Alcohol

Drug Interactions:

"7 DRUG INTERACTIONS See Table 1 for clinically significant drug interactions with naproxen. Table 1: Clinically Significant Drug Interactions with naproxen Drugs That Interfere with Hemostasis Clinical Impact: • Naproxen and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of naproxen and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone. Intervention: Monitor patients with concomitant use of naproxen tablets or naproxen sodium tablets with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding see Warnings and Precautions (5.12) . Aspirin Clinical Impact: A pharmacodynamic (PD) study has demonstrated an interaction in which 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 (see 12.2 Pharmacodynamics) . 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 PD study due to the longer washout period. 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 see Warnings and Precautions (5.2) . Intervention: Because there may be an increased risk of cardiovascular events following 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 where appropriate. Concomitant use of naproxen tablets or naproxen sodium tablets and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding see Warnings and Precautions (5.12) . Naproxen tablets or naproxen sodium tablets are not substitutes for low dose aspirin for cardiovascular protection. ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers Clinical Impact: • NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers

(ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Intervention: • During concomitant use of naproxen tablets or naproxen sodium tablets and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of naproxen tablets or naproxen sodium tablets and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function see Warnings and Precautions (5.6) . • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter. Diuretics Clinical Impact: Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis. Intervention: During concomitant use of naproxen tablets or naproxen sodium tablets with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects see Warnings and Precautions (5.6) . Digoxin Clinical Impact: The concomitant use of naproxen with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Intervention: During concomitant use of naproxen tablets or naproxen sodium tablets and digoxin, monitor serum digoxin levels. Lithium Clinical Impact: NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance . The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis. Intervention: During concomitant use of naproxen tablets or naproxen sodium tablets and lithium, monitor patients for signs of lithium toxicity. Methotrexate Clinical Impact: Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction). Intervention: During concomitant use of naproxen tablets or naproxen sodium tablets and methotrexate, monitor patients for methotrexate toxicity. Cyclosporine Clinical Impact: Concomitant use of naproxen tablets or naproxen sodium tablets and cyclosporine may increase cyclosporine’s nephrotoxicity. Intervention: During concomitant use of naproxen tablets or naproxen sodium tablets and cyclosporine, monitor patients for signs of worsening renal function. NSAIDs and Salicylates Clinical Impact: Concomitant use of naproxen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy see Warnings and Precautions (5.2) . Intervention: The concomitant use of naproxen with other NSAIDs or salicylates is not recommended. Pemetrexed Clinical Impact: Concomitant use of naproxen tablets and naproxen sodium tablets and

pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information). Intervention: During concomitant use of naproxen tablets and naproxen sodium tablets and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration. Antacids and Sucralfate Clinical Impact: Concomitant administration of some antacids (magnesium oxide or aluminum hydroxide) and sucralfate can delay the absorption of naproxen. Intervention: Concomitant administration of antacids such as magnesium oxide or aluminum hydroxide, and sucralfate with naproxen tablets and naproxen sodium tablets is not recommended. Cholestyramine Clinical Impact: Concomitant administration of cholestyramine can delay the absorption of naproxen. Intervention: Concomitant administration of cholestyramine with naproxen tablets or naproxen sodium tablets is not recommended. Probenecid Clinical Impact: Probenecid given concurrently increases naproxen anion plasma levels and extends its plasma half-life significantly. Intervention: Patients simultaneously receiving naproxen tablets or naproxen sodium tablets and probenecid should be observed for adjustment of dose if required. Other albumin-bound drugs Clinical Impact: Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound drugs such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin . Intervention: Patients simultaneously receiving naproxen tablets or naproxen sodium tablets and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required. Drug/Laboratory Test Interactions Bleeding times Clinical Impact: Naproxen may decrease platelet aggregation and prolong bleeding time. Intervention: This effect should be kept in mind when bleeding times are determined. Porter-Silber test Clinical Impact: 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. Intervention: Although 17-hydroxy-corticosteroid measurements (Porter-Silber test) do not appear to be artifactually 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. Urinary assays of 5-hydroxy indoleacetic acid (5HIAA) Clinical Impact: Naproxen may interfere with some urinary assays of 5-hydroxy indoleacetic acid (5HIAA). Intervention: This effect should be kept in mind when urinary 5-hydroxy indoleacetic acid is determined. Drugs that Interfere with Hemostasis (e.g. warfarin, aspirin, SSRIs/SNRIs): Monitor patients for bleeding who are concomitantly taking naproxen tablets or naproxen

sodium tablets with drugs that interfere with hemostasis. Concomitant use of naproxen tablets or naproxen sodium tablets and analgesic doses of aspirin is not generally recommended. (7) ACE inhibitors, Angiotensin Receptor Blockers (ARB), or Beta-Blockers: Concomitant use with naproxen tablets or naproxen sodium tablets may diminish the antihypertensive effect of these drugs. Monitor blood pressure. (7) ACE Inhibitors and ARBs: Concomitant use with naproxen tablets or naproxen sodium tablets in elderly, volume depleted, or those with renal impairment may result in deterioration of renal function. In such high risk patients, monitor for signs of worsening renal function. (7) Diuretics: NSAIDs can reduce natriuretic effect of furosemide and thiazide diuretics. Monitor patients to assure diuretic efficacy including antihypertensive effects. (7) Digoxin: Concomitant use with naproxen tablets or naproxen sodium tablets can increase serum concentration and prolong half-life of digoxin. Monitor serum digoxin levels. (7)"

Precautions:
No information available

Description:

"11 DESCRIPTION Naproxen Tablets, USP and Naproxen Sodium Tablets, USP are nonsteroidal anti-inflammatory drugs available as follows: Naproxen Tablets, USP are available as follows for oral administration: 250 mg: circular, light orange colored, flat, uncoated tablets, engraved with ‘G’ and ‘32’ on either side of a break line on one side and ‘250’ on the other side. 375 mg: oval, light orange colored, biconvex, uncoated tablets, engraved with ‘G32’ on one side and ‘375’ on the other side. 500 mg: capsule shaped, light orange colored, uncoated tablets, debossed with ‘G’ and ‘32’ on either side of a break line on one side and ‘500’ on the other side. The inactive ingredients are croscarmellose sodium, iron oxide red, iron oxide yellow, magnesium stearate, microcrystalline cellulose and povidone. Naproxen Sodium Tablets, USP are available as follows for oral administration: 275 mg: blue, oval, film-coated tablets with ‘G 0’ engraved on one side and ‘275’ engraved on the other side. 550 mg: blue colored, modified capsule shaped, biconvex, film-coated tablets, engraved with ‘G’ and ‘0’ on either side of a break line and a break line on the other side. The inactive ingredients are colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone and talc. The coating suspension for the naproxen sodium 275 mg and 550 mg tablet contains FD&C blue#2, iron oxide red, hypromellose, polyethylene glycol and titanium dioxide. Naproxen, USP is a propionic acid derivative related to the arylacetic acid group of nonsteroidal anti-inflammatory drugs. The chemical names for naproxen, USP and naproxen sodium, USP are (S)-6-methoxy--methyl-2-naphthaleneacetic acid and (S)-6-methoxy--methyl-2-naphthaleneacetic acid, sodium salt, respectively.

Naproxen, USP has a molecular weight of 230.26 g/mol and a molecular formula of C 14 H 14 O 3 . Naproxen sodium, USP has a molecular weight of 252.24 g/mol and a molecular formula of C 14 H 13 NaO 3 . Naproxen, USP and naproxen sodium, USP have the following structures, respectively: Naproxen Naproxen Sodium Naproxen, USP is a white to off-white crystalline powder. It is soluble in chloroform, dehydrated alcohol and alcohol; sparingly soluble in ether, insoluble in water. Naproxen sodium, USP is a white to almost white crystalline powder, soluble in water and methanol; sparingly soluble in ethanol. NaproxinStructure NaproxinNaStructure"

Indications and Usage:

"1 INDICATIONS AND USAGE Naproxen tablets and naproxen sodium tablets are indicated for: the relief of the signs and symptoms of: • rheumatoid arthritis • osteoarthritis • ankylosing spondylitis • Polyarticular Juvenile Idiopathic Arthritis Naproxen tablets and naproxen sodium tablets are also indicated for: the relief of signs and symptoms of: • tendonitis • bursitis • acute gout the management of: • pain • primary dysmenorrhea Naproxen tablets and naproxen sodium tablets are non-steroidal anti-inflammatory drugs indicated for: the relief of the signs and symptoms of: • rheumatoid arthritis • osteoarthritis • ankylosing spondylitis • polyarticular juvenile idiopathic arthritis Naproxen tablets and naproxen sodium tablets are also indicated for: the relief of signs and symptoms of: • tendonitis • bursitis • acute gout the management of: • pain • primary dysmenorrhea"

Warnings:
No information available

Pregnancy:

"8.1 Pregnancy Risk Summary Use of NSAIDs, including naproxen tablets and naproxen sodium tablets, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of naproxen tablets or naproxen sodium tablets use between about 20 and 30 weeks of gestation, and avoid naproxen tablets and naproxen sodium tablets use at about 30 weeks of gestation and later in pregnancy (see Clinical Considerations, Data). Premature Closure of Fetal Ductus Arteriosus Use of NSAIDs, including naproxen tablets and naproxen sodium tablets, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Oligohydramnios/Neonatal Renal Impairment Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal

renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies in rats, rabbits, and mice no evidence of teratogenicity or fetal harm when naproxen was administered during the period of organogenesis at doses 0.13, 0.26, and 0.6 times the maximum recommended human daily dose of 1500 mg/day, respectively see Data . Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as naproxen, resulted in increased pre-and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses. The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Clinical Considerations Fetal/Neonatal Adverse Reactions Premature Closure of Fetal Ductus Arteriosus: Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including naproxen tablets and naproxen sodium tablets, can cause premature closure of the fetal ductus arteriosus (see Data). Oligohydramnios/Neonatal Renal Impairment: If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If naproxen tablets or naproxen sodium tablets treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue naproxen tablets and naproxen sodium tablets, and follow up according to clinical practice (see Data). Labor or Delivery There are no studies on the effects of naproxen tablets or naproxen sodium tablets during labor or delivery. In animal studies, NSAIDS, including naproxen, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth. Data Human Data There is some evidence to suggest that when inhibitors of prostaglandin synthesis are used to delay preterm labor, there is an increased risk of neonatal complications such as necrotizing enterocolitis, patent ductus arteriosus, and intracranial hemorrhage. Naproxen treatment given in late pregnancy to delay parturition has been associated with persistent pulmonary hypertension, renal dysfunction, and abnormal prostaglandin E levels in preterm infants. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly starting at 30-weeks of gestation, or third trimester) should be avoided. Premature Closure of Fetal Ductus Arteriosus: Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause

premature closure of the fetal ductus arteriosus. Oligohydramnios/Neonatal Renal Impairment: Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with 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. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis. Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain. Animal Data Reproduction studies have been performed in rats at 20 mg/kg/day (0.13 times the maximum recommended human daily dose of 1500 mg/day based on body surface area comparison), rabbits at 20 mg/kg/day (0.26 times the maximum recommended human daily dose, based on body surface area comparison), and mice at 170 mg/kg/day (0.6 times the maximum recommended human daily dose based on body surface area comparison) with no evidence of impaired fertility or harm to the fetus due to the drug."

Overdosage:

"10 OVERDOSAGE Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but were rare see Warnings and Precautions (5.1 , 5.2) .Because naproxen sodium may be rapidly absorbed, high and early blood levels should be anticipated. A few patients have experienced convulsions, but it is not clear whether or not these were drug-related. It is not known what dose of the drug would be life threatening see Warnings and Precautions (5.1 , 5.2 , 5.4 , 5.6) . Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four

hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding. For additional information about overdosage treatment contact a poison control center (1-800-222-1222)."