SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Naproff 550 mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance

Naproxen sodium 550 mg

Excipients

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

NAPROFF is presented as white to off-white, round, biconvex film-coated tablets in blister package with 10 and 20 film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the treatment of symptoms and signs for osteoarthritis, rheumatoid arthritis and ankylosing spondylitis and treatments of acute gout arthritis, acute musculoskeletal pain, postoperative pain and dysmenorrhoea.

4.2 Posology and method of administration

Posology/frequency and time of administration:

In treatment of pain, primary dysmenorrhea, acute tendinitis and bursitis:

The recommended starting dose is 550 mg, continued with 550 mg tablets every 12 hours or 275 mg tablet every 6 to 8 hours. The starting daily dose should not exceed 1375 mg and then 1100 mg.

Acute gout:

The recommended starting dose is 825 mg then continued with 275 mg every 8 hours.

During long-term therapy, the dose can be adjusted to increase or decrease according to the clinical response of the patient.

Daily doses can be increased up to 1500 mg up to 6 months in patients who tolerated well the low doses to provide anti-inflammatory/analgesic activity at higher levels when needed. At such high doses, doctor should observe that the increased clinical benefit is potentially more than the increased risk.

Route of administration:

It should be swallowed with enough water via oral route.

It should be taken after meals.

Additional information relating to specific populations:

Renal/Hepatic impairment:

If renal function tests are impaired, it should not be used.

Caution should be taken when using in patients with impaired liver function.

One or more of the liver function tests have been reported to be elevated with nonsteroidal anti-inflammatory drugs.

Pediatric population:

NAPROFF should not be used in children under 16 years of age because safety and efficiency studies are not completed. However, only in juvenile rheumatoid arthritis, it should be used at 10 mg/kg/day dose for 12-hour intervals in children older than 5 years.

Geriatric population:

Since elimination of the drug in the elderly may reduce, caution should be taken at the dose and the lowest effective dose should be used.

The patient should be monitored closely for risk of gastrointestinal bleeding during NSAID therapy.

4.3 Contraindications

NAPROFF is contraindicated in patients who are known to be hypersensitive to naproxen sodium.

It should not be used in patients with asthma, urticaria or allergic type reactions as a result of intake of aspirin or other NSAIDs. Severe, rarely fatal, anaphylacxis-like reactions based on

NSAIDs have been reported in such patients (See section 4.4 – Special warnings and precautions for use).

NAPROFF is contraindicated in the treatment of peri-operative pain in coronary artery bypass graft (CABG) surgery (See section 4.4 – Special warnings and precautions for use).

NAPROFF is contraindicated in patients with previously had or currently active gastrointestinal bleeding or perforation associated with previous NSAID therapy, in patients with active or recurrent peptic ulcer/haemorrhage (two or more times, individually proven ulcers or bleeding).

It should not be used in patients with severe renal, hepatic insufficiency or severe heart failure.

It is contraindicated in the last trimester of pregnancy.

4.4 Special warnings and precautions for use

Cardiovascular (CV) risk
NSAIDs may cause fatal CV thrombotic events, myocardial infarction and increased risk of stroke. This risk may increase depending on the duration of use. The risk may be higher in patients with CV disease or those with CV disease risk factors.
NAPROFF is contraindicated in the treatment of pain before coronary artery bypass surgery.

Gastrointestinal (GI) risks
NSAIDs cause serious GI adverse effects, such as bleeding, ulceration, stomach or intestinal perforation, which can be fatal. These adverse events may occur at any time, with or without a prior stimulating symptom.
Elderly patients have a higher risk in regard of serious GI effects.

Warnings
In patients at risk for Alzheimer's disease, it should be used with caution.

Cardiovascular effects

Cardiovascular Thrombotic Events

Clinical trials of various COX-2 selective and non-selective NSAIDs for up to three years have shown that the risk of serious cardiovascular (CV) thrombotic events, myocardial infarction and stroke, that may be fatal, are increased. COX-2 selective or non-selective all NSAIDs may have similar risks. Patients who are known to have CV disease or CV risk factors are at greater risk. In patients treated with NSAIDs, the lowest effective dose should be used as soon as possible to minimize the potential risk of CV. Doctors and patients should be prepared for such symptoms even if they have not already had CV symptoms. Patients should be informed about serious CV symptoms and/or findings and what to do if they occur.

There is no consistent evidence that the use of aspirin together reduces the increased risk of severe CV thrombotic events associated with the use of NSAIDs. The combined use of aspirin and NSAIDs increases the risk of developing severe gastrointestinal (GI) events (See section 4.4 – Special warnings and precautions for use).

It has been found that the incidence of myocardial infarction and stroke is increased in two large, controlled clinical trials of COX-2 selective NSAIDs in the first 10-14 days of pain treatment following CABG surgery (See section 4.3 – Contraindications).

Hypertension

NSAIDs that include NAPROFF cause to develop new hypertension or worsening of existing hypertension and each of these disorders can contribute to increase risk of CV events. In patients who use thiazide or loop diuretics while taking NSAIDs, the response to these therapeutics may be impaired. NSAIDs that include NAPROFF should be used with caution in patients with hypertension. During onset of NSAID therapy and during treatment, the blood pressure (BP) should be monitored closely.

Congestive Heart Failure and Oedema

In some patients receiving NSAIDs, fluid retention and oedema have been observed. NAPROFF should be used with caution in patients with fluid retention or heart failure.

Caution should be taken when using in patients with sodium restriction, including heart failure, heart function impairment, liver function impairment and hypertension. These risks increase after using more than 10 days.

Gastrointestinal Effects- Risk of Ulceration, Bleeding and Perforation

NSAIDs that include NAPROFF, can cause severe gastrointestinal (GI) adverse events such as inflammation, bleeding, ulceration, stomach, intestine and colon perforation, which can be fatal. These serious adverse events can be developed at any time in patients treated with NSAIDs, without any stimulating symptoms or with stimulating symptoms. Only one of the five patients with developed severe adverse events in the upper GI tract during NSAID therapy is symptomatic. Upper GI track ulcers, intensive bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. This tendency continues in long-term use and increases the possibility of serious GI event development at any time during treatment. However, even short-term treatment is not risk-free.

NSAIDs should be prescribed very carefully in patients with prior ulcer or gastrointestinal bleeding history. In patients with a prior history of peptic ulcer and/or gastrointestinal bleeding and using NSAIDs, the risk of GI bleeding was 10-fold higher than in patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include the concomitant use of oral corticosteroids or anti-coagulants, long-term use of NSAIDs, smoking, using of alcohol, advanced age and general state impairment. Most spontaneous notices of fatal GI events, belong to the elderly or patients who have unwell general health condition, hence caution must be taken in the treatment of these patient groups.

In patients treated with NSAID, the lowest effective dose should be used as soon as possible to minimize the risk of a potential GI event. Doctors and patients should be prepared for indications and symptoms of GI bleeding and ulceration that may develop during NSAID use, and if they are suspected of serious GI adverse events, evaluation and treatment should be initiated immediately. This approach should be the discontinuation of NSAIDs until the serious GI adverse event disappears. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

Long term administration of NSAIDs has resulted in renal papillary necrosis and other renal damage. Renal toxicity was also observed in patients who have prostaglandins with compensatory activity in providing renal perfusion. The use of non-steroidal anti-

inflammatory drugs in these patients may lead to a reduction in the production of prostaglandins as a dose-dependent and secondly to a decrease in renal blood flow, which leads to an obvious acceleration of renal decompensation. The risk of this reaction is higher in patients with renal function impairment, heart insufficiency and hepatic insufficiency, who are taking diuretic and ACE inhibitors and elderly patients. By discontinuing treatment with NSAIDs, usually returning to the pre-treatment state occurs.

Advanced Kidney Disease

There is no controlled clinical trial data for the use of naproxen which is in content of NAPROFF, in people with advanced renal disease. Therefore, NAPROFF is not recommended in people with advanced renal disease. If NAPROFF is to be used, the monitoring closely for renal function of patients is suitable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients who are not previously exposed to NAPROFF. NAPROFF should not be given to patients with aspirin triad. This symptom complex typically develops in patients with or without nasal polyps, in asthmatic patients who undergo rhinitis or in patients who exhibit potentially fatal, severe bronchospasm after aspirin or other NSAID intake (See section CONTRAINDICATIONS AND PRECAUTIONS - pre-existing asthma). Emergency intervention should be considered in cases which develop anaphylactoid reaction.

Ocular effects

Ocular changes that could be attributed to naproxen application have not been shown in studies. In rare cases, undesirable ocular disorders such as papillitis, retrobulbar optic neuritis and papilledema have been reported by NSAID users, including naproxen, but causal and effect relationship has not been found; therefore, ophthalmologic examination should be performed in patients with visual impairment during naproxen treatment.

Skin Reactions

NSAIDs that include NAPROFF may cause serious adverse skin reactions 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 warned against

to signs and symptoms of severe skin disorders and drug use should be discontinued if skin rash or one of the signs for other hypersensitivity occur.

Pregnancy

In the last period of pregnancy, as with other NSAIDs, NAPROFF use should be avoided since it may cause premature closing of the ductus arteriosus.

Precautions

General

NAPROFF is not used instead of corticosteroids or for treatment of corticosteroid failure. Sudden discontinuation of corticosteroids may lead to the exacerbation of the disease. In patients on prolonged corticosteroid therapy, if a decision is made to discontinue corticosteroid treatment, treatment should have tapered slowly.

Pharmacological activity of NAPROFF for reducing fever and inflammation may reduce the usability of diagnostic findings for determination of complications which are non-infectious anticipated, predicted to be painful.

Hepatic Effects

Borderline elevations of one or more liver enzyme tests may occur in up to in 15% of patients who take NSAIDs that include NAPROFF. These laboratory abnormalities may progress, may remain essentially unchanged or may be transient during treatment. In clinical trials of NSAIDs, significant elevations of ALT and AST (three or more times the upper limit of normal value) have been reported in approximately 1% of patients. Rare severe hepatic reactions including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some of them with fatal outcomes) have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with NAPROFF. If clinical signs and symptoms consistent with liver disease occur (e.g. eosinophilia, associated with rash, etc.), therapy with NAPROFF should be discontinued.

Hematological Effects

Anemia is sometimes seen in patients receiving NSAIDs, including NAPROFF. The reason is that fluid retention, hidden or obvious GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including NAPROFF, should check their hemoglobin or hematocrit if they exhibit any signs or symptoms of anemia.

NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, or of shorter duration, and reversible. Such as patients with coagulopathies or who take anti-coagulants, patients who were adversely affected by changes in platelet function and who take NAPROFF should be carefully followed.

Pre-existing asthma

In patients with asthma, it may be aspirin-sensitive asthma. Aspirin use in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since it has been reported that there is cross-reactivity, between aspirin and other non-steroidal anti-inflammatory drugs including bronchospasm, in such aspirin sensitive patients, NAPROFF should not be administered and should be used with caution in patients who have previously had asthma.

Information for patients

Patients should be informed by the following subjects before and during treatment.

- As with other NSAIDs, naproxen sodium can cause serious CV side effects, such as myocardial infarction or stroke, which can cause hospitalization or even death. Although serious CV side effects may occur without any warning symptoms, patients should be careful in terms of signs and symptoms such as chest pain, shortness of breath, weakness, impaired speech, and should consult the doctor when any sign of the disease is observed. Patients should be informed in terms of the importance of this observation. (See section 4.4 Special warnings and precautions for use-Cardiovascular effects)
- As with other NSAIDs, naproxen sodium may cause serious GI side effects such as ulceration and hemorrhage which can cause GI disease, and rarely cause hospitalization or even death. Although severe GI system ulceration and hemorrhage may occur without any warning symptoms, patients should be careful in terms of

symptoms and signs of ulceration and bleeding and should consult their doctor if any signs or symptoms of the disease show, such as epigastric pain, dyspepsia, melena and hematemesis. Patients should be informed in terms of the importance of this observation. (See section 4.4 Special warnings and precautions for use-Risk of Gastrointestinal Effects-Ulceration, Bleeding and Perforation)

- As with other NSAIDs, naproxen sodium can cause serious dermatologic side effects such as exfoliative dermatitis, SJS and TEN, which can cause hospitalization or even death. Although severe skin reactions can occur without any warning, patients should be careful if they observed symptoms and signs of skin rash and papilla, fever or other symptoms of hypersensitivity, and should consult the doctor if any signs or symptoms of the disease are observed. If any rash occurs in the patients, it should be advised that they should discontinue the drug immediately and advice to the doctor as soon as possible.
- Patients should report symptoms and signs of an unexplained weight gain or oedema to their doctors quickly.
- Patients should be informed of the symptoms and signs of hepatotoxicity (nausea, fatigue, lethargy, jaundice, tenderness on the right upper quadrant and symptoms similar to cold). If these occur, patients should terminate the treatment and should take rapid medical treatment.
- Patients should be informed about the findings of the anaphylactic reaction (difficulty in breathing, swelling of face and throat). When these occur, patients should be warned quickly to emergency services (See section 4.4 Special precautions and precautions).
- In the last period of pregnancy, as with other NSAIDs, naproxen sodium should not be taken because it can cause premature closing of the ductus arteriosus.

Laboratory tests

Doctors should closely monitor the signs and symptoms of GI bleeding, as serious GI tract ulceration and bleeding may occur without any warning symptoms. Complete blood count and chemical profile should be regularly monitored in patients who are treated for a long time with NSAIDs. Naproxen sodium treatment should be discontinued if clinical signs and

symptoms consistent with liver or renal disease develop, systemic symptoms occur (eosinophilia, rash, etc.) or abnormal liver tests continue or worsen.

4.5 Interaction with other medicinal products and other forms of interaction

Co-administration of NAPROFF and other NSAIDs is not recommended because of the cumulative risk of triggering serious adverse events associated with NSAIDs.

Co-administration with antacid or cholestyramine may delay the absorption of naproxen sodium, but it does not affect the amount of absorption.

Naproxen sodium is highly bound to plasma albumin; therefore, there is potential for theoretically interacting with other drugs that bind to albumin such as coumarin-type anticoagulants, sulfonylureas, hydantoins, other NSAID drugs and aspirin. Patients who take a hydantoin, sulphonamide or sulphonylurea with NAPROFF should be monitored for dose adjustment as needed.

Although no significant interaction is observed between naproxen sodium and coumarin-type anticoagulants in clinical trials, NSAIDs may enhance the effects of anticoagulants such as warfarin. Naproxen sodium reduces platelet aggregation and prolongs bleeding time. While the bleeding time determination, this effect should not be forgotten.

Probenecid

Caution should be taken when administering with probenecid, because it increases plasma levels of naproxen sodium and an increase in half-life of naproxen has been reported with this combination.

Cyclosporin

As with all NSAIDs caution is advised when cyclosporin is co-administered because of the increased risk of nephrotoxicity.

Mifepristone

NSAIDs should not be used for 8 - 12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

Beta blockers

NAPROFF may reduce anti-hypertensive effects of beta-blockers.

Cardiac glycosides

NSAIDs may exacerbate cardiac failure, reduce glomerular filtration rate and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.

Tacrolimus

There is a possible risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine

There is an increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

SSRIs

There is an increased risk of gastrointestinal bleeding when selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.

Steroids

As with all NSAIDs, caution should be taken when co-administering with corticosteroids because of the increased risk of gastrointestinal ulceration or bleeding.

If steroid dosage is to be reduced or discontinued during treatment, steroid dosage should be slowly reduced and patients should be closely monitored for adverse effects such as exacerbations of adrenal insufficiency and arthritis symptoms.

Quinolones

Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking quinolones may have an increased risk of developing convulsions.

ACE-inhibitors

It has been reported that NSAIDs may reduce the antihypertensive efficacy of ACE inhibitors. This interaction should be observed in patients receiving ACE-inhibitors with NSAIDs.

Aspirin

When NAPROFF is administered with aspirin, the protein binding is reduced, but the clearance of free NAPROFF does not change. The clinical significance of this interaction is

unknown; however, as with other NSAIDs, the use of aspirin and naproxen sodium in combination is not recommended due to the increment of adverse event potential.

Furosemide

As in post-marketing studies, it has been shown that NAPROFF may reduce the natriuretic effect of furosemide and thiazides in some patients in clinical trials. This response has been associated with the inhibition of renal prostaglandin synthesis. In treatment with NSAIDs, patients should be closely monitored for signs of renal insufficiency as well as providing diuretic efficacy (see section 4.4 Special warnings and precautions).

Lithium

NSAIDs have caused with elevated plasma lithium levels and reduced renal lithium clearance. The average lithium concentration increased by 15% and renal clearance reduced by about 20%. These effects have been associated with the inhibition for renal prostaglandin synthesis of NSAIDs. Therefore, when NSAIDs and lithium are used together, patients should be carefully monitored for lithium toxicity signs.

Methotrexate

It has been reported that NSAIDs competitively inhibit the accumulation of methotrexate in rabbit kidney sections. For this reason they may increase the toxicity of methotrexate. Caution should be taken when NSAIDs use in combination with methotrexate.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic. Therefore, those who use these drugs together have a higher risk of serious GI bleeding than those who use them separately.

It is suggested that NAPROFF therapy be temporarily discontinued 48 hours before adrenal function tests are performed, because naproxen sodium may affect some tests for 17-ketogenic steroids incorrectly. Similarly, NAPROFF may interfere with some assays of urinary 5-hydroxyindoleacetic acid (5HIAA).

Concomitant administration of NAPROFF tablets with food may delay the absorption of naproxen sodium, but does not affect its absorption amount.

Additional information of special population

Pediatric population:

No interaction studies related to the pediatric population have been identified.

Geriatric Population:

As any NSAID, care should be taken in the treatment of elderly patients (65 years and older).

4.6 Pregnancy and lactation

General recommendation

Pregnancy category is C at 1st and 2nd trimester, D at 3rd trimester.

Women of childbearing potential / Contraception

It should not be used in women who are planning to become pregnant.

Pregnancy period

There is not enough data on the use of Naproxen sodium in pregnant women during the 1st and 2nd trimester of pregnancy.

Investigations on animals have shown that reproductive toxicity exists. The potential risk for humans is unknown.

For naproxen sodium, there are harmful pharmacological effects on pregnancy and/or fetus/newborn during the 3rd trimester of pregnancy.

NAPROFF should not be used during pregnancy unless it is absolutely necessary (unless the doctor think that it is absolutely necessary).

Caution should be taken while it is given to pregnant women.

As with this kind of other drugs, naproxen occurs a delay in birth in animals and also affects the human fetal cardiovascular system (ductus arteriosus occlusion). Therefore, if NAPROFF is not exactly necessary, it should not be used during pregnancy.

NAPROFF is not recommended in labour because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affects foetal blood circulation and inhibits uterus contractions, with an increased bleeding tendency in both mother and child.

Lactation period

Naproxen anion has been found in milk of breastfeeding mothers at a concentration of about 1% of the concentration found in the plasma. The use of prostaglandin inhibiting drugs in breastfeeding mothers is not recommended due to possible undesirable effects on newborns.

Fertility

As with any drug known to inhibit cyclooxygenase / prostaglandin synthesis, the use of NAPROFF may impair fertility and should not be used in women who are planning to become pregnant. Discontinuation of NAPROFF should be considered in women with a pregnancy difficulty or have undergone infertility studies.

4.7 Effects on ability to drive and use machines

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of NAPROFF. If patients experience these or similar undesirable effects, they should be careful when performing activities which require attention.

4.8 Undesirable effects

Side effects observed with naproxen sodium are classified as follows in body systems: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Infections and infestations

Uncommon: Aseptic meningitis

Blood and lymphatic system disorders

Common: Haemolytic anemia

Uncommon: Aplastic anemia, leucopenia, thrombocytopenia agranulocytosis, eosinophilia

Immune system disorders

Uncommon: Anaphylactoid reactions

Metabolism and nutrition disorders

Uncommon: Hyperkalaemia

Psychiatric disorders

Uncommon: Depression, sleep disorder, insomnia, confusion and hallucinations.

Nervous system disorders

Common: Dizziness, drowsiness, headache, light sensitivity, retrobulbar optic neuritis, impairment of concentration

Uncommon: Convulsions, cognitive dysfunction

Eye disorders

Common: Visual disturbances, corneal opacity

Uncommon: Papillitis, papilloedema.

Ear and labyrinth disorders

Uncommon: Hearing impairment, paracousis, tinnitus, vertigo

Cardiac disorders

Common: Palpitations, oedema, congestive heart failure, sodium retention

Vascular disorders

Uncommon: Hypertension, vasculitis

Very rare: Myocardial infarction, stroke

Respiratory, thoracic and mediastinal disorders

Common: Dyspnoea

Uncommon: Pulmonary oedema, asthma, eosinophilic pneumonitis

Gastrointestinal disorders

Common: Peptic ulcer, perforation, bleeding which is sometimes fatal in the elderly, heartburn, nausea, oesophagitis, vomiting, diarrhoea, stomach bloating, constipation, dyspepsia, abdominal pain

Uncommon: Non-peptic gastro-intestinal ulceration, melaena, haematemesis, stomatitis, ulcerative stomatitis, ulcerative colitis, exacerbation of Crohn's disease, pancreatitis, gastritis

Hepatobiliary disorders

Rare: Fatal hepatitis, jaundice, abnormal liver functions.

Skin and subcutaneous tissue disorders

Common: Itching, skin eruption, skin spot, purpura, skin rash, ecchymoses

Uncommon: Sweating, alopecia and toxic epidermal necrolysis, erythema multiforme, bullosa reactions due to Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reaction, follicular urticaria, photoallergic-sensitivity reactions, angioneurotic oedema

Musculoskeletal, connective tissue and bone disorders

Uncommon: Myalgia, muscle weakness

Renal and urinary disorders

Common: Renal disorders

Uncommon: Haematuria, interstitial nephritis, nephrotic syndrome, renal failure, renal papillary necrosis

Pregnancy, puerperium states and perinatal disorders

Uncommon: Female infertility

General disorders and administration site conditions

Common: Oedema, thirst

Uncommon: Pyrexia, malaise and fatigue

Investigations

Uncommon: Abnormalities in liver function tests, increase in serum creatinine

4.9 Overdose and treatment

Symptoms

Headache, convulsion, coma, pyrosis, nausea, vomiting, epigastric pain, GI bleeding, rarely diarrhea, disorientation, excitation, drowsiness, dizziness, tinnitus, fainting. In cases of significant poisoning, acute renal failure and liver damage may occur.

Respiratory depression and coma may be seen after nonsteroidal antiinflammatory drug intake but this case is rare.

In the case of a naproxen sodium overdose, transient prolongation of prothrombin time due to hypothrombinaemia may be due to the selective inhibition of vitamin K-dependent clotting factors.

Seizures have been seen in a few patients, but it is unclear whether they related to naproxen. It is not known which dose of Naproxen sodium is life-threatening.

Treatment
Patients should be treated symptomatically if necessary. Activated charcoal should be considered within 1 hour after the doses are taken which may be toxic. Alternatively, gastric lavage should be considered within 1 hour of taking life-threatening overdoses in adults.

Good urination should be guaranteed.

Kidney and liver functions should be closely monitored.

After the doses that can be toxic are taken, the patients should be observed for at least four hours.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other precautions should be taken according to the clinical condition of the patient.

Since naproxen sodium binds to proteins at high rate, hemodialysis does not lower plasma naproxen sodium concentrations. However, in a patient who took naproxen and has renal insufficiency, hemodialysis may still be appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic

ATC-code: M01AE02

Naproxen sodium is a nonsteroidal anti-inflammatory with anti-inflammatory and analgesic activity. It affects by inhibiting cyclooxygenase (COX-1 and COX-2) enzymes that catalyze the formation of naproxen prostaglandins thus prostaglandin synthesis like as other nonsteroidal analgesic anti-inflammatory drugs.

Naproxen sodium is not a central nervous system depressant and does not activate metabolism enzymes.

5.2 Pharmacokinetic properties

Absorption

Naproxen sodium is freely soluble in water and is completely and quickly absorbed from the gastrointestinal tract after oral administration. The pain relief as a result of this rapid and complete absorption, begins noticeably after 20 minutes of administration. It reaches the peak plasma level in 1-2 hours and normally after 4-5 doses, this peak level becomes constant.

Distribution

Average plasma half-life is approximately 13 hours and more than 99% of the treatment doses bind to protein.

Biotransformation

Naproxen is metabolized to 6-0-desmethyl Naproxen in liver commonly.

Elimination

Approximately 95% of the drug is excreted as naproxen, 6-0-desmethyl naproxen and its conjugates in the urine. The rate of excretion corresponds exactly to the rate of absence of the drug from the plasma.

Characteristic properties in the patients

Age and gender

Safety of Naproxen sodium in pediatrics is not known since any study has been performed in pediatrics. However, only at juvenile rheumatoid arthritis, in children over 5 years, it should be taken at 10mg/kg/day dose, 12-hour intervals.

Renal impairment

Pharmacokinetics of Naproxen sodium has not been demonstrated in patient with renal impairment. Based on the knowledge that naproxen is metabolized and its metabolites are excreted by the kidneys, there is a potential for naproxen metabolites to accumulate in the presence of renal failure. Elimination of naproxen is reduced in patients with severe renal

insufficiency. Products containing naproxen are not recommended in patients with moderate-severe renal insufficiency (creatinine clearance <30 ml / min).

5.3 Preclinical safety data

Carcinogenicity

Naproxen was administered with food to rats for 24 months at doses of 8, 16 and 24mg/kg/day. Carcinogenicity was not seen.

Mutagenicity

Mutagenicity was not seen in Salmonella typhimurium, Sachharomyces cerevisiae, and mouse lymphoma tests.

Fertility

Naproxen did not affect the fertility of rats when administered orally at doses of 30mg/kg/day to males and 20mg/kg/day to females.

Teratogenicity

Teratogenicity was not seen when Naproxen is administered orally at doses of 20mg/kg/day during organogenesis to rats and rabbits.

Perinatal/Postnatal Reproduction

Oral administration of naproxen to pregnant rats at doses of 2, 10 and 20mg/kg/day during the third trimester of pregnancy resulted in difficult labour. These are known effects of this class of compounds and were demonstrated in pregnant rats with acetyl salicylic acid and indomethacin.

Acute oral toxicity LD50: 248 mg/kg (rats)

Oral LD50: 500 mg/kg (rats)

Oral LD50: 1200 mg/kg (mice)

Oral LD50: 4000 mg/kg (hamsters)

Oral LD50: > 1000 mg/kg (dogs)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose pH101

Polyvinylpyrrolidone (Povidone K30)

Talc

Magnesium stearate

Opadry White Y-1-7000:

- Hydroxy propyl methyl cellulose
- Titanium dioxide (E171)
- Polyethylene glycol (PEG 400)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store below 30ºC at room temperature by protecting from light.

6.5 Nature and contents of container

1 Al foil-PVC blister containing 10 tablets, in a carton box.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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