID.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Alafenamide: (Moderate) Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and tenofovir alafenamide may result in additive nephrotoxicity. Monitor for renal toxicity if concomitant use is required. (Moderate) Monitor for nonsteroidal antiinflammatory drug (NSAID) or emtricitabine-related adverse events during concomitant use. Concomitant use may increase NSAID or emtricitabine concentrations. Coadministration of drugs that reduce renal function or compete for active tubular secretion, such as NSAIDs and emtricitabine, may increase the risk of adverse reactions. (Moderate) The plasma concentrations of naproxen may be decreased when administered concurrently with elvitegravir. Patients may experience decreased analgesic or anti-inflammatory effects when these drugs are coadministered. Elvitegravir is a CYP2C9 inducer, while naproxen is a CYP2C9 substrate.
Elvitegravir; Cobicistat; Emtricitabine; Tenofovir Disoproxil Fumarate: (Moderate) Avoid administering tenofovir, PMPA concurrently with or recently after a nephrotoxic agent, such as high-dose or multiple nonsteroidal antiinflammatory drugs (NSAIDs). Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after high-dose or multiple NSAIDs were initiated in patients who appeared stable on tenofovir. Consider alternatives to NSAIDs in patients at risk for renal dysfunction. If these drugs must be coadministered, carefully monitor the estimated creatinine creatinine, serum phosphorus, urine glucose, and urine protein prior to, and periodically during, treatment. (Moderate) Monitor for nonsteroidal antiinflammatory drug (NSAID) or emtricitabine-related adverse events during concomitant use. Concomitant use may increase NSAID or emtricitabine concentrations. Coadministration of drugs that reduce renal function or compete for active tubular secretion, such as NSAIDs and emtricitabine, may increase the risk of adverse reactions. (Moderate) The plasma concentrations of naproxen may be decreased when administered concurrently with elvitegravir. Patients may experience decreased analgesic or anti-inflammatory effects when these drugs are coadministered. Elvitegravir is a CYP2C9 inducer, while naproxen is a CYP2C9 substrate.

Emtricitabine: (Moderate) Monitor for nonsteroidal antiinflammatory drug (NSAID) or emtricitabine-related adverse events during concomitant use. Concomitant use may increase NSAID or emtricitabine concentrations. Coadministration of drugs that reduce renal function or compete for active tubular secretion, such as NSAIDs and emtricitabine, may increase the risk of adverse reactions.
Emtricitabine; Rilpivirine; Tenofovir alafenamide: (Moderate) Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and tenofovir alafenamide may result in additive nephrotoxicity. Monitor for renal toxicity if concomitant use is required. (Moderate) Monitor for nonsteroidal antiinflammatory drug (NSAID) or emtricitabine-related adverse events during concomitant use. Concomitant use may increase NSAID or emtricitabine concentrations. Coadministration of drugs that reduce renal function or compete for active tubular secretion, such as NSAIDs and emtricitabine, may increase the risk of adverse reactions.
Emtricitabine; Rilpivirine; Tenofovir Disoproxil Fumarate: (Moderate) Avoid administering tenofovir, PMPA concurrently with or recently after a nephrotoxic agent, such as high-dose or multiple nonsteroidal antiinflammatory drugs (NSAIDs). Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after high-dose or multiple NSAIDs were initiated in patients who appeared stable on tenofovir. Consider alternatives to NSAIDs in patients at risk for renal dysfunction. If these drugs must be coadministered, carefully monitor the estimated creatinine creatinine, serum phosphorus, urine glucose, and urine protein prior to, and periodically during, treatment. (Moderate) Monitor for nonsteroidal antiinflammatory drug (NSAID) or emtricitabine-related adverse events during concomitant use. Concomitant use may increase NSAID or emtricitabine concentrations. Coadministration of drugs that reduce renal function or compete for active tubular secretion, such as NSAIDs and emtricitabine, may increase the risk of adverse reactions.
Emtricitabine; Tenofovir alafenamide: (Moderate) Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and tenofovir alafenamide may result in additive nephrotoxicity. Monitor for renal toxicity if concomitant use is required. (Moderate) Monitor for nonsteroidal antiinflammatory drug (NSAID) or emtricitabine-related adverse events during concomitant use. Concomitant use may increase NSAID or emtricitabine concentrations. Coadministration of drugs that reduce renal function or compete for active tubular secretion, such as NSAIDs and emtricitabine, may increase the risk of adverse reactions.
Emtricitabine; Tenofovir Disoproxil Fumarate: (Moderate) Avoid administering tenofovir, PMPA concurrently with or recently after a nephrotoxic agent, such as high-dose or multiple nonsteroidal antiinflammatory drugs (NSAIDs). Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after high-dose or multiple NSAIDs were initiated in patients who appeared stable on tenofovir. Consider alternatives to NSAIDs in patients at risk for renal dysfunction. If

these drugs must be coadministered, carefully monitor the estimated creatinine creatinine, serum phosphorus, urine glucose, and urine protein prior to, and periodically during, treatment. (Moderate) Monitor for nonsteroidal antiinflammatory drug (NSAID) or emtricitabine-related adverse events during concomitant use. Concomitant use may increase NSAID or emtricitabine concentrations. Coadministration of drugs that reduce renal function or compete for active tubular secretion, such as NSAIDs and emtricitabine, may increase the risk of adverse reactions.
Enalapril, Enalaprilat: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Enalapril; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Enoxaparin: (Major) Whenever possible, discontinue agents which may enhance the risk of hemorrhage, including nonsteroidal antiinflammatory drugs, before initiation of enoxaparin therapy. If coadministration is essential, conduct close clinical and laboratory monitoring.
Entecavir: (Moderate) The manufacturer of entecavir recommends monitoring for adverse effects when coadministered with NSAIDs. Entecavir is primarily eliminated by the kidneys; NSAIDs can affect renal function. Concurrent administration may increase the serum concentrations of entecavir and adverse events.
Eplerenone: (Major) Monitor serum potassium and serum creatinine concentrations within 3 to 7 days of initiating coadministration of eplerenone and nonsteroidal antiinflammatory drugs (NSAIDs), and monitor blood pressure. The concomitant use of other potassium-sparing antihypertensives with NSAIDs has been shown to reduce the

antihypertensive effect in some patients and result in severe hyperkalemia in patients with impaired renal function. Patients who develop hyperkalemia may continue eplerenone with proper dose adjustment; eplerenone dose reduction decreases potassium concentrations.
Epoprostenol: (Moderate) NSAIDs may decrease the effect of antihypertensive agents through various mechanisms, including renal and peripheral vasoactive pathways.
Eptifibatide: (Moderate) Monitor for signs and symptoms of bleeding during concomitant platelet inhibitor and chronic nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of bleeding.
Erlotinib: (Moderate) Monitor for symptoms of gastrointestinal (GI) perforation (e.g., severe abdominal pain, fever, nausea, and vomiting) if coadministration of erlotinib with nonsteroidal antiinflammatory drugs (NSAIDs) is necessary. Permanently discontinue erlotinib in patients who develop GI perforation. The pooled incidence of GI perforation clinical trials of erlotinib ranged from 0.1% to 0.4%, including fatal cases. Patients receiving concomitant NSAIDs may be at increased risk of perforation.
Escitalopram: (Moderate) Monitor for signs and symptoms of bleeding during concomitant selective serotonin reuptake inhibitor (SSRI) and nonsteroidal antiinflammatory drug (NSAID) use due to increased risk for bleeding. Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding.
Esmolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Ethacrynic Acid: (Moderate) If a nonsteroidal anti-inflammatory drug (NSAID) and a diuretic are used concurrently, carefully monitor the patient for signs and symptoms of decreased renal function and diuretic efficacy. Patients taking diuretics and NSAIDs concurrently are at higher risk of developing renal insufficiency. NSAIDs may reduce the natriuretic effect of diuretics in some patients. NSAIDs have been associated with an inhibition of prostaglandin synthesis, which may result in reduced renal blood flow leading to renal insufficiency and increases in blood pressure that are often accompanied by peripheral edema and weight gain.
Ethanol: (Major) Advise patients to avoid alcohol and alcohol-containing products while taking NSAIDs. Concomitant ingestion of alcohol with NSAIDs increases the risk of developing gastric irritation and GI mucosal bleeding. Alcohol is a mucosal irritant and NSAIDs decrease platelet aggregation. Routine ingestion of alcohol and NSAIDs can cause significant GI bleeding, which may or may not be overt. Even occasional concomitant use of NSAIDs and alcohol should be avoided. Chronic alcohol ingestion is often associated with hypoprothrombinemia and this condition increases the risk of bleeding.

Ethiodized Oil: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when given to patients receiving a contrast agents. When possible, withhold NSAID therapy during administration of a contrast agent.
Etodolac: (Major) Avoid concomitant use of etodolac with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Famotidine: (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Felodipine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Fenofibric Acid: (Minor) At therapeutic concentrations, fenofibric acid is a mild-to-moderate inhibitor of CYP2C9. Concomitant use of fenofibric acid with CYP2C9 substrates, such as naproxen, has not been formally studied. Fenofibric acid may theoretically increase plasma concentrations of CYP2C9 substrates and could lead to toxicity for drugs that have a narrow therapeutic range. Monitor the therapeutic effect of naproxen during coadministration with fenofibric acid.
Fenoprofen: (Major) Avoid concomitant use of fenoprofen with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Floxuridine: (Major) Due to the thrombocytopenic effects of floxuridine, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Fludrocortisone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.

Flunisolide: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
FLUoxetine: (Moderate) Monitor for signs and symptoms of bleeding during concomitant selective serotonin reuptake inhibitor (SSRI) and nonsteroidal antiinflammatory drug (NSAID) use due to increased risk for bleeding. Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding.
Flurbiprofen: (Major) Avoid concomitant use of flurbiprofen with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Fluticasone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Fluticasone; Salmeterol: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Fluticasone; Umeclidinium; Vilanterol: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Fluticasone; Vilanterol: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
fluvoxaMINE: (Moderate) Monitor for signs and symptoms of bleeding during concomitant selective serotonin reuptake inhibitor (SSRI) and nonsteroidal antiinflammatory drug (NSAID) use due to increased risk for bleeding. Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding.
Fondaparinux: (Moderate) An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal antiinflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.
Formoterol; Mometasone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Foscarnet: (Minor) The risk of renal toxicity may be increased if foscarnet is used in conjuction with other nephrotoxic agents, such as nonsteroidal antiinflammatory drugs (NSAIDs). Monitor renal function carefully during concurrent therapy.

Fosinopril: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Fosinopril; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Fosphenytoin: (Minor) Naproxen is 99% bound to albumin. Thus, naproxen may displace other highly protein bound drugs from albumin or vice versa. If naproxen is used concurrently with hydantoins, monitor patients for toxicity from either drug.
Furosemide: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant furosemide and naproxen use. Nonsteroidal antiinflammatory drugs (NSAIDs) may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of loop diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Galantamine: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.

Ganciclovir: (Minor) Concurrent use of nephrotoxic agents, such as NSAIDs, with ganciclovir should be done cautiously to avoid additive nephrotoxicity. Monitor renal function carefully if concomitant therapy is required.
Garlic, Allium sativum: (Minor) Garlic, Allium sativum may produce clinically-significant antiplatelet effects; until more data are available, garlic should be used cautiously in patients receiving drugs with a known potential risk for bleeding such as nonsteroidal antiinflammatory drugs (NSAIDs).
Gemfibrozil: (Moderate) Use naproxen and gemfibrozil together with caution. Naproxen is a substrate of CYP2C8, and gemfibrozil is a strong CYP2C8 inhibitor. Coadministration may result in a significant increase in naproxen exposure. A dose reduction of naproxen may be required if used concomitantly with gemfibrozil.
Gemifloxacin: (Moderate) Use quinolones and nonsteroidal anti-inflammatory drugs (NSAIDs) concomitantly with caution due to potential increased risk of CNS stimulation and convulsive seizures. NSAIDs in combination with very high doses of quinolones have been shown to provoke convulsions in preclinical studies and postmarketing.
Gentamicin: (Moderate) It is possible that additive nephrotoxicity may occur in patients who receive nonsteroidal anti-inflammatory drugs (NSAIDs) concurrently with other nephrotoxic agents, such as gentamicin.
Gepotidacin: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.
Ginger, Zingiber officinale: (Minor) Patients receiving regular therapy with nonsteroidal antiinflammatory drugs (NSAIDs) should use ginger with caution, due to a theoretical risk of bleeding resulting from additive pharmacology related to the COX enzymes. However, clinical documentation of interactions is lacking. Several pungent constituents of ginger (Zingiber officinale) are reported to inhibit arachidonic acid (AA) induced platelet activation in human whole blood. The constituent (8)-paradol is the most potent inhibitor of COX-1 and exhibits the greatest anti-platelet activity versus other gingerol analogues. The mechanism of ginger-associated platelet inhibition may be related to decreased COX-1/Thomboxane synthase enzymatic activity.
Ginkgo, Ginkgo biloba: (Moderate) Monitor for signs or symptoms of bleeding with coadministration of ginkgo biloba and NSAIDs as an increased bleeding risk may occur. Although data are mixed, ginkgo biloba is reported to inhibit platelet aggregation and several case reports describe bleeding complications with ginkgo biloba, with or without concomitant drug therapy.

Glimepiride: (Moderate) NSAIDs may enhance hypoglycemia in diabetic patients via inhibition of prostaglandin synthesis, which indirectly increases insulin secretion. If NSAIDs are administered or discontinued in patients receiving oral antidiabetic agents, patients should be monitored for hypoglycemia or loss of blood glucose control. No clinically significant interaction between sulindac at daily doses of 400 mg and oral hypoglycemic agents has been observed. Sulindac, its sulfide metabolite, and sulfonylureas are highly bound to protein. Sulindac could displace the sulfonylureas, altering hypoglycemic activity. Careful patient monitoring is recommended to ensure that no change in their diabetes medicine dosage is required. A sulfonylurea dose adjustment may be needed, especially if sulindac doses greater than 400 mg daily are used or if the drug combination is used in patients with renal impairment or other metabolic defects that might increase sulindac blood concentrations.
glipiZIDE: (Moderate) NSAIDs may enhance hypoglycemia in diabetic patients via inhibition of prostaglandin synthesis, which indirectly increases insulin secretion. If NSAIDs are administered or discontinued in patients receiving oral antidiabetic agents, patients should be monitored for hypoglycemia or loss of blood glucose control. No clinically significant interaction between sulindac at daily doses of 400 mg and oral hypoglycemic agents has been observed. Sulindac, its sulfide metabolite, and sulfonylureas are highly bound to protein. Sulindac could displace the sulfonylureas, altering hypoglycemic activity. Careful patient monitoring is recommended to ensure that no change in their diabetes medicine dosage is required. A sulfonylurea dose adjustment may be needed, especially if sulindac doses greater than 400 mg daily are used or if the drug combination is used in patients with renal impairment or other metabolic defects that might increase sulindac blood concentrations.
glipiZIDE; metFORMIN: (Moderate) NSAIDs may enhance hypoglycemia in diabetic patients via inhibition of prostaglandin synthesis, which indirectly increases insulin secretion. If NSAIDs are administered or discontinued in patients receiving oral antidiabetic agents, patients should be monitored for hypoglycemia or loss of blood glucose control. No clinically significant interaction between sulindac at daily doses of 400 mg and oral hypoglycemic agents has been observed. Sulindac, its sulfide metabolite, and sulfonylureas are highly bound to protein. Sulindac could displace the sulfonylureas, altering hypoglycemic activity. Careful patient monitoring is recommended to ensure that no change in their diabetes medicine dosage is required. A sulfonylurea dose adjustment may be needed, especially if sulindac doses greater than 400 mg daily are used or if the drug combination is used in patients with renal impairment or other metabolic defects that might increase sulindac blood concentrations.
glyBURIDE: (Moderate) NSAIDs may enhance hypoglycemia in diabetic patients via inhibition of prostaglandin synthesis, which indirectly increases insulin secretion. If NSAIDs are administered or discontinued in patients receiving oral antidiabetic agents,

patients should be monitored for hypoglycemia or loss of blood glucose control. No clinically significant interaction between sulindac at daily doses of 400 mg and oral hypoglycemic agents has been observed. Sulindac, its sulfide metabolite, and sulfonylureas are highly bound to protein. Sulindac could displace the sulfonylureas, altering hypoglycemic activity. Careful patient monitoring is recommended to ensure that no change in their diabetes medicine dosage is required. A sulfonylurea dose adjustment may be needed, especially if sulindac doses greater than 400 mg daily are used or if the drug combination is used in patients with renal impairment or other metabolic defects that might increase sulindac blood concentrations.
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Gold: (Moderate) Due to the inhibition of renal prostaglandins by NSAIDs, concurrent use with other nephrotoxic agents, such as gold compounds, may lead to additive nephrotoxicity. Monitor renal function carefully during concurrent therapy.
guanFACINE: (Moderate) NSAIDs may decrease the effect of antihypertensive agents through various mechanisms, including renal and peripheral vasoactive pathways.
H2-blockers: (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Heparin: (Moderate) An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal antiinflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.
Hyaluronidase, Recombinant; Immune Globulin: (Moderate) Immune Globulin (IG) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients receiving known nephrotoxic drugs like nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates. Coadminister IG products at the minimum concentration available and the minimum rate of infusion practicable. Also, closely monitor renal

function.
Hydantoins: (Minor) Naproxen is 99% bound to albumin. Thus, naproxen may displace other highly protein bound drugs from albumin or vice versa. If naproxen is used concurrently with hydantoins, monitor patients for toxicity from either drug.
hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
hydroCHLOROthiazide, HCTZ; Moexipril: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
HYDROcodone; Ibuprofen: (Major) Avoid concomitant use of ibuprofen with any other NSAID due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Hydrocortisone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Hyoscyamine; Methenamine; Methylene Blue; Phenyl Salicylate; Sodium Biphosphate: (Major) Avoid concomitant use of naproxen with phenyl salicylate due to an increased risk of gastrointestinal toxicity and renal impairment, with little or no increase in efficacy.
Ibandronate: (Moderate) Monitor renal function and for gastrointestinal adverse events during concurrent use of intravenous or oral ibandronate, respectively, and nonsteroidal antiinflammatory drugs. Acute renal failure has been observed with intravenous ibandronate and concomitant use of other nephrotoxic agents may increase this risk. Additionally, the oral formulations of both medications have been associated with

gastrointestinal irritation although data suggest concomitant use introduces little additional risk for adverse effects for most patients.
Ibritumomab Tiuxetan: (Major) During and after therapy, avoid the concomitant use of Yttrium (Y)-90 ibrutumomab tiuxetan with drugs that interfere with platelet function such as nonsteroidal antiinflammatory drugs (NSAIDs); the risk of bleeding may be increased. If coadministration with NSAIDs is necessary, monitor platelet counts more frequently for evidence of thrombocytopenia. (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.
Ibuprofen lysine: (Major) Because ibuprofen lysine exerts similar pharmacologic characteristics to other systemic NSAIDs, including COX-2 inhibitors, additive pharmacodynamic effects, including a potential increase for additive adverse GI effects, may be seen if ibuprofen lysine is used with other NSAIDs. In general, concurrent use of ibuprofen lysine and another NSAID should be avoided.
Ibuprofen: (Major) Avoid concomitant use of ibuprofen with any other NSAID due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Ibuprofen; Famotidine: (Major) Avoid concomitant use of ibuprofen with any other NSAID due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers. (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Ibuprofen; Pseudoephedrine: (Major) Avoid concomitant use of ibuprofen with any other NSAID due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Iloprost: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related

decreases in renal function and an increased risk of stroke and coronary artery disease.
Immune Globulin IV, IVIG, IGIV: (Moderate) Immune Globulin (IG) products have been reported to be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Patients predisposed to acute renal failure include patients receiving known nephrotoxic drugs like nonsteroidal anti-inflammatory drugs (NSAIDs) and salicylates. Coadminister IG products at the minimum concentration available and the minimum rate of infusion practicable. Also, closely monitor renal function.
Indapamide: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the natriuretic effect of diuretics in some patients. NSAIDS have been associated with an inhibition of prostaglandin synthesis, which may result in reduced renal blood flow leading to renal insufficiency and increases in blood pressure that are often accompanied by peripheral edema and weight gain. Patients taking diuretics and NSAIDS concurrently are at higher risk of developing renal insufficiency. If an NSAID and a diuretic are used concurrently, carefully monitor the patient for signs and symptoms of decreased renal function and diuretic efficacy.
Indomethacin: (Major) Avoid concomitant use of indomethacin with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Inotersen: (Moderate) Use caution with concomitant use of inotersen and nonsteroidal antiinflammatory drugs (NSAIDs) due to the risk of glomerulonephritis and nephrotoxicity as well as the potential risk of bleeding from thrombocytopenia. Consider discontinuation of NSAIDs in a patient taking inotersen with a platelet count of less than 50,000 per microliter.
Iodine; Potassium Iodide, KI: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.
Iodixanol: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when given to patients receiving a contrast agents. When possible, withhold NSAID therapy during administration of a contrast agent.
Iohexol: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when given to patients receiving a contrast agents. When possible, withhold NSAID therapy during administration of a contrast agent.
Iomeprol: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when given to patients receiving a contrast agents. When possible, withhold NSAID therapy during administration of a contrast agent.
Ionic Contrast Media: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when given to patients receiving a contrast agents. When possible, withhold NSAID therapy during administration of a contrast agent.
Iopamidol: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when given to patients receiving a contrast agents. When

possible, withhold NSAID therapy during administration of a contrast agent.
Iopromide: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when given to patients receiving a contrast agents. When possible, withhold NSAID therapy during administration of a contrast agent.
Ioversol: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when given to patients receiving a contrast agents. When possible, withhold NSAID therapy during administration of a contrast agent.
Irbesartan: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Irbesartan; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Isosulfan Blue: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when given to patients receiving a contrast agents. When possible, withhold NSAID therapy during administration of a contrast agent.
Isradipine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to

maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Ivacaftor: (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as naproxen. In vitro studies showed ivacaftor to be a weak inhibitor of CYP2C9. Co-administration may lead to increased exposure to CYP2C9 substrates; however, the clinical impact of this has not yet been determined.
Ketoprofen: (Major) Avoid concomitant use of ketoprofen with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Ketorolac: (Contraindicated) Concomitant use of ketorolac with another NSAID is contraindicated. Increased adverse gastrointestinal effects are possible if ketorolac is used with other systemic nonsteroidal antiinflammatory drugs (NSAIDs).
Labetalol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
lamiVUDine; Tenofovir Disoproxil Fumarate: (Moderate) Avoid administering tenofovir, PMPA concurrently with or recently after a nephrotoxic agent, such as high-dose or multiple nonsteroidal antiinflammatory drugs (NSAIDs). Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after high-dose or multiple NSAIDs were initiated in patients who appeared stable on tenofovir. Consider alternatives to NSAIDs in patients at risk for renal dysfunction. If these drugs must be coadministered, carefully monitor the estimated creatinine creatinine, serum phosphorus, urine glucose, and urine protein prior to, and periodically during, treatment.
Landiolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Leflunomide: (Moderate) In vitro studies indicate that the M1 metabolite of leflunomide inhibits cytochrome P450 2C9, the enzyme responsible for the metabolism of many NSAIDs. Leflunomide altered protein binding and thus, increased the free fraction of ibuprofen by 13% to 50%. The clinical significance of the interactions with NSAIDs is unknown. There was extensive concomitant use of NSAIDs in phase III clinical studies of leflunomide in the treatment of rheumatoid arthritis, and no clinical differential effects were observed. However, because some NSAIDs have been reported to cause hepatotoxic effects, some caution may be warranted in their use with leflunomide.
Levamlodipine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and

symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Levobunolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
levoFLOXacin: (Moderate) Use quinolones and nonsteroidal anti-inflammatory drugs (NSAIDs) concomitantly with caution due to potential increased risk of CNS stimulation and convulsive seizures. NSAIDs in combination with very high doses of quinolones have been shown to provoke convulsions in preclinical studies and postmarketing.
Levomefolate: (Minor) L-methylfolate should be used cautiously in patients taking high doses of naproxen. Plasma concentrations of L-methylfolate may be reduced when used concomitantly with high doses of naproxen. Monitor patients for decreased efficacy of L-methylfolate if these agents are used together.
Levomilnacipran: (Moderate) Platelet aggregation may be impaired by SNRIs such as levomilnacipran due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving nonsteroidal antiinflammatory drugs (NSAIDs). Monitor for signs and symptoms of bleeding in patients taking levomilnacipran and NSAIDs.
Lisinopril: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Lisinopril; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted,

or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Lithium: (Moderate) Monitor serum lithium concentrations during concomitant nonsteroidal anti-inflammatory (NSAID) use; reduce the lithium dose based on serum lithium concentrations and clinical response. NSAIDs decrease renal blood flow, resulting in decreased renal clearance and increased serum lithium concentrations.
Lomustine, CCNU: (Major) Due to the bone marrow suppressive and thrombocytopenic effects of lomustine, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, ASA, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Losartan: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Losartan; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Lumacaftor; Ivacaftor: (Moderate) Although the clinical significance of this interaction is

unknown, concurrent use of naproxen and lumacaftor; ivacaftor may alter naproxen exposure; caution and monitoring are advised if these drugs are administered together. Naproxen is a substrate of CYP2C9 (primary) and CYP2C8. In vitro data suggest that lumacaftor; ivacaftor may induce and/or inhibit CYP2C8 and CYP2C9. The net effect on these substrates is not clear, but their exposure may be affected leading to decreased efficacy or increased or prolonged therapeutic effects and adverse events. (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as naproxen. In vitro studies showed ivacaftor to be a weak inhibitor of CYP2C9. Co-administration may lead to increased exposure to CYP2C9 substrates; however, the clinical impact of this has not yet been determined.
Lumacaftor; Ivacaftor: (Moderate) Although the clinical significance of this interaction is unknown, concurrent use of naproxen and lumacaftor; ivacaftor may alter naproxen exposure; caution and monitoring are advised if these drugs are administered together. Naproxen is a substrate of CYP2C9 (primary) and CYP2C8. In vitro data suggest that lumacaftor; ivacaftor may induce and/or inhibit CYP2C8 and CYP2C9. The net effect on these substrates is not clear, but their exposure may be affected leading to decreased efficacy or increased or prolonged therapeutic effects and adverse events.
Macimorelin: (Major) Avoid use of macimorelin with drugs that directly affect pituitary growth hormone secretion, such as nonsteroidal antiinflammatory drugs (NSAIDs). Healthcare providers are advised to discontinue NSAID therapy and observe a sufficient washout period before administering macimorelin. Use of these medications together may impact the accuracy of the macimorelin growth hormone test.
Mafenide: (Minor) Naproxen is 99% bound to albumin. Thus, naproxen may displace other highly protein bound drugs from albumin or vice versa. If naproxen is used concurrently with sulfonamides, monitor patients for toxicity from either drug.
Magnesium Hydroxide: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Magnesium Salicylate: (Major) Avoid concomitant use of naproxen with magnesium salicylate due to an increased risk of gastrointestinal toxicity and renal impairment, with little or no increase in efficacy.
Magnesium Salts: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Magnesium Sulfate; Potassium Sulfate; Sodium Sulfate: (Moderate) Use caution when prescribing sulfate salt bowel preparation in patients taking concomitant medications that may affect renal function such as nonsteroidal anti-inflammatory drugs (NSAIDs).
Mannitol: (Major) Avoid use of mannitol and nonsteroidal anti-inflammatory drugs (NSAIDs), if possible. If use together is necessary, carefully monitor the patient for signs and symptoms of decreased renal function and diuretic efficacy. Concomitant

administration of nephrotoxic drugs, such as NSAIDs, increases the risk of renal failure after administration of mannitol. NSAIDs may reduce the natriuretic effect of diuretics in some patients. NSAIDS have been associated with an inhibition of prostaglandin synthesis, which may result in reduced renal blood flow leading to renal insufficiency and increases in blood pressure that are often accompanied by peripheral edema and weight gain.
Mecamylamine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Meclofenamate Sodium: (Major) Avoid concomitant use of meclofenamate sodium with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Mefenamic Acid: (Major) Avoid concomitant use of mefenamic acid with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Meloxicam: (Major) Avoid concomitant use of meloxicam with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Meloxicam; Rizatriptan: (Major) Avoid concomitant use of meloxicam with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Mesalamine, 5-ASA: (Minor) The concurrent use of mesalamine with known nephrotoxic agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of nephrotoxicity.
Methenamine; Sodium Salicylate: (Major) Avoid concomitant use of naproxen with sodium salicylate due to an increased risk of gastrointestinal toxicity and renal impairment, with little or no increase in efficacy.
Methotrexate: (Major) Do not administer nonsteroidal anti-inflammatory drugs (NSAIDs) before or concomitantly with high doses of methotrexate, such as used in the treatment

of osteosarcoma. Concomitant administration of some NSAIDs with high dose methotrexate therapy has been reported to elevate and prolong serum methotrexate concentrations, resulting in deaths from severe hematologic and gastrointestinal toxicity. Use caution when NSAIDs are administered concomitantly with lower doses of methotrexate as they have been reported to reduce the tubular secretion of methotrexate in an animal model and may enhance its toxicity. Despite potential interactions, patients with rheumatoid arthritis (RA) are often receiving concurrent treatment with NSAIDs without apparent problems. However, these doses are lower than those used in psoriasis or malignancy; higher methotrexate doses may lead to unexpected toxicity in combination with NSAIDs. NSAIDs may be continued in patients with RA receiving treatment with methotrexate, although the possibility of increased toxicity has not been fully explored.
Methoxsalen: (Minor) Preclinical data suggest agents that inhibit prostaglandin synthesis such as naproxen could decrease the efficacy of photosensitizing agents used in photodynamic therapy. Avoidance of naproxen before and during photodynamic therapy may be advisable.
Methyldopa: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
methylPREDNISolone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
metOLazone: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular

effects of diuretics.
Metoprolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Metoprolol; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics. (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
miFEPRIStone: (Moderate) Mifepristone significantly increased exposure of drugs metabolized by CYP2C8/2C9 in interaction studies. Therefore, when mifepristone is used chronically, as in the treatment of Cushing's syndrome, use caution with coadministered CYP2C8/2C9 substrates, including the NSAIDs. Use the lowest doses of the substrate and patients should be monitored closely for adverse reactions.
Milnacipran: (Moderate) Platelet aggregation may be impaired by milnacipran due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving nonsteroidal antiinflammatory drugs (NSAIDs). Monitor for signs and symptoms of bleeding in patients taking milnacipran and NSAIDs.
mitoXANTRONE: (Major) Due to the thrombocytopenic effects of mitoxantrone, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Moexipril: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Mometasone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Moxifloxacin: (Moderate) Use quinolones and nonsteroidal anti-inflammatory drugs

(NSAIDs) concomitantly with caution due to potential increased risk of CNS stimulation and convulsive seizures. NSAIDs in combination with very high doses of quinolones have been shown to provoke convulsions in preclinical studies and postmarketing.
Nabumetone: (Major) Avoid concomitant use of nabumetone with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Nadolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Nebivolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Nelarabine: (Major) Due to the thrombocytopenic effects of nelarabine, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Neomycin: (Minor) It is possible that additive nephrotoxicity may occur in patients who receive NSAIDs concurrently with other nephrotoxic agents, such as aminoglycosides.
Neostigmine: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.
Neostigmine; Glycopyrrolate: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.
NiCARdipine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect

is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. NIFEdipine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. niMODipine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. Nisoldipine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive

medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Nizatidine: (Moderate) Avoid concomitant use of enteric-coated, delayed-release naproxen and H2-blockers due to the gastric pH elevating effects of H2-blockers. Enteric-coated, delayed-release naproxen tablets are designed to dissolve at a pH of 6 or more.
Non-Ionic Contrast Media: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when given to patients receiving a contrast agents. When possible, withhold NSAID therapy during administration of a contrast agent.
Ofloxacin: (Moderate) Use quinolones and nonsteroidal anti-inflammatory drugs (NSAIDs) concomitantly with caution due to potential increased risk of CNS stimulation and convulsive seizures. NSAIDs in combination with very high doses of quinolones have been shown to provoke convulsions in preclinical studies and postmarketing.
OLANZapine; FLUoxetine: (Moderate) Monitor for signs and symptoms of bleeding during concomitant selective serotonin reuptake inhibitor (SSRI) and nonsteroidal antiinflammatory drug (NSAID) use due to increased risk for bleeding. Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding.
Olmesartan: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Olmesartan; amLODIPine; hydroCHLOROthiazide, HCTZ: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving

concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.

Olmesartan; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.

Olopatadine; Mometasone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.

Omacetaxine: (Major) Avoid the concomitant use of omacetaxine and nonsteroidal

antiinflammatory drugs (NSAIDs) when the platelet count is less than 50,000 cells/microliter due to an increased risk of bleeding.
Omeprazole; Sodium Bicarbonate: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Oritavancin: (Moderate) Naproxen is metabolized by CYP2C9; oritavancin is a weak CYP2C9 inhibitor. Coadministration may result in elevated naproxen plasma concentrations. If these drugs are administered concurrently, monitor patients for NSAID-induced toxicity, such as nausea, GI bleeding, or renal dysfunction.
Oxaprozin: (Major) Avoid concomitant use of naproxen with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
PACLitaxel: (Major) Due to the thrombocytopenic effects of paclitaxel, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Pamidronate: (Moderate) Monitor renal function during concomitant pamidronate and nonsteroidal antiinflammatory drug use due to risk for additive nephrotoxicity.
PARoxetine: (Moderate) Monitor for signs and symptoms of bleeding during concomitant selective serotonin reuptake inhibitor (SSRI) and nonsteroidal antiinflammatory drug (NSAID) use due to increased risk for bleeding. Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding.
Pentamidine: (Major) Avoid concurrent or sequential use of pentamidine with naproxen. Coadministration may increase the risk for drug-induced nephrotoxicity. Closely monitor renal function if coadministration is unavoidable.
Pentosan: (Moderate) An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal antiinflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.
Pentostatin: (Major) Due to the thrombocytopenic effects of pentostatin, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Perindopril: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-

inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Perindopril; amLODIPine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Phenoxybenzamine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Phentolamine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an

antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Phenytoin: (Minor) Naproxen is 99% bound to albumin. Thus, naproxen may displace other highly protein bound drugs from albumin or vice versa. If naproxen is used concurrently with hydantoins, monitor patients for toxicity from either drug.
Photosensitizing agents (topical): (Moderate) Agents that inhibit prostaglandin synthesis such as nonsteroidal antiinflammatory drugs (NSAIDs), could decrease the efficacy of photosensitizing agents used in photodynamic therapy. Avoidance of NSAIDs before and during photodynamic therapy may be advisable.
PHYSostigmine: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.
Pindolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Pioglitazone; Glimepiride: (Moderate) NSAIDs may enhance hypoglycemia in diabetic patients via inhibition of prostaglandin synthesis, which indirectly increases insulin secretion. If NSAIDs are administered or discontinued in patients receiving oral antidiabetic agents, patients should be monitored for hypoglycemia or loss of blood glucose control. No clinically significant interaction between sulindac at daily doses of 400 mg and oral hypoglycemic agents has been observed. Sulindac, its sulfide metabolite, and sulfonylureas are highly bound to protein. Sulindac could displace the sulfonylureas, altering hypoglycemic activity. Careful patient monitoring is recommended to ensure that no change in their diabetes medicine dosage is required. A

sulfonylurea dose adjustment may be needed, especially if sulindac doses greater than 400 mg daily are used or if the drug combination is used in patients with renal impairment or other metabolic defects that might increase sulindac blood concentrations.
Piroxicam: (Major) Avoid concomitant use of naproxen with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Platelet Inhibitors: (Moderate) Monitor for signs and symptoms of bleeding during concomitant platelet inhibitor and chronic nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of bleeding.
Pneumococcal Vaccine, Polyvalent: (Moderate) Concomitant administration of antipyretics, such as nonsteroidal antiinflammatory drugs (NSAIDS), may decrease an individual's immunological response to the pneumococcal vaccine. A post-marketing study conducted in Poland using a non-US vaccination schedule (2, 3, 4, and 12 months of age) evaluated the impact of prophylactic oral acetaminophen on antibody responses to Prevnar 13. Data show that acetaminophen, given at the time of vaccination and then dosed at 6 to 8 hour intervals for 3 doses on a scheduled basis, reduced the antibody response to some serotypes after the third dose of Prevnar 13 when compared to the antibody responses of infants who only received antipyretics 'as needed' for treatment. However, reduced antibody responses were not observed after the fourth dose of Prevnar 13 with prophylactic acetaminophen.
Polyethylene Glycol; Electrolytes: (Moderate) Use caution when prescribing sulfate salt bowel preparation in patients taking concomitant medications that may affect renal function such as nonsteroidal anti-inflammatory drugs (NSAIDs).
Polyethylene Glycol; Electrolytes; Ascorbic Acid: (Moderate) Use caution when prescribing sulfate salt bowel preparation in patients taking concomitant medications that may affect renal function such as nonsteroidal anti-inflammatory drugs (NSAIDs).
Polymyxin B: (Major) The chronic coadministration of systemic polymyxins may increase the risk of developing nephrotoxicity, even in patients who have normal renal function. Nonsteroidal antiinflammatory drugs (NSAIDs) may increase the risk for nephrotoxicity when used concurrently. Monitor patients for changes in renal function if these drugs are coadministered. Since Polymyxin B is eliminated by the kidney, coadministration with other potentially nephrotoxic drugs, including nonsteroidal antiinflammatory drugs (NSAIDs), may theoretically increase serum concentrations of either drug.
Potassium Acetate: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.
Potassium Bicarbonate: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.

Potassium Chloride: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.
Potassium Citrate: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.
Potassium Citrate; Citric Acid: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.
Potassium Gluconate: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.
Potassium Iodide, KI: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.
Potassium: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk of hyperkalemia.
PRALAtrexate: (Major) Renal elimination accounts for approximately 34% of the overall clearance of pralatrexate. Concomitant administration of drugs that undergo substantial renal clearance, such as nonsteroidal antiinflammatory drugs (NSAIDs), may result in delayed clearance of pralatrexate.
Prasugrel: (Moderate) Monitor for signs and symptoms of bleeding during concomitant platelet inhibitor and chronic nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of bleeding.
Prazosin: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
prednisoLONE: (Moderate) Monitor for gastrointestinal toxicity during concurrent

corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
predniSONE: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Probenecid: (Major) Substantial increases in the plasma concentration of naproxen anion have been observed following concomitant administration with probenecid. Plasma concentrations of naproxen can be increased by 50% and its half-life increased to 37 hours. The mechanism of this interaction may be through the inhibition of the formation of naproxen's glucuronide metabolite as well as inhibition of renal clearance.
Probenecid; Colchicine: (Major) Substantial increases in the plasma concentration of naproxen anion have been observed following concomitant administration with probenecid. Plasma concentrations of naproxen can be increased by 50% and its half-life increased to 37 hours. The mechanism of this interaction may be through the inhibition of the formation of naproxen's glucuronide metabolite as well as inhibition of renal clearance.
Procarbazine: (Major) Due to the thrombocytopenic effects of procarbazine, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Propranolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
pyRIDostigmine: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.
Quinapril: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Quinapril; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal

function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Quinolones: (Moderate) Use quinolones and nonsteroidal anti-inflammatory drugs (NSAIDs) concomitantly with caution due to potential increased risk of CNS stimulation and convulsive seizures. NSAIDs in combination with very high doses of quinolones have been shown to provoke convulsions in preclinical studies and postmarketing.
Ramipril: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Reteplase, r-PA: (Moderate) NSAIDs can cause GI bleeding, inhibit platelet aggregation, prolong bleeding time; these pharmacodynamic effects may be increased when administered to patients receiving thrombolytic agents. Patients receiving these drugs concurrently should be monitored closely for bleeding.
Risedronate: (Minor) Monitor for gastrointestinal adverse events during concurrent use of risedronate and nonsteroidal antiinflammatory drugs. Both medications have been associated with gastrointestinal irritation although data suggest concomitant use introduces little additional risk for adverse effects for most patients.
Rivaroxaban: (Major) An additive risk of bleeding may be seen in patients receiving anticoagulants in combination with other agents known to increase the risk of bleeding such as nonsteroidal antiinflammatory drugs (NSAIDs). Monitor clinical and laboratory response closely during concurrent use.
Rivastigmine: (Moderate) NSAIDs may cause additive pharmacodynamic GI effects with cholinesterase inhibitors, leading to gastrointestinal intolerance. Patients receiving concurrent NSAIDs should be monitored closely for symptoms of active or occult gastrointestinal bleeding. While NSAIDs appear to suppress microglial activity, which in

turn may slow inflammatory neurodegenerative processes important for the progression of Alzheimer's disease (AD), there are no clinical data at this time to suggest that NSAIDs alone or as combined therapy with AD agents result in synergistic effects in AD.
Sacubitril; Valsartan: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Salsalate: (Major) Avoid concomitant use of naproxen with salsalate due to an increased risk of gastrointestinal toxicity and renal impairment, with little or no increase in efficacy.
Selective serotonin reuptake inhibitors: (Moderate) Monitor for signs and symptoms of bleeding during concomitant selective serotonin reuptake inhibitor (SSRI) and nonsteroidal antiinflammatory drug (NSAID) use due to increased risk for bleeding. Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding.
Sertraline: (Moderate) Monitor for signs and symptoms of bleeding during concomitant selective serotonin reuptake inhibitor (SSRI) and nonsteroidal antiinflammatory drug (NSAID) use due to increased risk for bleeding. Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding.
Sodium Bicarbonate: (Minor) Concomitant administration of antacids can delay the absorption of naproxen. Periodic antacid use should not be problematic as long as the antacid and enteric-coated naproxen administration are separated by at least 2 hours.
Sodium Phosphate Monobasic Monohydrate; Sodium Phosphate Dibasic Anhydrous: (Moderate) Concomitant use of medicines with potential to alter renal perfusion or function such as nonsteroidal anti-inflammatory drugs (NSAIDs) may increase the risk of acute phosphate nephropathy in patients taking sodium phosphate monobasic monohydrate; sodium phosphate dibasic anhydrous.
Sodium picosulfate; Magnesium oxide; Anhydrous citric acid: (Moderate) Use caution when prescribing sodium picosulfate; magnesium oxide; anhydrous citric acid in patients taking concomitant medications that may affect renal function such as nonsteroidal anti-inflammatory drugs (NSAIDs).
Sodium Sulfate; Magnesium Sulfate; Potassium Chloride: (Moderate) Monitor serum potassium concentrations closely if potassium supplements and nonsteroidal anti-inflammatory drugs (NSAIDs) are used together. Concomitant use may increase the risk

of hyperkalemia.
Sotalol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Sparsentan: (Moderate) Monitor for worsening renal function during concomitant use of sparsentan and nonsteroidal antiinflammatory drugs (NSAIDs), including selective cyclooxygenase (COX-2) inhibitors. Concomitant use increases the risk for nephrotoxicity, especially in patients with additional risk factors such as hypovolemia and chronic renal impairment.
Spironolactone: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant spironolactone and nonsteroidal antiinflammatory drug (NSAID) use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Spironolactone; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant spironolactone and nonsteroidal antiinflammatory drug (NSAID) use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Streptomycin: (Moderate) It is possible that additive nephrotoxicity may occur in patients who receive nonsteroidal anti-inflammatory drugs (NSAIDs) concurrently with other nephrotoxic agents, such as streptomycin.
Sucralfate: (Moderate) Separate sucralfate and naproxen administration by at least 2 hours. Concomitant administration of sucralfate and enteric-coated or delayed-release naproxen tablets can delay the absorption of naproxen.
sulfADIAZINE: (Minor) Naproxen is 99% bound to albumin. Thus, naproxen may displace other highly protein bound drugs from albumin or vice versa. If naproxen is used concurrently with sulfonamides, monitor patients for toxicity from either drug.
Sulfamethoxazole; Trimethoprim, SMX-TMP, Cotrimoxazole: (Minor) Naproxen is 99%

bound to albumin. Thus, naproxen may displace other highly protein bound drugs from albumin or vice versa. If naproxen is used concurrently with sulfonamides, monitor patients for toxicity from either drug.
sulfaSALAzine: (Minor) Naproxen is 99% bound to albumin. Thus, naproxen may displace other highly protein bound drugs from albumin or vice versa. If naproxen is used concurrently with sulfonamides, monitor patients for toxicity from either drug.
Sulfonamides: (Minor) Naproxen is 99% bound to albumin. Thus, naproxen may displace other highly protein bound drugs from albumin or vice versa. If naproxen is used concurrently with sulfonamides, monitor patients for toxicity from either drug.
Sulfonylureas: (Moderate) NSAIDs may enhance hypoglycemia in diabetic patients via inhibition of prostaglandin synthesis, which indirectly increases insulin secretion. If NSAIDs are administered or discontinued in patients receiving oral antidiabetic agents, patients should be monitored for hypoglycemia or loss of blood glucose control. No clinically significant interaction between sulindac at daily doses of 400 mg and oral hypoglycemic agents has been observed. Sulindac, its sulfide metabolite, and sulfonylureas are highly bound to protein. Sulindac could displace the sulfonylureas, altering hypoglycemic activity. Careful patient monitoring is recommended to ensure that no change in their diabetes medicine dosage is required. A sulfonylurea dose adjustment may be needed, especially if sulindac doses greater than 400 mg daily are used or if the drug combination is used in patients with renal impairment or other metabolic defects that might increase sulindac blood concentrations.
Sulindac: (Major) Avoid concomitant use of naproxen with any other NSAID, including COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Sulopenem Etzadroxil; Probenecid: (Major) Substantial increases in the plasma concentration of naproxen anion have been observed following concomitant administration with probenecid. Plasma concentrations of naproxen can be increased by 50% and its half-life increased to 37 hours. The mechanism of this interaction may be through the inhibition of the formation of naproxen's glucuronide metabolite as well as inhibition of renal clearance.
Tacrolimus: (Moderate) Monitor patients for signs of worsening renal function during coadministration of tacrolimus and nonsteroidal antiinflammatory drugs. Coadministration may increase the risk for drug-induced nephrotoxicity.
Telavancin: (Minor) Concurrent or sequential use of telavancin with drugs that inhibit renal prostaglandins such as nonsteroidal antiinflammatory drugs (NSAIDS) may lead to additive nephrotoxicity. Closely monitor renal function and adjust telavancin doses based on calculated creatinine clearance.
Telmisartan: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs.

In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Telmisartan; amLODIPine: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Telmisartan; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Temozolomide: (Major) Myelosuppression, primarily neutropenia and thrombocytopenia, is the dose-limiting toxicity of temozolomide. Due to the thrombocytopenic effects of temozolomide, an additive risk of bleeding may be seen in

patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, ASA, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Tenecteplase: (Moderate) NSAIDs can cause GI bleeding, inhibit platelet aggregation, prolong bleeding time; these pharmacodynamic effects may be increased when administered to patients receiving thrombolytic agents. Patients receiving these drugs concurrently should be monitored closely for bleeding.
Tenofovir Alafenamide: (Moderate) Concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and tenofovir alafenamide may result in additive nephrotoxicity. Monitor for renal toxicity if concomitant use is required.
Tenofovir Disoproxil Fumarate: (Moderate) Avoid administering tenofovir, PMPA concurrently with or recently after a nephrotoxic agent, such as high-dose or multiple nonsteroidal antiinflammatory drugs (NSAIDs). Cases of acute renal failure, some requiring hospitalization and renal replacement therapy, have been reported after high-dose or multiple NSAIDs were initiated in patients who appeared stable on tenofovir. Consider alternatives to NSAIDs in patients at risk for renal dysfunction. If these drugs must be coadministered, carefully monitor the estimated creatinine creatinine, serum phosphorus, urine glucose, and urine protein prior to, and periodically during, treatment.
Terazosin: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Teriflunomide: (Moderate) Increased monitoring is recommended if teriflunomide is administered concurrently with CYP2C8 substrates, such as naproxen. In vivo studies demonstrated that teriflunomide is an inhibitor of CYP2C8. Coadministration may lead to increased exposure to CYP2C8 substrates; however, the clinical impact of this has not yet been determined. Monitor for increased adverse effects, including additive hepatotoxicity.

Tezacaftor; Ivacaftor: (Minor) Increased monitoring is recommended if ivacaftor is administered concurrently with CYP2C9 substrates, such as naproxen. In vitro studies showed ivacaftor to be a weak inhibitor of CYP2C9. Co-administration may lead to increased exposure to CYP2C9 substrates; however, the clinical impact of this has not yet been determined.
Thiazide diuretics: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Thioguanine, 6-TG: (Major) Due to the thrombocytopenic effects of thioguanine, an additive risk of bleeding may be seen in patients receiving concomitant anticoagulants, NSAIDs, platelet inhibitors, including aspirin, strontium-89 chloride, and thrombolytic agents. In addition, large doses of salicylates (>= 3-4 g/day) can cause hypoprothrombinemia, an additional risk factor for bleeding.
Thrombolytic Agents: (Moderate) NSAIDs can cause GI bleeding, inhibit platelet aggregation, prolong bleeding time; these pharmacodynamic effects may be increased when administered to patients receiving thrombolytic agents. Patients receiving these drugs concurrently should be monitored closely for bleeding.
Ticagrelor: (Moderate) Monitor for signs and symptoms of bleeding during concomitant platelet inhibitor and chronic nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of bleeding.
Timolol: (Moderate) Monitor blood pressure during concomitant beta-blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of beta-blockers may be diminished by NSAIDs.
Tirofiban: (Moderate) Monitor for signs and symptoms of bleeding during concomitant platelet inhibitor and chronic nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of bleeding.
Tobacco: (Major) Advise patients to avoid smoking tobacco while taking nonsteroidal anti-inflammatory drugs (NSAIDs). Concomitant use of NSAIDs with tobacco smoking may enhance the risk of gastrointestinal side effects, including peptic ulcer and GI bleeding. Patients using tobacco and NSAIDs concurrently should be monitored closely for GI adverse reactions.
Tobramycin: (Moderate) It is possible that additive nephrotoxicity may occur in patients who receive nonsteroidal anti-inflammatory drugs (NSAIDs) concurrently with other nephrotoxic agents, such as tobramycin.
Tolmetin: (Major) Avoid concomitant use of naproxen with any other NSAID, including

COX-2 inhibitors, due to the risk of additive serious NSAID toxicities including but not limited to GI bleeding, GI perforation, or peptic ulcers.
Torsemide: (Moderate) If a nonsteroidal anti-inflammatory drug (NSAID) and a diuretic are used concurrently, carefully monitor the patient for signs and symptoms of decreased renal function and diuretic efficacy. Patients taking diuretics and NSAIDs concurrently are at higher risk of developing renal insufficiency. NSAIDs may reduce the natriuretic effect of diuretics in some patients. NSAIDs have been associated with an inhibition of prostaglandin synthesis, which may result in reduced renal blood flow leading to renal insufficiency and increases in blood pressure that are often accompanied by peripheral edema and weight gain.
Trandolapril: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Trandolapril; Verapamil: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease. (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin-converting enzyme (ACE) inhibitor and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of ACE inhibitors may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of ACE inhibitors and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
traZODone: (Moderate) Platelet aggregation may be impaired by trazodone due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in

patients receiving nonsteroidal antiinflammatory drugs (NSAIDs). Patients should be instructed to monitor for signs and symptoms of bleeding while taking trazodone concurrently with medications that impair platelet function and to promptly report any bleeding events to the practitioner.
Treprostinil: (Moderate) NSAIDs may decrease the effect of antihypertensive agents through various mechanisms, including renal and peripheral vasoactive pathways.
Triamcinolone: (Moderate) Monitor for gastrointestinal toxicity during concurrent corticosteroid and nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of GI bleeding.
Triamterene: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant triamterene and naproxen use. Nonsteroidal antiinflammatory drugs (NSAIDs) may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Triamterene; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant triamterene and naproxen use. Nonsteroidal antiinflammatory drugs (NSAIDs) may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Urea: (Moderate) Nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the natriuretic effect of diuretics in some patients. NSAIDS have been associated with an inhibition of prostaglandin synthesis, which may result in reduced renal blood flow leading to renal insufficiency and increases in blood pressure that are often accompanied by peripheral edema and weight gain. Patients taking diuretics and NSAIDS concurrently are at higher risk of developing renal insufficiency. If an NSAID and a diuretic are used concurrently, carefully monitor the patient for signs and symptoms of decreased renal function and diuretic efficacy.
valACYclovir: (Moderate) Monitor patients for signs of worsening renal function during coadministration of valacyclovir and nonsteroidal antiinflammatory drugs.

Coadministration may increase the risk for drug-induced nephrotoxicity.
valGANciclovir: (Minor) Concurrent use of nephrotoxic agents, such as NSAIDs, with valganciclovir should be done cautiously to avoid additive nephrotoxicity.
Valsartan: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible.
Valsartan; hydroCHLOROthiazide, HCTZ: (Moderate) Monitor blood pressure and renal function periodically during concomitant angiotensin II blocker and nonsteroidal anti-inflammatory drug (NSAID) use. The antihypertensive effect of angiotensin II blockers may be diminished by NSAIDs. In persons who are elderly, volume-depleted, or with compromised renal function, coadministration of angiotensin II blockers and NSAIDs may result in deterioration of renal function, including possible acute renal failure; these effects are usually reversible. (Moderate) Monitor blood pressure as well as for signs of worsening renal function and loss of diuretic efficacy, including antihypertensive effects, during concomitant nonsteroidal antiinflammatory drug (NSAID) and thiazide diuretic use. NSAIDs may cause a dose-dependent reduction in renal blood flow, which may precipitate overt renal decompensation, and concomitant diuretic use increases the risk of this reaction. NSAIDs have been shown to reduce the natriuretic effect of thiazide diuretics and are associated with fluid retention which may blunt the cardiovascular effects of diuretics.
Vancomycin: (Minor) It is possible that additive nephrotoxicity may occur in patients who receive NSAIDs concurrently with other nephrotoxic agents, including vancomycin.
Vemurafenib: (Minor) Concomitant use of vemurafenib and naproxen may result in increased naproxen concentrations. Vemurafenib is a CYP2C9 and CYP1A2 inhibitor and naproxen is a CYP2C9 and CYP1A2 substrate. Patients should be monitored for toxicity.
Venlafaxine: (Moderate) Platelet aggregation may be impaired by venlafaxine due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving nonsteroidal antiinflammatory drugs (NSAIDs). Monitor patients for signs and symptoms of bleeding when coadministering venlafaxine with NSAIDs.
Verapamil: (Moderate) If nonsteroidal anti-inflammatory drugs (NSAIDs) and an antihypertensive drug are concurrently used, carefully monitor the patient for signs and symptoms of renal insufficiency and blood pressure control. Doses of antihypertensive medications may require adjustment in patients receiving concurrent NSAIDs. NSAIDs, to varying degrees, have been associated with an elevation in blood pressure. This effect is most significant in patients receiving concurrent antihypertensive agents and long-term NSAID therapy. NSAIDs cause a dose-dependent reduction in prostaglandin

formation, which may result in a reduction in renal blood flow leading to renal insufficiency and an increase in blood pressure that are often accompanied by peripheral edema and weight gain. Patients who rely upon renal prostaglandins to maintain renal perfusion may have acute renal blood flow reduction with NSAID usage. Elderly patients may be at increased risk of adverse effects from combined long-term NSAID therapy and antihypertensive agents, especially diuretics, due to age-related decreases in renal function and an increased risk of stroke and coronary artery disease.
Verteporfin: (Moderate) Use caution if coadministration of verteporfin with nonsteroidal anti-inflammatory drugs is necessary due to the risk of decreased verteporfin efficacy. Oxaprozin may additionally worsen photosensitivity. Verteporfin is a light-activated drug. Once activated, local damage to neovascular endothelium results in a release of procoagulant and vasoactive factors resulting in platelet aggregation, fibrin clot formation, and vasoconstriction. Concomitant use of drugs that decrease platelet aggregation like nonsteroidal anti-inflammatory drugs could decrease the efficacy of verteporfin therapy.
Vigabatrin: (Minor) Vigabatrin is not significantly metabolized; however, it is an inducer of CYP2C9. In theory, decreased exposure of drugs that are extensively metabolized by CYP2C9, such as naproxen, may occur during concurrent use of vigabatrin.
Vilazodone: (Moderate) Platelet aggregation may be impaired by vilazodone due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving nonsteroidal antiinflammatory drugs (NSAIDs). Patients should be instructed to monitor for signs and symptoms of bleeding while taking vilazodone concurrently with NSAIDs and to promptly report any bleeding events to the practitioner.
Voclosporin: (Moderate) Concomitant use of voclosporin and nonsteroidal anti-inflammatory drugs (NSAIDs) may result in additive nephrotoxicity. Monitor for renal toxicity if concomitant use is required.
Vorapaxar: (Moderate) Monitor for signs and symptoms of bleeding during concomitant platelet inhibitor and chronic nonsteroidal antiinflammatory drug (NSAID) use. Concomitant use increases the risk of bleeding.
Voriconazole: (Moderate) The hepatic isoenzyme CYP2C9 is responsible for the metabolism of many NSAIDs. Voriconazole is known to be an inhibitor of CYP2C9 and may lead to increased plasma levels of some NSAIDs, such as naproxen. The clinical significance of this potential interaction is unknown. Monitor for NSAID-related side-effects, such as fluid retention or GI irritation, and adjust the dose of the NSAID if needed.
Vortioxetine: (Moderate) Platelet aggregation may be impaired by vortioxetine due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in

patients receiving nonsteroidal antiinflammatory drugs (NSAIDs). Bleeding events related to drugs that inhibit serotonin reuptake have ranged from ecchymosis to life-threatening hemorrhages. Patients should be instructed to monitor for signs and symptoms of bleeding while taking vortioxetine concurrently with medications which impair platelet function and to promptly report any bleeding events to the practitioner. Warfarin: (Moderate) Monitor patients for signs or symptoms of bleeding during concurrent use of warfarin and nonsteroidal antiinflammatory drugs (NSAIDs). To minimize the potential for GI bleeding, use the lowest effective NSAID dose for the shortest possible duration. If signs or symptoms of bleeding occur, promptly evaluate and treat. Systemic hematological effects may also occur with the use of topical NSAIDs. NSAIDs inhibit platelet aggregation and may prolong bleeding time in some patients. Zoledronic Acid: (Moderate) Monitor renal function during concomitant zoledronic acid and nonsteroidal antiinflammatory drug use due to risk for additive nephrotoxicity.

Adverse Reaction

abdominal pain, anorexia, cholecystitis, cholelithiasis, colitis, constipation, diarrhea, dyspepsia, eructation, flatulence, gastritis, GI bleeding, GI perforation, glossitis, hematemesis, melena, nausea, oral ulceration, peptic ulcer, pyrosis (heartburn), stomatitis, vomiting, weight loss, xerostomia

The most frequently reported reactions to naproxen are gastrointestinal (GI) adverse events and may be more frequent with higher doses. NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, GI bleeding, ulceration (peptic ulcer), and GI perforation (gastric or intestinal). These events can be fatal and can occur at any time during therapy. Upper GI ulcers, bleeding, or perforation occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for a year, with trends continuing with longer duration of use. Constipation, pyrosis (heartburn), abdominal pain, and nausea occur in 3% to 9% of patients. Dyspepsia was reported in less than 3% to 14% of patients. Diarrhea has occurred in less than 3% to 9% of patients. Flatulence, gastritis, vomiting, dysphagia, and stomatitis are reported less frequently (less than 3%). Gastrointestinal adverse events noted in less than 1% of patients during naproxen trials include GI bleeding, anorexia, cholecystitis, cholelithiasis, eructation, GI hemorrhage, rectal hemorrhage, aphthous stomatitis, ulcerative stomatitis, oral ulceration, peptic ulcer, periodontal abscess, cardiospasm, colitis, gastroenteritis, GI disorder, rectal disorder, tooth disorder, melena, esophagus ulcer, necrosis, and non-peptic GI ulcer. In patients taking NSAIDs in general, flatulence, GI bleeding, GI perforation, GI ulcers (gastric, duodenal), and vomiting were reported in 1% to 10%, while xerostomia and glossitis were reported in less than 1%. GI

events noted in postmarketing reports include GI perforation, hematemesis, colitis, exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease), non-peptic GI ulceration, ulcerative stomatitis, and peptic ulcer. Adverse effects reported by patients with rheumatoid arthritis appear to be more severe and frequent with higher dosages (1.5 g/day) than with lower dosages (750 mg/day). Gastrointestinal bleeding or erosive gastritis can be minor or life-threatening and may result from a combination of direct irritant action on the stomach mucosa and a prolonged bleeding time, due to changes in platelet aggregation. Weight loss has been reported in less than 1% of patients during naproxen clinical trials. Weight changes and appetite changes have occurred in less than 1% of patients taking NSAIDs. The incidence of gastrointestinal events in pediatric trials was similar to adult trials.

dysphagia, esophageal stricture, esophageal ulceration, esophagitis, odynophagia

Esophagitis (< 1%) and esophageal ulceration (< 1%) have been reported in patients receiving NSAIDs, such as naproxen. NSAID-induced esophagitis is characterized by sudden onset odynophagia, pyrosis (heartburn), retrosternal pain, and dysphagia. Severe complications such as esophageal ulceration, esophageal stricture, bleeding, and perforation have been reported rarely. Risk factors for NSAID-induced esophageal effects include taking the medication without water and at night. Symptoms usually resolve within days to weeks after stopping the medication.

agranulocytosis, anemia, aplastic anemia, eosinophilia, hemolytic anemia, leukopenia, lymphadenopathy, pancytopenia, prolonged bleeding time, thrombocytopenia

Naproxen glucuronide, a metabolite of naproxen, may cause immune-mediated thrombocytopenia. Widespread petechial hemorrhages were noted 10 to 25 days after naproxen initiation in 3 subjects. All 3 adults had improvement in their platelet counts from 3 to 8 x 109/L to within the normal concentration range 5 to 7 days after naproxen discontinuation and prednisone receipt. The sera from each subject had antibodies against platelets in the presence of naproxen glucuronide. Anemia has occurred in NSAID-treated individuals. This may be related to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. NSAIDs may increase the risk of bleeding events. If an individual treated with an NSAID has any signs or symptoms of anemia, monitor hemoglobin or hematocrit. Consider monitoring complete blood count (CBC) periodically in individuals on long-term NSAID treatment. Anemia and prolonged bleeding time have been reported with naproxen in 1% to 10% of subjects in clinical trials. Other hematologic adverse events (less than 1%) reported with naproxen include aplastic anemia, hemolytic anemia, thrombocytopenia, abnormal red

and white blood cells, agranulocytosis, leukopenia, eosinophilia, and granulocytopenia. Lymphadenopathy and pancytopenia were noted in less than 1% of subjects taking NSAIDs. In controlled clinical trials with about 80 pediatric subjects and in open-label clinical studies with 400 pediatric subjects with polyarticular articular juvenile idiopathic arthritis, the incidence of prolonged bleeding time was greater in pediatric subjects compared to adults.

amnesia, anxiety, asthenia, coma, confusion, depression, diplopia, dizziness, drowsiness, emotional lability, hallucinations, headache, hypertonia, insomnia, malaise, medication overuse headache, muscle paralysis, myasthenia, neuritis, paresthesias, seizures, subdural hematoma, tremor, vertigo, withdrawal

The most common adverse CNS reactions with naproxen include headache (3% to 15%) and drowsiness (3% to 9%). Vertigo, lightheadedness, paresthesias, asthenia, and insomnia are reported in less than 3% of patients during naproxen trials. Dizziness has been reported in less than 3% to 9% of patients. Other CNS reactions occur less frequently (less than 1%), including depression, malaise, anxiety, hypertonia, nervousness, neuralgia, neuritis, amnesia, confusion, abnormal coordination, diplopia, emotional lability, subdural hematoma, muscle paralysis, dream abnormalities, cognitive dysfunction, muscle weakness (myasthenia), and an inability to concentrate (impaired concentration). Adverse events noted in postmarketing reports include depression, dream abnormalities, insomnia, myalgia, muscle weakness, cognitive dysfunction, and seizures. Somnolence, tremor, coma, and hallucinations were noted in less than 1% of patients taking NSAIDs. Overuse of drugs for treating acute headaches, including NSAIDs, may lead to medication overuse headache. Patients may experience migraine-like daily headaches or a significant increase in migraine attack frequency. Discontinuation of the overused drug and treatment of withdrawal symptoms (e.g., transient worsening of headache) may be necessary. Advise patients about the risks of medication overuse (e.g., use of naproxen for at least 15 days/month or any combination of therapy for at least 10 days/month) and encourage them to keep a written record of headache frequency and drug use.

amblyopia, blurred vision, conjunctivitis, corneal opacification, keratoconjunctivitis, lacrimation, ocular pain, optic neuritis, papilledema, visual impairment

Visual impairment or disturbance, such as blurred vision, has been reported in < 3% of patients using naproxen. Other ocular adverse events reported in < 1% of patients included amblyopia, scleritis, cataracts, conjunctivitis, keratoconjunctivitis, lacrimation

disorder, and ocular pain. Corneal opacification, papillitis, retrobulbar optic neuritis, and papilledema have been noted in post-marketing reports.

hearing loss, tinnitus

Tinnitus (3—9%), hearing disturbances (< 3%), hearing loss / deafness (< 1%), ear disorder (< 1%), and otitis media (< 1%) have occurred with naproxen during clinical trials. Additionally, hearing impairment, has been noted in post-marketing reports. Also, 6 cases of hearing loss have been reported in the literature. Two of the 6 patients had a post-treatment audiogram, which revealed a permanent severe bilateral sensorineural hearing loss. Of the other patients, 2 had recovery and 2 had no recovery of their hearing loss. Tinnitus and hearing loss have also occurred with the nonsteroidal anti-inflammatory drugs (NSAIDs) piroxicam and ketorolac. The hearing loss from NSAID usage is believed to be due to altered cochlear sensory cell function from tissue ischemia as a result of an imbalance between vasodilatory prostaglandins and vasoconstricting leukotrienes. Although no known morphologic changes are known to occur, hearing loss may be permanent. Coadministration of other ototoxic drugs, such as gentamicin or furosemide, may increase the risk of ototoxicity. Most ototoxic drugs have at least additive ototoxic interactions. Further, NSAIDs can be nephrotoxic, and impaired renal function can increase the ototoxic potential of NSAIDs. Patients taking long-term NSAIDs should be directly questioned about tinnitus and hearing loss.

elevated hepatic enzymes, hepatic failure, hepatic necrosis, hepatitis, hepatomegaly, jaundice, pancreatitis, splenomegaly

Rare cases of jaundice (< 1%), hepatic necrosis (< 1%), and fatal hepatitis or hepatic failure have been reported in patients receiving naproxen. Hepatosplenomegaly (hepatomegaly and splenomegaly) and pancreatitis have been reported in < 1% of patients. Elevated hepatic enzymes occur in up to 15% of patients receiving NSAIDs. Elevations that are greater than three times the upper limit of normal have occurred in fewer than 1% of patients who received naproxen. Hepatic enzyme abnormalities may progress, stabilize, or regress with continued naproxen use. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. Evaluate patients with signs or symptoms of liver dysfunction such as an abnormal liver test result for the development of a more severe hepatic reaction. Naproxen should be discontinued if clinical signs or symptoms consistent with liver disease develop or if systemic manifestations such as eosinophilia or rash occur.

aseptic meningitis, photophobia

Naproxen has been associated with aseptic meningitis (incidence of < 1% in clinical

trials) but a causal relationship has not been established. Ibuprofen has been the most common NSAID implicated in this adverse reaction; however, cases have been reported with sulindac, tolmetin, diclofenac, ketoprofen, rofecoxib, and piroxicam. Aseptic meningitis from one NSAID does not preclude use of another NSAID; most patients can be treated with another drug without incident. However, one patient with Sjogren's syndrome experienced aseptic meningitis after receipt of naproxen, ibuprofen, and rofecoxib at different times; aseptic meningitis developed about a week after each drug exposure, and the symptoms abated roughly 2 days following each drug cessation. The occurrence of aseptic meningitis is not related to NSAID chemical class or prostaglandin inhibition. A Type III or IV immunological hypersensitivity reaction is the proposed mechanism of action. Drug-induced aseptic meningitis usually occurs shortly after drug initiation but can occur after years of drug usage. Although NSAID-induced aseptic meningitis is primarily reported in patients with systemic lupus erythematosus (SLE), healthy patients and patients with other disease states such as ankylosing spondylitis, connective tissue disease, osteoarthritis, and rheumatoid arthritis have developed NSAID-induced aseptic meningitis. Symptoms of aseptic meningitis include confusion, drowsiness, general feeling of illness, severe headache, nausea, nuchal rigidity, and photophobia. As aseptic meningitis is a diagnosis of exclusion, the suspected drug should be discontinued and not restarted unless a rechallenge is desired.

azotemia, dysmenorrhea, dysuria, edema, flank pain, glomerulonephritis, glycosuria, hematuria, hyperkalemia, hyponatremia, increased urinary frequency, interstitial nephritis, menorrhagia, nephrotic syndrome, nocturia, oliguria, peripheral edema, polyuria, proteinuria, pyuria, renal failure (unspecified), renal papillary necrosis, urinary incontinence, urinary retention, vaginitis

Renal disease including renal function abnormality, interstitial nephritis, nephrotic syndrome, hematuria, glomerulonephritis, hyperkalemia, renal failure (unspecified), and renal papillary necrosis have occurred in fewer than 1% of patients receiving naproxen. Overall abnormal renal function has been reported in < 1% of patients receiving NSAIDs. It is well known that vasodilatory renal prostaglandins and the potent vasoconstrictor angiotensin II work in concert to maintain renal blood flow. Inhibition of prostaglandin synthesis by NSAIDs potentiates water reabsorption. Renal toxicity has been reported in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. Other genitourinary adverse events reported in < 1% of patients include dysmenorrhea, dysuria, nocturia, prostate disorder, breast carcinoma or neoplasm, urinary incontinence, kidney calculus, menorrhagia, metrorrhagia, nephrosclerosis, kidney pain (flank pain), pyuria, abnormal urine, increased urinary frequency, urinary retention, uterine spasm, vaginitis, and menstrual disorders. Edema occurred in < 1 % to 9% and peripheral edema was reported in < 3% of patients receiving naproxen. Oliguria,

polyuria, proteinuria, glycosuria, azotemia, and albuminuria have been reported in < 1% of patients receiving NSAIDs. Hyponatremia due to water intoxication has been reported with NSAID use. Monitoring of the patient's fluid status and renal function is recommended.

angina, arrhythmia exacerbation, bleeding, bundle-branch block, heart failure, hypertension, hypotension, migraine, myocardial infarction, palpitations, peripheral vasodilation, phlebitis, pulmonary edema, sinus tachycardia, stroke, syncope, thromboembolism, vasculitis

NSAIDs, including naproxen, may cause an increased risk of serious cardiovascular thromboembolism, myocardial infarction (< 1%), and stroke, which can be fatal. Estimates of increased relative risk range from 10—50% or more, based on the drug and dose studied. The risk may increase with increased exposure, as measured in dose or duration. Significant cardiovascular risk has been observed within days to weeks of NSAID initiation. The relative increase in cardiovascular thrombotic events over baseline appears to be similar in patients with or without cardiovascular disease or risk factors for cardiovascular disease; however, patients with known cardiovascular disease or risk factors may be at greater risk because of a higher baseline risk of events. Hypertension was noted in < 3% of patients taking naproxen in clinical trials; in general, NSAIDs can lead to new onset or worsening hypertension, which may contribute to the increased incidence of cardiovascular events. Palpitations were noted in < 3% of patients taking naproxen in clinical trials. Adverse events noted in < 1% of patients included pulmonary edema, angina pectoris, coronary artery disease, deep thrombo-phlebitis, peripheral vasodilation, vascular anomaly, arrhythmia exacerbation, bundle-branch block, abnormal ECG, heart failure, hemorrhage (bleeding), migraine, aortic stenosis, syncope, vasculitis, and sinus tachycardia. Fluid retention caused by naproxen can elevate blood pressure, especially in patients with hypertension. Hypotension has been reported in < 1% of patients taking NSAIDs. In adults (76% White, 14% Black) with stable hypertension (systolic < 150 mmHg) and normal renal function, the mean change from baseline in average 24-hour systolic pressure was -0.8 +/- 1.1 mmHg and diastolic pressure was -1 +/- 0.6 mmHg after 6 weeks of naproxen 500 mg twice daily. Blood pressure was measured every 20 minutes during 24-hour ambulatory monitoring, and no antihypertensive drug changes were allowed (all patients took at least an angiotensin converting enzyme inhibitor or an angiotensin-2 receptor blocker). Similar findings were obtained when blood pressure was measured in a clinic between 7 and 11 in the morning. Of the 101 patients, an increase in the systolic blood pressure of 0—10 mmHg occurred in 37%, an increase in 10—20 mmHg occurred in 7%, and a > 20 mmHg increase occurred in 2%. Furthermore, of 57 patients who had a baseline ambulatory systolic blood pressure < 135 mmHg, 11 had a reading of >= 135 mmHg at week 6.

Inform patients of the signs and symptoms of CV events, and advise them to seek medical help immediately if such signs or symptoms occur.

acne vulgaris, alopecia, anaphylactoid reactions, angioedema, bullous rash, chills, contact dermatitis, diaphoresis, dyspnea, ecchymosis, erythema multiforme, erythema nodosum, exfoliative dermatitis, fixed drug eruption, lichen planus-like eruption, lupus-like symptoms, photosensitivity, pneumonitis, pruritus, pseudoporphyria, purpura, rash, skin necrosis, skin ulcer, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, xerosis

NSAIDs can cause serious and potentially fatal skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and fixed drug eruption (FDE), which may present as a more severe variant known as generalized bullous fixed drug eruption (GBFDE). These serious events may occur without warning. Inform individuals about the signs and symptoms of serious skin reactions and instruct them to discontinue use of the NSAID at the first appearance of skin rash or any other sign of hypersensitivity. Diaphoresis (less than 3%), dyspnea (3% to 9%), ecchymosis (3% to 9%), pruritus (9% or less), purpura (less than 3%), rash (9% or less), and skin eruptions (3% to 9%) were reported with naproxen during clinical trials and probably causally related. Other allergic or dermatologic adverse reactions reported with naproxen in less than 1% of subjects during clinical trials or postmarketing and probably causally related include acne vulgaris, alopecia, anaphylactoid reactions, angiodermatitis, angioedema, bullous rash including SJS and FDE, chills, contact dermatitis, eczema, erythema multiforme, erythema nodosum, eosinophilic pneumonitis, exfoliative dermatitis, herpes simplex, herpes zoster, lichen planus-like eruption, nail disorder, photosensitive dermatitis, photosensitivity including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa, pustular reaction, skin necrosis, skin neoplasm, skin ulcer, subcutaneous nodule, systemic lupus erythematoses (lupus-like symptoms), TEN, urticaria, and xerosis. If skin fragility, blistering, or other symptoms suggestive of pseudoporphyria occur, discontinue treatment and monitor the individual. Advise individuals to seek emergency help if an anaphylactic reaction occurs.

arthralgia, back pain, bone fractures, bone pain, muscle cramps, myalgia, ptosis

Musculoskeletal adverse events that occurred in 3—9% of patients taking naproxen in clinical trials included back pain and pain. Muscle cramps (leg), myalgia, arthralgia, joint disorder, and tendon disorder were reported in < 3% of patients. Adverse events noted in < 1% of patients include bone disorder, spontaneous bone fractures, fibro-tendinitis, bone pain, ptosis, general muscle spasm, and bursitis.

dehydration, hypercholesterolemia, hyperglycemia, hyperuricemia, hypoglycemia, hypokalemia, metabolic alkalosis

Hyperglycemia and thirst have been reported in less than 3% of patients during naproxen clinical trials. Other metabolic and nutritional adverse events reported in less than 1% of patients include hypoglycemia, hypercholesterolemia, metabolic alkalosis, dehydration, decreased glucose tolerance, hyperuricemia, and hypokalemia.

cystitis, infection, influenza

Infectious adverse events reported during naproxen trials include general infection (3% to 9%), urinary tract infection (3% to 9%), influenza-like syndrome (10%), cystitis (less than 3%), abscess (less than 1%), pneumonia (less than 1%), and pyelonephritis (less than 1%). Adverse events related to NSAID therapy and occurring in less than 1% include infection, sepsis, and pneumonia.

bronchospasm, cough, epistaxis, pharyngitis, respiratory depression, rhinitis, sinusitis

Respiratory adverse events that have been noted in naproxen clinical trials include pharyngitis (3—9%), rhinitis (3—9%), sinusitis (3—9%), bronchitis (< 3%), increased cough (< 3%), asthma or bronchospasm (< 1%), pulmonary disorder (< 1%), epistaxis (< 1%), respiratory distress (< 1%), and respiratory disorder (< 1%). Asthma and respiratory depression have been reported in < 1% of patients taking NSAIDs.

chest pain (unspecified), fever, pelvic pain

General adverse events reported during naproxen clinical trials include fever (less than 3%), injury or accident (less than 3%), chest pain (unspecified) (less than 3%), nuchal rigidity (less than 1%), neck pain (less than 1%), enlarged abdomen (less than 1%), carcinoma (less than 1%), cellulitis (less than 1%), LE syndrome (less than 1%), mucous membrane disorder (less than 1%), and pelvic pain (less than 1%). Death was reported in less than 1% of patients taking NSAIDs.

infertility

NSAIDs may delay or prevent prostaglandin-mediated rupture of ovarian follicles, which has been associated with reversible infertility. Small studies with NSAIDs demonstrated a reversible delay in ovulation. Consider withdrawal of NSAIDs in people who may become pregnant who have difficulties conceiving or who are undergoing infertility evaluation.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), a multi-organ hypersensitivity reaction, has occurred with NSAIDs. Some of these events have been life-threatening or fatal. DRESS typically presents as fever, rash, and/or lymphadenopathy in conjunction with other organ system involvement including hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Early manifestations such as fever and lymphadenopathy may be present without evidence of a rash. Discontinue the NSAID in patients presenting with such signs and symptoms in whom an alternative etiology cannot be identified.

diagnostic test interference, laboratory test interference

The pharmacological activity of NSAIDs in reducing inflammation, and possibly fever, may result in diagnostic test interference by diminishing the utility of these diagnostic signs in detecting infection. Naproxen may also cause laboratory test interference. Naproxen may cause decreased platelet aggregation and prolonged bleeding time. Keep this effect in mind when bleeding times are determined. Additionally, the administration of naproxen may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-di-nitrobenzene used in this assay. Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artificially altered, it is suggested that therapy with naproxen be temporarily discontinued 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used. Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA).

Description

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) of the propionic acid chemical class. This medicine possesses antipyretic and analgesic properties. Naproxen is a propionic acid derivative related to ibuprofen, ketoprofen, flurbiprofen, and fenoprofen. Many pharmacodynamic similarities exist among these agents, which are usually better tolerated than aspirin or indomethacin. All NSAIDs, including naproxen, carry an increased risk of serious gastrointestinal adverse effects including bleeding, ulceration, and perforation of the stomach or intestines, and may cause an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction, and stroke. The FDA approved labeling of both the OTC and prescription products stress dosing at the lowest effective dose for the shortest possible duration, as the risk for adverse effects may increase with increased use. A retrospective review by FDA Advisory

Committees of short-term efficacy trials of non-prescription strength naproxen indicated that an increase in CV events was not apparent during the studies. However, it is important to note that CV risk was not the focus of the studies, and further information is needed to determine if a cause and effect relationship exists between non-prescription strength NSAID use and adverse cardiovascular outcomes. Naproxen is available as the anion and as the sodium salt; all formulations liberate naproxen as the active drug. Naproxen has been shown superior to ergotamine in the treatment of migraine. Naproxen was approved by the FDA in 1976. In January 1994, the FDA granted permission to market naproxen in a nonprescription form (e.g., Aleve).

Mechanism Of Action

Mechanism of Action: Naproxen competitively inhibits both cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, by blocking arachidonate binding resulting in analgesic, antipyretic, and anti-inflammatory pharmacologic effects. The enzymes COX-1 and COX-2 catalyze the conversion of arachidonic acid to prostaglandin G2 (PGG2), the first step of the synthesis prostaglandins and thromboxanes that are involved in rapid physiological responses. COX isoenzymes are also responsible for a peroxidase reaction, which is not affected by NSAIDs. In addition, NSAIDs do not suppress leukotriene synthesis by lipoxygenase pathways. COX-1 is constitutively expressed in almost all tissues, while COX-2 appears to only be constitutively expressed in the brain, kidney, bones, reproductive organs, and some neoplasms (e.g., colon and prostate cancers). COX-1 is responsible for prostaglandin synthesis in response to stimulation by circulating hormones, as well as maintenance of normal renal function, gastric mucosal integrity, and hemostasis. However, COX-2 is inducible in many cells in response to certain mediators of inflammation (e.g., interleukin-1, tumor necrosis factor, lipopolysaccharide, mitogens, and reactive oxygen intermediates).•Anti-inflammatory Activity: The anti-inflammatory mechanism of naproxen is due to decreased prostaglandin synthesis via inhibition of COX-1 and COX-2. It appears that the anti-inflammatory effects may be primarily due to inhibition of the COX-2 isoenzyme. However, COX-1 is expressed at some sites of inflammation. COX-1 is expressed in the joints of rheumatoid arthritis or osteoarthritis patients, especially the synovial lining, and it is the primary enzyme of prostaglandin synthesis in human bursitis. Naproxen is slightly more selective for COX-1 than COX-2.•Analgesic Activity: Naproxen is effective in cases where inflammation has caused sensitivity of pain receptors (hyperalgesia). It appears prostaglandins, specifically prostaglandins E and F, are responsible for sensitizing the pain receptors; therefore, naproxen has an indirect analgesic effect by inhibiting the production of further prostaglandins and does not directly affect hyperalgesia or the pain threshold.•Antipyretic Activity: Naproxen promotes a return to a normal body temperature set point in the hypothalamus by suppressing the synthesis of prostaglandins, specifically PGE2, in circumventricular organs in and near the

hypothalamus. Naproxen may mask fever in some patients, especially with high or chronic dosing.•GI Effects: Gastrointestinal side effects of naproxen are primarily contributed to COX-1 inhibition; however, potential role of COX-2 inhibition in the GI tract has not been fully elucidated.•Platelet Effects: The inhibition of platelet aggregation seen with naproxen is due to dose-dependent inhibition of COX-1 in platelets leading to decreased levels of platelet thromboxane A2 and an increase in bleeding time (see Adverse Reactions). The inhibition of platelet aggregation is reversible upon discontinuation of naproxen. This differs from aspirin, which irreversibly binds to COX-1 in platelets inhibiting this enzyme for the life of the cell. In an in vitro study, naproxen inhibited thromboxane production and platelet aggregation by 88% for up to 8 hours. Naproxen inhibited COX-1 (measured as thromboxane B2 generation in clotting whole blood) to a greater extent as compared to ibuprofen, diclofenac, or meloxicam (94.9%, 88.7%, 49.5%, and 53.3%, respectively). Clinically, naproxen may provide some cardioprotection benefits. However, naproxen produces less consistent inhibition of thromboxane A2 than low-dose aspirin, and in clinical trials, the cardioprotective effects of naproxen have been inconsistent.•Renal Effects: In the kidney, prostaglandins, produced by both COX-1 and COX-2, are important regulators of sodium and water reabsorption through PGE2 and of renal function and hemodynamics via PGI2 in response to vasoconstrictive factors (e.g., endothelin-1, a factor that increases peripheral vascular resistance) and through effects on the renin-angiotensin system. In conditions where renal blood flow is dependent upon prostaglandin synthesis, administration of NSAIDs can result in significant decreases in renal blood flow leading to acute renal failure. In addition, alterations in sodium and water reabsorption may worsen increased blood pressure, which can be significant in selected individuals.•Bone Effects: Nonsteroidal anti-inflammatory drugs appear to suppress bone formation via inhibition of COX-2. In vivo data from rabbits revealed a significant reduction of bone growth with both naproxen and rofecoxib as compared with placebo. Bone resorption does not appear to be a mechanism that leads to decreased net bone formation, as the number of CD51 positive osteoclast-like cells per section was decreased with either NSAID as compared with drinking water alone. As determined from in vitro data, NSAIDs appear to arrest the osteoblast cell cycle at the G(0)/G(1) phase and induce cytotoxicity and cell death of osteoblasts primarily by apoptosis rather than by necrosis.

Pharmacokinetics

Naproxen is administered orally. It is more than 99% bound to albumin. At doses more than 500 mg/day, a less than proportional increase in plasma concentrations occurs due to increased clearance because of saturation of plasma protein binding. It is extensively metabolized in the liver to 6-O-desmethyl naproxen. Both naproxen and 6-O-desmethyl naproxen are further metabolized to their respective acylglucoronide conjugated metabolites. Urinary excretion is the predominant elimination pathway. Approximately

95% of naproxen is excreted in the urine with less than 1% as unchanged drug, less than 1% as 6-O-desmethyl naproxen, and 66% to 92% as their conjugates. Small amounts, 3% or less of an administered dose, is excreted in the feces. The naproxen anion has a plasma half-life of 12 to 17 hours.

Affected cytochrome P450 isoenzymes and drug transporters: CYP1A2, CYP2C8, CYP2C9
Naproxen is a substrate of the hepatic cytochrome isoenzymes CYP1A2, CYP2C8, and CYP2C9; CYP2C9 appears to be the main substrate pathway.

Route-Specific Pharmacokinetics

- **Oral Route**

The different dosage forms of naproxen are bioequivalent in terms of extent of absorption (AUC) and peak concentration; however, the products do differ in their pattern of absorption. Naproxen and naproxen sodium are rapidly and completely absorbed from the GI tract. Onset of pain relief can be within 1 hour in patients taking naproxen and 30 minutes in patients taking naproxen sodium. The analgesic effect has been found to last for up to 12 hours. Peak plasma concentrations of naproxen are achieved 2 to 4 hours and 1 to 2 hours after ingestion of naproxen and naproxen sodium, respectively. The difference in rates between the 2 products is due to the increased aqueous solubility of the sodium salt of naproxen. The enteric polymer coating for enteric-coated naproxen dissolves above pH 6. Enteric-coated naproxen dissolves primarily in the small intestine rather than in the stomach, so the absorption of the drug is delayed until the stomach is emptied. When enteric-coated naproxen was given to fasted subjects, peak plasma concentrations were achieved about 4 to 6 hours after the first dose (range: 2 to 12 hours). When enteric-coated naproxen was given with food, peak plasma concentrations were achieved in about 12 hours (range: 4 to 24 hours). The presence of food prolonged the time the tablets remained in the stomach, time to first detectable serum naproxen concentrations, and time to maximal naproxen concentrations, but did not affect peak naproxen concentrations. The elimination half-life of naproxen is unchanged across products ranging from 12 to 17 hours. Steady-state concentrations are reached in 4 to 5 days.

- **Hepatic Impairment**

Naproxen pharmacokinetics have not been determined in patients with hepatic insufficiency. In patients with chronic alcoholic hepatic disease and other diseases with decreased or abnormal plasma proteins (i.e., hypoalbuminemia), the total plasma concentration of naproxen may be reduced, but the plasma concentration of unbound naproxen is increased.

- **Renal Impairment**

Naproxen pharmacokinetics have not been determined in patients with renal insufficiency. Naproxen metabolites may accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment.

- **Pediatrics**

In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen concentrations after a single naproxen suspension 5 mg/kg dose were found to be similar to those in normal adults after a 500 mg dose. The terminal half-life appears to be similar in pediatric and adult patients.

- **Geriatric**

Although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is less than 1% of the total naproxen concentration. Unbound trough naproxen concentrations in elderly subjects have been reported to range from 0.12% to 0.19% of total naproxen concentration, compared with 0.05% to 0.075% in younger subjects. The clinical significance of this finding is unclear.

Administration

For storage information, see specific product information within the How Suppled section.

Oral Administration

Administer with milk, food, or antacids (preferably aluminum and magnesium hydroxide containing antacids) to minimize GI irritation. For self-medication, administer with a full glass of water or other liquid.

Oral Solid Formulations

EC-Naprosyn delayed-release tablets: Do not break, crush, or chew.

Oral Liquid Formulations

Oral suspension: Shake well before use. Administer using the measuring cup provided or other calibrated device appropriate for accurate administration of liquid medications.

Maximum Dosage Limits

- **Adults**
  Naproxen 1500 mg/day PO; Naproxen sodium up to 1650 mg/day PO for limited periods. For non-prescription use: 660 mg/day PO.
- **Geriatric**
  Naproxen 1500 mg/day PO; Naproxen sodium up to 1650 mg/day PO for limited periods. For non-prescription use: 660 mg/day PO.
- **Adolescents**
  Naproxen 1500 mg/day PO; Naproxen sodium up to 1650 mg/day PO for limited periods. For non-prescription use: 660 mg/day PO.
- **Children**
  >= 12 years: In clinical practice, 20 mg/kg/day PO not to exceed 1000 mg/day PO; for non-prescription use, 660 mg/day PO.
  2 to < 12 years: In clinical practice, 20 mg/kg/day PO not to exceed 1000 mg/day PO; non-prescription (self medication) use is not recommended.
  < 2 years: Safety and efficacy have not been established.
- **Infants**
  Safety and efficacy have not been established.
- **Neonates**
  Safety and efficacy have not been established.

Dosage Forms

- Aleve 220mg Caplet
- Aleve 220mg Caplet
- Aleve 220mg Gelcap Tablet
- Aleve 220mg Liquid Gel Capsule
- Aleve 220mg Liquid Gel Capsule
- Aleve 220mg Tablet
- Aleve Arthritis 220mg Caplet
- Aleve Arthritis 220mg Caplet
- Aleve Arthritis 220mg Gelcap Tablet
- Aleve Arthritis 220mg Liquid Gel Capsule
- Aleve Arthritis 220mg Tablet
- Aleve-D 12 Hour Sinus & Cold 220mg-120mg Extended-Release Caplet
- Aleve-D 12 Hour Sinus & Headache 220mg-120mg Extended-Release Caplet
- All Day Pain Relief 220mg Tablet
- All Day Relief 220mg Caplet
- All Day Relief 220mg Tablet

- All Day Relief 220mg Tablet
- Anaprox DS 550mg Tablet
- Anaprox DS 550mg Tablet
- CAREALL Naproxen Sodium 220mg Tablet
- CVS All Day Pain Relief 220mg Caplet
- CVS All Day Pain Relief 220mg Tablet
- CVS Naproxen Sodium 220mg Caplet
- CVS Naproxen Sodium 220mg Liquid Gel Capsule
- CVS Naproxen Sodium 220mg Tablet
- CVS Sinus & Cold-D Non-Drowsy 220mg-120mg Extended-Release Caplet
- EC-Naprosyn 375mg Delayed-Release Tablet
- EC-Naprosyn 500mg Delayed-Release Tablet
- EC-Naprosyn 500mg Delayed-Release Tablet
- EnovaRX - Naproxen 10% in Microderm External Cream Compounding Kit
- EnovaRX - Naproxen 10% in Microderm External Cream Compounding Kit
- Equaline Naproxen Sodium 220mg Caplet
- Equaline Naproxen Sodium 220mg Tablet
- Equate 12 Hour All Day Pain Relief 220mg Caplet
- Equate All Day Pain Relief 220mg Caplet
- Equate Naproxen Sodium 220mg Caplet
- Equate Non-Drowsy Sinus & Cold-D 12 Hour 220mg-120mg Extended-Release Caplet
- Equipto Naproxen External Cream Compounding Kit
- Foster & Thrive All Day Pain Relief 220mg Caplet
- GNP Naproxen Sodium 220mg Caplet
- GNP Naproxen Sodium 220mg Caplet
- GNP Naproxen Sodium 220mg Capsule
- GNP Naproxen Sodium 220mg Liquid Gel Capsule
- GNP Naproxen Sodium 220mg Tablet
- GNP Naproxen Sodium 220mg Tablet
- GNP Naproxen Sodium 220mg Tablet
- GNP Sinus & Cold-D 220mg-120mg Extended-Release Caplet
- GoodSense All Day Pain Relief 220mg Caplet
- GoodSense Naproxen Sodium 220mg Caplet
- GoodSense Naproxen Sodium 220mg Caplet
- GoodSense Naproxen Sodium 220mg Tablet
- HEB RX Act All Day Pain Relief 220mg Tablet
- Kirkland Naproxen Sodium 220mg Caplet
- Leader All Day Pain Relief 220mg Caplet
- Leader All Day Pain Relief 220mg Tablet

- Leader All Day Sinus & Cold-D Non-Drowsy 220mg-120mg Extended-Release Caplet
- Leader Naproxen Sodium 220mg Liquid Gel Capsule
- Naprelan 375 Controlled-Release Tablet
- Naprelan 500 Controlled-Release Tablet
- Naprelan 500 Controlled-Release Tablet
- Naprelan 750 Controlled-Release Tablet
- Naprosyn 125mg/5mL Suspension
- Naprosyn 125mg/5mL Suspension
- Naprosyn 500mg Tablet
- Naproxen 125mg/5mL Oral suspension
- Naproxen 250mg Oral tablet
- Naproxen 375mg Oral tablet
- Naproxen 375mg Oral tablet, extended release
- Naproxen 375mg Oral tablet, gastro-resistant
- Naproxen 375mg, Esomeprazole Magnesium 20mg Oral tablet, gastro-resistant
- Naproxen 500mg Oral tablet
- Naproxen 500mg Oral tablet, extended release
- Naproxen 500mg Oral tablet, gastro-resistant
- Naproxen 500mg, Esomeprazole Magnesium 20mg Oral tablet, gastro-resistant
- Naproxen 750mg Oral tablet, extended release
- Naproxen Bulk powder
- Naproxen Sodium 220mg Oral capsule, liquid filled
- Naproxen Sodium 220mg Oral tablet
- Naproxen Sodium 275mg Oral tablet
- Naproxen Sodium 375mg Oral tablet
- Naproxen Sodium 550mg Oral tablet
- Naproxen Sodium Bulk powder
- Premier Value Naproxen Sodium 220mg Caplet
- Premier Value Naproxen Sodium 220mg Caplet
- Premier Value Naproxen Sodium 220mg Tablet
- Publix All Day Relief 220mg Caplet
- Publix All Day Relief 220mg Tablet
- Quality Choice Naproxen Sodium 220mg Caplet
- Quality Choice Naproxen Sodium 220mg Liquid Filled Capsule
- Quality Choice Naproxen Sodium 220mg Tablet
- RITE AID All Day Pain Relief 220mg Caplet
- RITE AID Naproxen Sodium 220mg Caplet
- RITE AID Naproxen Sodium 220mg Liquid Gel Capsule
- RITE AID Naproxen Sodium 220mg Tablet
- Select Brand Naproxen Sodium 220mg Caplet

- Sudafed Sinus 12 Hour Pressure + Pain Caplet
- Today's Health Naproxen 220mg Tablet
- Top Care All Day Pain Relief 220mg Caplet
- Top Care All Day Pain Relief 220mg Tablet
- Top Care Naproxen Sodium 220mg Liquid Gel Capsule
- up & up Naproxen Sodium 220mg Caplet
- Wal-Proxen 220mg Tablet
- Walgreens All Day Pain Relief 220mg Caplet
- Walgreens All Day Pain Relief 220mg Liquid Gel Capsule
- Walgreens All Day Pain Relief 220mg Tablet
- Walgreens All Day Relief 220mg Tablet
- Walgreens All Day Sinus & Cold D 220mg-120mg Extended-Release Caplet
- Walgreens Naproxen Sodium 220mg Liquid Gel Capsule

Dosage Adjustment Guidelines

Hepatic Impairment

Although specific guidelines are not available, dosage reduction may be necessary in patients with hepatic dysfunction.

Renal Impairment

CrCl >= 30 ml/min: No dosage adjustment needed.
CrCl < 30 ml/min: Not recommended.