NAPROXEN SODIUM

SKELAN® 550

Rx

550 mg FILM-COATED TABLET
Non-Steroidal Anti-inflammatory Drug

FORMULATION
Each film-coated tablet contains:
Naproxen (as Sodium)..... 550 mg

PRODUCT DESCRIPTION
Naproxen Sodium (Skelan® 550) 550 mg is a powder-blue, elliptical, film-coated tablet, plain on both sides.

CLINICAL PHARMACOLOGY
Pharmacodynamics
Naproxen Sodium is a non-steroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic activity by inhibiting cyclooxygenase (COX)-1 and COX-2 isoenzymes resulting in inhibition of prostaglandin synthesis. Pain relief with Naproxen Sodium usually begins within 30 minutes compared with 1 hour for plain Naproxen.
Pharmacokinetics
Naproxen and Naproxen Sodium are readily absorbed from the gastrointestinal tract with Naproxen Sodium dissolving more rapidly in gastric juice than plain Naproxen. Thus, Naproxen Sodium is more rapidly absorbed with peak plasma concentrations occurring about 1 to 2 hours after oral administration compared with 2 to 4 hours for naproxen, Naproxen Sodium's oral bioavailability is 95%. The rate but not the extent of absorption is decreased when Naproxen or Naproxen Sodium is taken with food. Naproxen has a volume of distribution of 0.16 L/kg and is more than 99% plasma protein bound. Naproxen plasma concentrations increase proportionately with doses up to 500 mg daily. Increased clearance due to saturation of plasma proteins is seen at higher doses. Naproxen diffuses into synovial fluid, crosses the placenta and is also distributed in small amounts into breast milk. Naproxen's plasma half-life is about 13 hours.
Naproxen is extensively metabolized in the liver with about 95% of a dose excreted in the urine as Naproxen and 6-desmethylnaproxen and their conjugates and less than 5% of a dose is excreted in the feces.

INDICATIONS
- For the symptomatic relief of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, tendinitis, bursitis, and acute gout
- For the management of pain including headache, migraine, post-operative pain, post-partum pain, and primary dysmenorrhea

DOSAGE AND ADMINISTRATION
As with other NSAIDs, the lowest effective dose should be used for the shortest possible time.
This medicine is given orally and preferably taken with or after food.
Recommended Adult Dose: One tablet twice a day, or, as prescribed by a physician.
- Do not exceed 2 tablets in each 24-hour period.
- Use only as directed by a physician.

CONTRAINDICATIONS
- Hypersensitivity to Naproxen Sodium, aspirin or other NSAIDs, or to any ingredient in the product
- Patients who have experienced asthma, urticaria, or allergic reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactoid reactions to NSAIDs have been reported in such patients.
- Patients with active or a history of peptic/gastrointestinal (GI) ulcers, chronic dyspepsia, bleeding or perforation related to previous NSAID therapy
- Patients with active or a history of recurrent peptic ulcer/hemorrhage (2 or more distinct episodes of proven ulceration or bleeding) unrelated to previous NSAID therapy
- Patients with severe renal, hepatic or cardiac failure
- During the last trimester of pregnancy
- **Contraindicated in the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery.**

WARNINGS AND PRECAUTIONS

Cardiovascular Risk
• Naproxen may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal. All NSAIDs may have a similar risk. The risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Gastrointestinal Risk
• NSAIDs, including Naproxen, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Cardiovascular Effects
Cardiovascular Thrombotic Events
Clinical trials using COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, myocardial infarction and stroke, which can be fatal. Patients with known CV disease or risk factors for CV disease may be at greater risk. To minimize the potential risk for an adverse CV event in patients treated with an NSAID, the lowest effective dose should be used for the shortest duration possible. Physicians and patients should be alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed on the signs and/or symptoms of serious CV events and the steps to take if they occur.
There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID does increase the risk of serious GI events.

Hypertension
NSAIDs can lead to the onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including Naproxen, should be used with caution in patients with hypertension. Blood pressure should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Congestive Heart Failure and Edema
Fluid retention and edema (including peripheral edema) have been seen in some patients taking NSAIDs. Use Naproxen Sodium with caution in patients with fluid retention, hypertension or heart failure. It is important to consider the sodium content of Naproxen Sodium (each tablet of Naproxen Sodium 550 mg contains 50 mg of sodium) in patients whose overall intake of sodium must be severely restricted.

Gastrointestinal Effects
NSAIDs, including Naproxen, can cause serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small or large intestines, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs.
NSAIDs should be prescribed with extreme caution in those with a history of ulcer disease or gastrointestinal bleeding since these patients have a greater than 10-fold increased risk for developing a GI bleed compared with patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age and poor general health status. Elderly patients, in particular, are at greater risk for serious gastrointestinal events.
The lowest effective dose should be used for the shortest possible duration to minimize the potential risk for an adverse GI event. Physicians and patients should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. Alternate therapies that do not involve NSAIDs should be considered especially for high-risk patients.

Renal Effects
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, hypovolemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and angiotensin converting enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease
Naproxen sodium is not recommended in patients with advanced renal disease.

Anaphylactoid Reactions (see Contraindications)
Anaphylactoid reactions may occur in patients without known prior exposure to NSAIDs. Naproxen should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Naproxen should be administered with caution in patients with preexisting asthma and emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions
As with other NSAIDs, Naproxen can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including Naproxen. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continued therapy. Notable elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST), approximately three or more times the upper limit of normal, have been reported in approximately 1% of patients. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some with fatal outcomes have been reported.
Patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with NSAIDs including Naproxen. Discontinue Naproxen if clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g., eosinophilia, rash).
While chronic alcoholic liver disease and probably other diseases which cause decreased or abnormal plasma proteins (albumin) reduce the total plasma concentration of Naproxen, it increases the plasma concentration of unbound Naproxen. Dosage adjustment of Naproxen Sodium may be necessary in these patients. The lowest effective dose is recommended.

Hematologic Effects
Anemia is sometimes seen in patients receiving NSAIDs, including Naproxen. This may be due to fluid retention, occult or gross GI blood loss or an incompletely described effect on erythropoiesis. Patients on long-term treatment with NSAIDs, including Naproxen, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia.
In some patients, NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time. Unlike aspirin, their effect on platelet function is quantitatively less, of short duration and reversible. Patients receiving Naproxen who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

General Precautions
- Naproxen and other Naproxen-containing products should not be used concomitantly since they all circulate in the plasma as the Naproxen anion.
- Naproxen Sodium is not a corticosteroid substitute and cannot be used to treat corticosteroid insufficiency.
- Patients with initial hemoglobin values of 10 g or less who are to receive long-term therapy should have hemoglobin values determined periodically.
- The antipyretic and anti-inflammatory action of Naproxen Sodium may diminish the use of these diagnostic signs in detecting complications of presumed non-infectious, non-inflammatory painful conditions.
- Ophthalmic studies are recommended if any change or disturbance in vision occurs. Adverse eye findings have been seen in animal studies with drugs of this class.

INTERACTIONS WITH OTHER MEDICAMENTS

CONCOMITANT DRUG	EFFECTS
Protein-Bound Drugs (e.g., hydantoins, sulfonamides and sulfonylureas)	• Naproxen is highly protein bound and can be displaced from binding sites or it can displace other protein-bound drugs such as hydantoins, sulfonamides and sulfonylureas from binding sites. Carefully monitor patients who are receiving naproxen concomitantly with any of these drugs for possible dosage adjustment or adverse effects.
ACE Inhibitors (e.g., captopril, fosinopril, imidapril, enalapril) **and Angiotensin-II Receptor Antagonists** (e.g., losartan, telmisartan)	• NSAIDs may diminish the antihypertensive effect and blood pressure response to ACE inhibitors or angiotensin II receptor antagonists.
Antacids (e.g., magnesium oxide, aluminum hydroxide), sucralfate	• Concomitant administration of naproxen with antacids or sucralfate may delay the absorption of naproxen.
Anticoagulants/Thrombolytic agents (e.g., warfarin, heparin, streptokinase)	• The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that when used concomitantly, there is a higher risk of serious GI bleeding compared with either drug used alone. Administration of naproxen with warfarin results in a slight increase in free warfarin in serum, but does not affect the hypoprothrombinemic effect of warfarin. Caution should be exercised when giving naproxen to patients taking any anticoagulant or thrombolytic agent.
Anti-platelet Agents (e.g., clopidogrel, cilostazol, dipyridamole)	• There is an increased risk of bleeding when anti-platelet agents and Naproxen are given concomitantly in patients who have coagulation disorders.
Aspirin and other NSAIDs (e.g., ibuprofen, mefenamic acid, ketorolac, diclofenac)	• Concomitant use of naproxen, aspirin or any other NSAID increases the risk for serious GI events. Thus, patients taking Naproxen should not take aspirin or other NSAIDs. There is no consistent evidence that low-dose aspirin mitigates the increased risk of serious CV events associated with NSAIDs. • Aspirin taken concomitantly with naproxen may decrease protein binding of Naproxen, but clearance of free (unbound) Naproxen does not seem to be altered. The clinical importance of this pharmacokinetic interaction has not been established.
ß-adrenergic blocking agents (e.g., propranolol)	• Naproxen may interfere with the antihypertensive effects of propranolol.
Cardiac glycosides (e.g., digoxin)	• NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate (GFR) and increase plasma cardiac glycoside levels when given together with cardiac glycosides.
Cholestyramine	• Naproxen's absorption may be delayed by concomitant cholestyramine administration.
Ciclosporin, Tacrolimus	• Caution is advised when ciclosporin or tacrolimus is given together with a NSAID because of the increased risk of nephrotoxicity.
Corticosteroids	• Caution is advised when corticosteroids are given together with a NSAID because of the increased risk of GI ulceration or bleeding.
Diuretics	• Naproxen can reduce the natriuretic effect of furosemide or thiazide diuretics. This response has been attributed to inhibition of renal prostaglandin synthesis. Patients should be monitored closely for signs of renal failure as well as to assure diuretic efficacy during concomitant therapy with NSAIDs.
Lithium	• NSAIDs including Naproxen may increase lithium concentrations and reduce renal lithium clearance leading to an increased risk of lithium toxicity.
Methotrexate	• NSAIDs may inhibit renal elimination and enhance toxicity of methotrexate by decreasing renal perfusion via inhibition of renal prostaglandin synthesis or by competing for renal elimination. Administration of Naproxen with methotrexate should be done with caution.
Mifepristone	• NSAIDs should not be taken for 8 to 12 days after mifepristone administration since NSAIDs can reduce the effects of mifepristone.
Quinolone Antibiotics	• Animal data indicate that NSAIDs may increase the risk of convulsions associated with quinolone antibiotics; patients taking quinolones may have an increased risk of convulsions.
Probenecid	• Probenecid may increase Naproxen plasma levels and increase its plasma half-life.
Selective Serotonin Reuptake Inhibitors (SSRIs) (e.g., fluoxetine, citalopram, sertraline)	• An increased risk of bleeding may occur when Naproxen and SSRIs are taken concomitantly.
Tolbutamide	• A study in patients with diabetes mellitus showed no interference by Naproxen on the effect of tolbutamide on plasma glucose concentrations.

Laboratory Test Interaction
- When bleeding times are determined, keep in mind that naproxen may decrease platelet aggregation and prolong bleeding time.
- Naproxen may increase urinary values of 17-ketogenic steroids due to its interaction with the M-dinitrobenzene used in the assay. Discontinue naproxen therapy temporarily for 72 hours before adrenal function tests are performed if the Porter-Silber test is to be used.
- Interference with urinary assays of 5-hydroxy indoleacetic acid may also be caused by naproxen.

STATEMENT ON USAGE FOR HIGH-RISK GROUPS
PREGNANCY AND LACTATION
Pregnancy
Pregnancy Category C. Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.
Naproxen use during pregnancy (particularly the last trimester) is not recommended because of the known effects of NSAIDs on the fetal cardiovascular system (closure of ductus arteriosus).

Lactation
Naproxen is distributed into the milk of lactating women. Naproxen use should be avoided in breastfeeding women to prevent possible adverse effects.

USE IN CHILDREN
Naproxen Sodium 550 mg tablet is not recommended for pediatric use.

USE IN THE ELDERLY
The unbound plasma fraction of naproxen is increased in geriatric patients. Naproxen Sodium should be given with caution to elderly patients when high doses are required; some dosage adjustments are needed. It is prudent to use the lowest effective dose when treating elderly patients. The elderly have less tolerance for gastrointestinal ulceration and bleeding. Many spontaneous reports of fatal adverse gastrointestinal effects associated with NSAIDs involve geriatric patients.

ADVERSE EFFECTS
Body as a Whole: angioneurotic edema, thirst, menstrual disorders, pyrexia, infection, sepsis, anaphylactic/anaphylactoid reactions, death
Gastrointestinal: heartburn, abdominal pain, nausea, vomiting, constipation, diarrhea, dyspepsia, stomatitis, flatulence, GI bleeding/perforation, gastrointestinal ulcers (peptic/gastric/duodenal) ,hematemesis ,pancreatitis ,colitis ,exacerbation of inflammatory bowel disease (ulcerative colitis, Crohn's disease), nonpeptic GI ulcers, ulcerative stomatitis, esophagitis, dry mouth, gastritis, glossitis, eructation, melena, rectal bleeding
Central Nervous System: headache, dizziness, drowsiness, lightheadedness, vertigo, inability to concentrate, depression, hallucinations, dream abnormalities, insomnia, malaise, myalgia, muscle weakness, aseptic meningitis, cognitive dysfunction, tremors, convulsions, anxiety, asthenia, confusion, nervousness, paresthesia, somnolence, coma
Cardiovascular: peripheral edema, pulmonary edema, palpitations, congestive heart failure, vasculitis, hypertension, hypotension, tachycardia, syncope, arrhythmia, myocardial infarction
Dermatologic: pruritus, skin eruptions, ecchymoses, sweating, purpura, alopecia, urticaria, skin rashes, toxic epidermal necrolysis, erythema multiforme, erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematoses, bullous reactions, Stevens-Johnson syndrome, photosensitive dermatitis, exfoliative dermatitis, photosensitivity reactions including rare cases resembling porphyria cutanea tarda (pseudoporphyria) or epidermolysis bullosa; discontinue naproxen treatment and monitor patient when skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur
Hepatobiliary: jaundice, elevated liver enzymes, abnormal liver function tests, hepatitis, hepatic failure
Hemic and lymphatic: eosinophilia, leukopenia, thrombocytopenia, agranulocytosis, granulocytopenia, hemolytic anemia, aplastic anemia, lymphadenopathy, pancytopenia, increased bleeding time
Metabolic: hyperglycemia, hypoglycemia, weight changes, appetite changes
Respiratory: eosinophilic pneumonitis, asthma, respiratory depression, pneumonia, dyspnea
Special Senses: tinnitus, hearing disturbances, hearing impairment, corneal opacity, papillitis, retrobulbar optic neuritis, papilledema, visual disturbances, blurred vision, conjunctivitis
Urogenital: glomerular nephritis, hematuria, hyperkalemia, interstitial nephritis, nephrotic syndrome, renal disease, renal failure, renal papillary necrosis, raised serum creatinine, cystitis, dysuria, oliguria/polyuria, proteinuria, abnormal renal function
Reproduction: infertility

OVERDOSAGE AND TREATMENT
Symptoms of Naproxen overdosage may include lethargy, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, transient alterations in liver function, hypoprothrombinemia, renal dysfunction, metabolic acidosis, apnea, disorientation, and vomiting. Gastrointestinal bleeding, hypertension, acute renal failure, respiratory depression, and coma may also occur. Anaphylactoid reactions may also occur following an overdose. Because high levels of Naproxen Sodium may be rapidly absorbed, high and early blood levels should be anticipated. Convulsions which may or may not be drug-related have also been reported. Manage overdosage by symptomatic and supportive care. Hemodialysis will not decrease Naproxen plasma concentration because it is highly protein-bound. Patients seen within 4 hours of ingestion may be treated with emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg body weight in children) and/or osmotic cathartic. As with hemodialysis, forced diuresis, alkalinization of urine or hemoperfusion may not be useful due to high protein binding.

STORAGE CONDITIONS: Keep the product out of sight and reach of children. Store at temperatures not exceeding 30°C.

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph AND Unilab at (+632) 858-1000 or productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY: Box of 100 tablets (in aluminum foil strips x 4s) (DR-XY27226)

CAUTION: Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

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Manufactured by AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan, Biñan, Laguna, Philippines
for UNILAB, Inc.
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

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