

For the use of Registered Medical Practitioner Only
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WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

See full prescribing information for complete boxed warning.

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

1. Generic Name and Brand Name

Naproxen Tablets I.P. 500mg

Naproprym™

2. Qualitative and Quantitative composition

Each uncoated tablet contains:

Naproxen I.P. 500mg

Excipients q.s.

3. Dosage form and strength

Refer section 1 & 2

4. Clinical Particulars**4.1. Therapeutic Indication**

Steroidal anti-inflammatory agent indicated in the treatment of rheumatoid arthritis.

4.2. Posology and method of administration

The recommended dosage of naproxen is 500 mg orally twice daily.

4.3. Contraindications

- Hypersensitivity to naproxen, naproxen sodium, or to any of the excipients.
- Since the potential exists for cross-sensitivity reactions, naproxen should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory / analgesic drugs induce the syndrome of asthma, rhinitis, nasal polyps or urticaria. These reactions have the potential of being fatal. Severe anaphylactic-like reactions to naproxen have been reported in such patients.
- Severe heart failure, hepatic failure and renal failure.
- Naproxen is contraindicated during the last trimester of pregnancy.
- Active or previous acute peptic ulcer.
- History of upper gastrointestinal bleeding or perforation related to previous NSAIDs therapy two or more distinct episodes of proven ulceration or bleeding.

- Use with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors.

4.4. Special Warnings and precautions for use

In all patients:

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms. Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

Elderly:

The elderly and/or debilitated patients are particularly susceptible to the adverse effects of NSAIDs, especially gastrointestinal bleeding and perforation, which may be fatal. Prolonged use of NSAIDs in these patients is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

The antipyretic and anti-inflammatory activities of Naproxen may reduce fever and inflammation, thereby diminishing their utility as diagnostic signs.

Respiratory disorders:

Caution is required if administered to patients suffering from or with a previous history of, bronchial asthma or allergic disease since NSAIDs have been reported to precipitate bronchospasm in such patients.

Gastrointestinal bleeding, ulceration and perforation:

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation, and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.

Naproxen has been found to be well tolerated by patients exhibiting dyspepsia with other similar agents. None the less, episodes of gastro-intestinal bleeding have been reported in patients with naproxen therapy.

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of gastrotoxicity, or bleeding, such as corticosteroids, or anticoagulants such as warfarin, selective serotonin- reuptake inhibitors or anti-platelet agents such as aspirin.

When GI bleeding or ulceration occurs in patients receiving naproxen, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated.

Renal Effects

There have been reports of impaired renal function, renal failure, acute interstitial nephritis, haematuria, proteinuria, renal papillary necrosis and occasionally nephrotic syndrome associated with naproxen.

Renal failure linked to reduced prostaglandin production:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists and the elderly. Renal function should be monitored in these patients.

Use in patients with impaired renal function:

As naproxen is eliminated to a large extent (95%) by urinary excretion via glomerular filtration, it should be used with great caution in patients with impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients and patients should be adequately hydrated. Naproxen is contraindicated in patients having a baseline creatinine clearance of less than 30ml/minute. Certain patients, specifically those whose renal blood flow is compromised, such as in extracellular volume depletion, cirrhosis of the liver, sodium restriction, congestive heart failure, and pre-existing renal disease, should have renal function assessed before and during naproxen therapy. Some elderly patients in whom impaired renal function may be expected, as well as patients using diuretics, may also fall within this category. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding.

Use in patients with impaired liver function:

Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for naproxen dosing is unknown but it is prudent to use the lowest effective dose.

As with other non-steroidal anti-inflammatory drugs, elevations of one or more liver function tests may occur. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. Severe hepatic reactions, including jaundice and hepatitis (some cases of hepatitis have been fatal) have been reported with this drug as with other non-steroidal anti-inflammatory drugs. Cross reactivity has been reported.

Use in patients with cardiovascular impairment:

Caution should be exercised in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Although sodium retention has not been reported in metabolic studies, it is possible that patients with questionable or compromised cardiac function may be at a greater risk when taking Naproxen.

Haematological:

Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen-containing products are administered.

Patients at high risk of bleeding or those on full anti-coagulation therapy (e.g. dicoumarol derivatives) may be at increased risk of bleeding if given naproxen-containing products concurrently.

Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

Anaphylactic (anaphylactoid) reactions:

Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to aspirin, other non-steroidal anti-inflammatory drugs or naproxen-containing products. They may also occur in individuals with a history of angio-oedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps.

Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

Steroids:

If steroid dosage is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Ocular effects:

Studies have not shown changes in the eye attributable to naproxen administration. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilloedema, have been reported in users of NSAIDs including naproxen, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disturbances during treatment with naproxen-containing products should have an ophthalmological examination.

Cardiovascular and cerebrovascular effects:

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy. Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, some risk cannot be excluded.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration.

Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

Dermatological/ Severe cutaneous adverse reactions (SCARs):

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, (SJS) and Lyell syndrome/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), have been reported very rarely in association with the use of NSAIDs. Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Naproxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

SJS, and TEN, and DRESS, which can be life-threatening or fatal, have been reported post-marketing in association with Naproxen treatment. If signs and symptoms suggestive of these reactions appear, Naproxen should be withdrawn immediately.

If the patient has developed SJS, or TEN or DRESS with the use of Napropym, treatment with Napropym must not be restarted and should be permanently discontinued.

Combination with other NSAIDs:

The combination of naproxen-containing products and other NSAIDs, including cyclooxygenase-2 selective inhibitors, is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

4.5. Drugs 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 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.
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. 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.
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 Cardio protection 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 and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding.
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 and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of naproxen and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function. • 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 with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects
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 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 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 and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of naproxen and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention	During concomitant use of naproxen and cyclosporine, monitor patients for signs of worsening renal function.
Pemetrexed	
Clinical Impact:	Concomitant use of naproxen and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity.
Intervention	During concomitant use of naproxen 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 is not recommended.
Cholestyramine	
Clinical Impact:	Concomitant administration of cholestyramine can delay the absorption of naproxen.
Intervention	Concomitant administration of cholestyramine with naproxen 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 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 and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.
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-dinitrobenzene 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.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Risk Summary

Use of NSAIDs, including naproxen, 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 use between about 20 and 30 weeks of gestation, and avoid naproxen use at about 30 weeks of gestation and later in pregnancy.

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including naproxen, 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. 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, can cause premature closure of the fetal ductus arteriosus.

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 treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue naproxen, and follow up according to clinical practice.

Labor or Delivery

There are no studies on the effects of naproxen 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.

Lactation

Risk Summary

The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for naproxen and any potential adverse effects on the breastfed infant from the naproxen or from the underlying maternal condition.

Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including naproxen, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including naproxen, in women who have difficulties conceiving or who are undergoing investigation of infertility.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Pediatric dosing recommendations for polyarticular juvenile idiopathic arthritis are based on well-controlled studies. There are no adequate effectiveness or dose-response data for other pediatric conditions, but the experience in polyarticular juvenile idiopathic arthritis and other use experience have established that single doses of 2.5 to 5 mg/kg (as naproxen suspension), with total daily dose not exceeding 15 mg/kg/day, are well tolerated in pediatric patients over 2 years of age.

Geriatric Use

The hepatic and renal tolerability of long-term naproxen administration was studied in two double-blind clinical trials involving 586 patients. Of the patients studied, 98 patients were age 65 and older and 10 of the 98 patients were age 75 and older. Naproxen was administered at doses of 375 mg twice daily or 750 mg twice daily for up to 6 months. Transient abnormalities of laboratory tests assessing hepatic and renal function were noted in some patients, although there were no differences noted in the occurrence of abnormal values among different age groups.

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects.

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. The clinical significance of this finding is unclear, although it is possible that the increase in free naproxen concentration could be associated with an increase in the rate of adverse events per a given dosage in some elderly patients. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients. As with other drugs used in the elderly, it is prudent to use the lowest effective dose.

Experience indicates that geriatric patients may be particularly sensitive to certain adverse effects of nonsteroidal anti-inflammatory drugs. Elderly or debilitated patients seem to tolerate peptic ulceration or bleeding less well when these events do occur. Most spontaneous reports of fatal GI events are in the geriatric population.

Naproxen is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Geriatric patients may be at a greater risk for the development of a form of renal toxicity precipitated by reduced prostaglandin formation during administration of nonsteroidal anti-inflammatory drugs.

Hepatic Impairment

Caution is advised when high doses are required and some adjustment of dosage may be required in these patients. It is prudent to use the lowest effective dose.

Renal Impairment

Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (creatinine clearance <30 mL/min).

4.7. Effects on ability to drive and use machines

Some patients may experience drowsiness, dizziness, vertigo, insomnia, fatigue, visual disturbances or depression with the use of Naproxen. If patients experience these or similar undesirable effects, they should not drive or operate machinery.

4.8. Undesirable effects

The following adverse events have been reported with NSAIDs and with naproxen.

Gastrointestinal disorders

The most commonly observed adverse events are gastrointestinal in nature. Heartburn, nausea, vomiting, constipation, diarrhoea, flatulence, dyspepsia, abdominal discomfort and epigastric distress. More serious reactions which may occur are gastro-intestinal bleeding, which is sometimes fatal, particularly in the elderly (see section 4.4), inflammation, ulceration, perforation, and obstruction of the upper and lower gastrointestinal tract, melaena, haematemesis, stomatitis, exacerbation of ulcerative colitis and Crohn's disease, oesophagitis, gastritis and pancreatitis.

Blood and lymphatic system disorders

Neutropenia, thrombocytopenia, granulocytopenia including agranulocytosis, eosinophilia, leucopenia, aplastic anaemia and haemolytic anaemia.

Immune system disorders

Hypersensitivity reactions have been reported following treatment with NSAIDs in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs. These may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and, more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Metabolic and nutrition disorders

Hyperkalaemia.

Psychiatric disorders

Insomnia, dream abnormalities, depression, confusion and hallucinations.

Nervous system disorders

Convulsions, dizziness, headache, lightheadedness, drowsiness, paraesthesia, retrobulbar optic neuritis, inability to concentrate and cognitive dysfunction have been reported. Aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).

Eye Disorders

Visual disturbances, corneal opacity, papillitis and papilloedema.

Ear and Labyrinth disorders

Tinnitus, hearing disturbances including impairment and vertigo.

Cardiac disorders

Oedema, palpitations, hypertension, cardiac failure and congestive heart failure have been reported.

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

Vascular disorders

Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders

Dyspnoea, asthma, eosinophilic pneumonitis and pulmonary oedema

Hepatobiliary disorders

Jaundice, fatal hepatitis and abnormal liver function tests.

Skin and subcutaneous tissue disorders

Skin rashes including fixed drug eruption, itching (pruritus), urticaria, ecchymoses, purpura, sweating. Alopecia, erythema multiforme, Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reaction, SLE, epidermal necrolysis, very rarely toxic epidermal necrolysis, photosensitivity reactions (including cases in which skin resembles porphyria cutanea tarda “pseudoporphyria”) or epidermolysis bullosa-like reactions which may occur rarely and drug reaction with eosinophilia and systemic symptoms (DRESS). The frequency of DRESS is not known.

If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Musculoskeletal and connective tissue disorders

Myalgia and muscle weakness.

Renal and urinary disorders

Neuropathy and nephrotoxicity in various forms, including, but not limited to, glomerular nephritis, interstitial nephritis, nephrotic syndrome, haematuria, raised serum creatinine, renal papillary necrosis and renal failure.

Reproductive system and breast disorders

Female infertility.

General disorders and administration site conditions

Thirst, pyrexia, fatigue and malaise.

4.9. Overdose

Symptoms following acute NSAID overdoses 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. 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. Manage patients with symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. 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 overdose (5 to 10 times the recommended dosage). Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

5. Pharmacological properties

5.1. Mechanism of action

Naproxen has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of naproxen, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Naproxen is a potent inhibitor of prostaglandin synthesis in vitro. Naproxen concentrations reached during therapy have produced in vivo effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because naproxen is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral.

5.2. Pharmacodynamic properties

In a healthy volunteer study, 10 days of concomitant administration of naproxen 220 mg once-daily with low-dose immediate-release aspirin (81 mg) showed an interaction with the antiplatelet activity of aspirin as measured by % serum thromboxane B2 inhibition at 24 hours following the day 10 dose [98.7% (aspirin alone) vs 93.1% (naproxen and aspirin)]. The interaction was observed even following discontinuation of naproxen on day 11 (while aspirin dose was continued) but normalized by day 13. In the same study, the interaction was greater when naproxen was administered 30 minutes prior to aspirin [98.7% vs 87.7%] and minimal when aspirin was administered 30 minutes prior to naproxen [98.7% vs 95.4%].

Following administration of naproxen 220 mg twice-daily with low-dose immediate release aspirin (first naproxen dose given 30 minutes prior to aspirin), the interaction was minimal at 24 h following day 10 dose [98.7% vs 95.7%]. However, the interaction was more prominent after discontinuation of naproxen (washout) on day 11 [98.7% vs 84.3%] and did not normalize completely by day 13 [98.5% vs 90.7%].

5.3. Pharmacokinetic properties

Naproxen is rapidly and completely absorbed from the gastrointestinal tract with an in vivo bioavailability of 95%. The elimination half-life of naproxen ranges from 12 to 17 hours. Steady-state levels of naproxen are reached in 4 to 5 days, and the degree of naproxen accumulation is consistent with this half-life.

Distribution

Naproxen has a volume of distribution of 0.16 L/kg. At therapeutic levels naproxen is greater than 99% albumin bound. At doses of naproxen greater than 500 mg/day there is less than proportional increase in plasma levels due to an increase in clearance caused by saturation of plasma protein binding at higher doses (average trough C_{ss} 36.5, 49.2 and 56.4 mg/L with 500, 1000 and 1500 mg daily doses of naproxen, respectively). The naproxen anion has been found in the milk of lactating women at a concentration equivalent to approximately 1% of maximum naproxen concentration in plasma.

Elimination

Metabolism

Naproxen is extensively metabolized in the liver to 6-O-desmethyl naproxen, and both parent and metabolites do not induce metabolizing enzymes. Both naproxen and 6-O-desmethyl naproxen are further metabolized to their respective acylglucuronide conjugated metabolites.

Excretion

The clearance of naproxen is 0.13 mL/min/kg. Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen (<1%), 6-O-desmethyl naproxen (<1%) or their conjugates (66% to 92%). The plasma half-life of the naproxen anion in humans ranges from 12 to 17 hours. The corresponding half-lives of both naproxen's metabolites and conjugates are shorter than 12 hours, and their rates of excretion have been found to coincide closely with the rate of naproxen clearance from the plasma. Small amounts, 3% or less of the administered dose, are excreted in the feces. In patients with renal failure metabolites may accumulate.

Specific Populations

Pediatric

In pediatric patients aged 5 to 16 years with arthritis, plasma naproxen levels following a 5 mg/kg single dose of naproxen suspension were found to be similar to those found in normal adults following a 500 mg dose. The terminal half-life appears to be similar in pediatric and adult patients. Pharmacokinetic studies of naproxen were not performed in pediatric patients younger than 5 years of age. Pharmacokinetic parameters appear to be similar following administration of naproxen tablets in pediatric patients.

Geriatric

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in the elderly, although the unbound fraction is <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.

Hepatic Impairment

Naproxen pharmacokinetics has not been determined in subjects with hepatic insufficiency. Chronic alcoholic liver disease and probably other diseases with decreased

or abnormal plasma proteins (albumin) reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased.

Renal Impairment

Naproxen pharmacokinetics has not been determined in subjects with renal insufficiency. Given that naproxen, its metabolites and conjugates are primarily excreted by the kidney, the potential exists for naproxen metabolites to accumulate in the presence of renal insufficiency. Elimination of naproxen is decreased in patients with severe renal impairment.

Drug Interaction Studies

Aspirin

When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

A 2-year study was performed in rats to evaluate the carcinogenic potential of naproxen at rat doses of 8, 16, and 24 mg/kg/day (0.05, 0.1, and 0.16 times the maximum recommended human daily dose of 1500 mg/day based on a body surface area comparison). No evidence of tumorigenicity was found.

Mutagenesis

Naproxen tested positive in the in vivo sister chromatid exchange assay for but was not mutagenic in the in vitro bacterial reverse mutation assay (Ames test).

Impairment of Fertility

Male rats were treated with 2, 5, 10, and 20 mg/kg naproxen by oral gavage for 60 days prior to mating and female rats were treated with the same doses for 14 days prior to mating and for the first 7 days of pregnancy. There were no adverse effects on fertility noted (up to 0.13 times the MRDH based on body surface area).

7. Description

White to off white colored, biconvex, capsule shaped, uncoated tablets having break line on one side and plain on other side.

8. Pharmaceutical particulars

8.1. Incompatibilities

NA

8.2. Shelf-life

Refer pack

8.3. Packaging information

Alu-PVC Blister Pack of 10 Tablets

8.4. Storage and handling instructions

Store protected from light, at a temperature not exceeding 30°C.

9. Patient Counselling Information

Inform patients, families, or their caregivers should be informed of the following information before initiating therapy with Naproxen and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately.

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding.

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop naproxen and seek immediate medical therapy.

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur.

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur.

Serious Skin Reactions, including DRESS. Advise patients to stop taking naproxen immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible.

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including naproxen, may be associated with a reversible delay in ovulation.

Fetal Toxicity

Inform pregnant women to avoid use of naproxen and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment

with naproxen is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios, if treatment continues for longer than 48 hours.

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of naproxen with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy. Alert patients that NSAIDs may be present in “over the counter” medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with naproxen until they talk to their healthcare provider.

Dosing Instructions

Instruct patients on how to measure and take the correct dose of naproxen and to always use a calibrated measuring device when administering naproxen to ensure the dose is measured and administered accurately. If the prescribed concentration is changed, instruct patients on how to correctly measure the new dose to avoid errors.

10. Details of manufacturer

Manufactured by:

Innova Captab Ltd.

1281/1, Hilltop Industrial Estate, Near EPIP Phase-I, Jharmajri, Baddi,
Distt. Solan (H.P.), India.

Marketed by:

Abbott Healthcare Pvt. Ltd.

Angel Space, Bldg. D-4, Gala No. 1 to 3 & 11 to 13 Ground Floor,
101 to 106 & 111 to 116 First Floor, 201 to 206 & 211 to 216 2nd Floor,
Pimplas, Dist. Thane, Bhiwandi-421 302, Maharashtra, India.

TM – Trademark of Abbott Healthcare Pvt. Ltd.

11. Details of Permission or license number with date

Mfg. Lic. No.: MNB/16/970 dated 26-Oct-23

12. Date of revision

Version 1.0 dated 9-Jun-25

For product complaints and queries please write to webmasterindia@abbott.com