SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

APRALJIN FORTE 550 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Active substance:
Naproxen sodium 550.0 mg

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet.
White film coated, odorless, homogenous oblong tablets, scored on one side and "APJ 550" embossed on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of signs and symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, and acute gout, acute musculoskeletal system pains, postoperative pain and dysmenorrhea.

4.2 Posology and method of administration

Posology/frequency and duration of administration
In the treatment of pain, primary dysmenorrhea, acute musculoskeletal system pains:
Recommended initial dosage is 550 mg followed by 550 mg every 12 hours or 275 mg very 6-8 hours. Initial total daily dosage should not exceed 1375 mg and 1100 mg thereafter.

Acute gout:
Recommended initial dosage is 825 mg followed by 275 mg every 8 hours. During prolonged treatment, dosage may be adjusted according to clinical response of patient.

If higher levels of anti-inflammatory/analgesic effect are required, dosage may be increased to 1500 mg for up to 6 months in patients tolerating the lower dosages well. At these high dosages, the doctor should observe that the clinical benefits outweigh the potential risks.

Method of administration
The tablets should be taken orally with enough water and after meals.

Additional information regarding special populations

Renal/Hepatic Impairment
Should not be used in patients if renal function tests are impaired.
Caution is advised in patients with impaired liver function.

One or more of the liver function tests have been reported to be elevated with non-steroidal anti-inflammatory medicines.

Pediatric population
Since the safety and efficacy tests are incomplete, APRALJIN FORTE should not be used in children less than 16 years of age. Only for juvenile rheumatoid arthritis it is recommended in dosages of 10 mg/kg/day every 12 hours in children older than 5 years of age.

Geriatric population
Dosing should be made carefully in elderly patients as elimination may be decreased, the lowest effective dose should be used.

Patients should be closely monitored during treatment with NSAID's for gastrointestinal bleeding risk.

4.3 Contraindications

APRALJIN FORTE is contraindicated in patients with known hypersensitivity to naproxen sodium.

Should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see section 4.4).

APRALJIN FORTE is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see section 4.4).

APRALJIN FORTE is contraindicated patients with a history of gastrointestinal bleeding or perforation related to previous NSAID therapy, active, or history of peptic ulcer/or active gastrointestinal bleeding (two or more distinct episodes of proven ulceration or bleeding).

Should not be used in patients with severe heart failure, hepatic failure and renal failure.

It is also contraindicated in the third trimester of pregnancy.

4.4 Special warnings and precautions for use

Cardiovascular (CV) risk
- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

APRALJIN FORTE is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal (GI) risks
- NSAIDs cause serious 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 with or without any previous warning symptoms. Elderly patients are at greater risk for serious GI events.

Warnings
Should be used carefully in patients with Alzheimer's disease.

Cardiovascular effects

Cardiovascular Thrombotic Incidents

Clinical trials of several 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. All NSAIDs, both COX-2 selective and nonselective, may have a similar risk. 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 remain alert for the development of such events, even in the absence of previous CV symptoms. Patients should be informed about 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 do increase the risk of serious GI events (see section 4.4).

Two large, controlled, clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke (see section 4.3).

Hypertension

NSAID's including APRALJIN FORTE can lead to onset of new hypertension or worsening of pre-existing 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. NSAID's including APRALJIN FORTE should be used with caution in patients with hypertension. Blood pressure (BP) 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 have been observed in some patients taking NSAID's. APRALJIN FORTE should be used with caution in patients with heart failure and fluid retention.

Caution is advised when used in patients with sodium restriction including heart failure, heart function disorders, liver function disorders and hypertension. The risk increases after 10 days of usage.

Gastrointestinal Effects - Ulceration Bleeding, and Perforation Risk

NSAIDs, including APRALJIN FORTE, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients, who develop a serious upper GI tract adverse event on NSAID therapy, is symptomatic. Upper GI tract ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAID's should be prescribed with extreme caution to patients with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a prior history of ulceration and/or gastrointestinal

bleeding who use NSAID's have a greater than 10-fold increased risk for developing a GI bleed compared to 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. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians 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. 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 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 nonsteroidal anti-inflammatory medicine 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, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease
There are no controlled clinical studies regarding the use of APRALJIN FORTE in patients with advanced renal disease. Therefore APRALJIN FORTE is not recommended in patients with advanced renal disease. If APRALJIN FORTE therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid reactions
As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to APRALJIN FORTE. APRALJIN FORTE should not be prescribed to patients with 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 (see sections 4.3 and 4.4 – existence of asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Ophthalmic effects
Some adverse eye findings have been reported which can be associated with 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 should have an ophthalmological examination.

Skin reactions
NSAIDs including APRALJIN FORTE can cause serious adverse skin reactions, including 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 medicine should be

discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy
In late pregnancy, as with other NSAID's APRALJIN FORTE should be avoided because it may cause premature closure of the ductus arteriosus.

Precautions

General
APRALJIN FORTE cannot be used to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may cause the exacerbation of the disease. If corticosteroid therapy is to be discontinued in patients receiving long-term corticosteroid therapy, treatment should be reduced slowly.

The pharmacological activity of APRALJIN FORTE in reducing fever and inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Hepatic effect
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including APRALJIN FORTE. These laboratory abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of 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 test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with APRALJIN FORTE. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg, eosinophilia, rash, etc.), APRALJIN FORTE should be discontinued.

Hematologic effect
Anemia is sometimes seen in patients receiving NSAIDs, including APRALJIN FORTE. This may be due to fluid retention, occult or gross GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including APRALJIN FORTE, should have their hemoglobin or hematocrit checked 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, of shorter duration, and reversible. Patients receiving APRALJIN FORTE who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other non-steroidal anti-inflammatory

medicines has been reported in such aspirin-sensitive patients, APRALJIN FORTE should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

Laboratory tests
Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their Complete Blood Count and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, naproxen sodium should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

The combination of APRALJIN FORTE and other NSAIDs is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

Concomitant administration of antacid or colestyramine can delay the absorption of naproxen but does not affect its extent.

Naproxen is highly bound to plasma albumin; it thus has a theoretical potential for interaction with other albumin-bound medicines such as coumarin-type anticoagulants, sulphonylureas, hydantoins, other NSAIDs, and aspirin. Patients simultaneously receiving naproxen and a hydantoin, sulphonamide or sulphonylurea should be observed for adjustment of dose if required.

Even though no significant interactions have been observed in clinical studies with naproxen and coumarin-type anticoagulants, NSAID's can increase the anticoagulant effects of anticoagulant medicines like warfarin. NSAIDs inhibit platelet aggregation and hereby prolong bleeding time. This effect should be taken into consideration when determining bleeding time.

Probenecid
Caution is advised when probenecid is administered concurrently as it increases naproxen plasma levels and this combination extends naproxen plasma half-life.

Cyclosporine
Due to increased risk of nephrotoxicity care should be taken while concomitant use of cyclosporine and NSAIDs.

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

Beta-blockers
APRALJIN FORTE can diminish hypertensive effect 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 potential risk of nephrotoxicity when NSAIDs are used in combination with tacrolimus.

Zidovudine
There is an increased risk of hematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of hemarthroses and hematoma in HIV(+) hemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

SSRI's
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.

Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids and the patient should be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

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

ACE inhibitors
Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin
When APRALJIN FORTE is administered with aspirin, its protein binding is reduced, although the clearance of free APRALJIN FORTE is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of naproxen and naproxen sodium and aspirin is not generally recommended because of the potential of increased adverse effects.

Furosemide
Clinical studies, as well as postmarketing observations, have shown that naproxen sodium can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see section 4.4), as well as to assure diuretic efficacy.

Lithium
NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate
NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin
The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both medicines together have a risk of serious GI bleeding higher than users of either medicine alone.

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

Concomitant administration of APRALJIN FORTE with food can delay the absorption of naproxen, but does not affect its extent.

Additional information regarding special populations

Pediatric population:
No interaction studies with the pediatric population have been identified.

Geriatric population
No interaction studies with the geriatric population have been identified.

4.6 Fertility, pregnancy and lactation

General advice
Pregnancy category: 1st and 2nd trimester C, 3rd trimester D.

Women of childbearing potential/Contraception
Should not be used in women who plan to become pregnant.

Pregnancy
There is no sufficient data on the use of naproxen sodium in pregnant women in the 1st and 2nd trimester.
Reproductive toxicity was observes in animal studies. Potential risk towards humans is unknown.
Naproxen sodium has harmful pharmacological effects on pregnancy and/or fetus/newborn in the 3rd trimester of pregnancy.
APRALJIN FORTE should not be used during pregnancy unless necessary (deemed as absolutely necessary by the doctor).
Caution is advised when prescribing to pregnant women.

As with other medicines of this type, naproxen produces delay in parturition in animals and also affects the human fetal cardiovascular system (closure of ductus arteriosus). Therefore APRALJIN FORTE should not be used during pregnancy unless absolutely necessary.

APRALJIN FORTE is not recommended in labor and delivery because, through their prostaglandin synthesis inhibitory effect, they may adversely affect fetal circulation and inhibit uterine contractions, thus increasing the risk of uterine hemorrhage.

Breast-feeding
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. Because of the possible adverse effects of prostaglandin-inhibiting medicines on neonates, use in nursing mothers should be avoided.

Fertility
The use of APRALJIN FORTE, as with any medicine known to inhibit cyclooxygenase/ prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of APRALJIN FORTE should be considered.

4.7 Effects on ability to drive and use machines
Taking APRALJIN FORTE may cause dizziness, vertigo, insomnia or depression are possible in some patients. If patients experiences these or similar undesirable effects, they should be careful while performing activities that require attention.

4.8 Undesirable effects
Side effects observed with naproxen sodium are classified body systems as follows:
Very common (≥1/10) common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

Infections and infestations
Uncommon: Aseptic meningitis

Blood and lymphatic system disorders
Common: Hemolytic anemia
Uncommon: aplastic anemia, leucopenia, thrombocytopenia agranulocytosis, eosinophilia

Immune system disorders
Uncommon: Anaphylactoid reactions

Metabolism and nutrition disorders
Uncommon: Hyperkalemia

Psychiatric disorders
Uncommon: Depression, sleep disturbances, insomnia, confusion, hallucinations

Nervous system disorders
Common: dizziness, lethargy, headache, sensitivity to light, retrobulbar optic neuritis, impaired concentration
Uncommon: Convulsions, mental dysfunction

Eye disorders
Common: Blurred vision, corneal opacity
Uncommon: Papillitis, papilledema

Ear and labyrinth disorders
Uncommon: Hearing disturbances including impairment, tinnitus, vertigo

Cardiac disorders
Common: Palpitations, edema, congestive heart failure, sodium retention

Vascular disorders
Uncommon: Hypertension, vasculitis
Very rare: Myocardial infarction, stroke

Respiratory, thoracic and mediastinal disorders
Common: Dyspnea
Uncommon: Pulmonary edema, asthma, eosinophilic pneumonia

Gastrointestinal disorders
Common: Peptic ulcer, perforation, bleeding which is likely to be fatal in elderly patients, heartburn, nausea, esophagitis, vomiting, diarrhea, scaly swelling, constipation, dyspepsia, abdominal pain
Uncommon: Nonpeptide gastrointestinal ulceration, melanoma, hematemesis, stomatitis, ulcerative stomatitis, ulcerative colitis and Crohn's disease, pancreatitis, gastritis

Hepatobiliary disorders
Rare: Fatal hepatitis, jaundice, abnormal liver function

Skin and subcutaneous tissue disorders
Common: Itching, urticaria, spots on the skin, purpura, skin rashes, ecchymosis
Uncommon: Sweating, hair loss and toxic epidermal necrolysis, erythema multiforme, bullous reactions due to Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reactions, follicular urticaria, photosensitivity reactions, angioneurotic edema

Muscular-skeletal, connective tissue and bone disorders
Uncommon: Myalgia, muscle weakness

Renal and urinary disorders
Common: Renal disorders
Uncommon: Hematuria, interstitial nephritis, nephrotic syndrome, renal failure, renal papillary necrosis

Pregnancy, puerperium and perinatal conditions
Uncommon: Female infertility

General disorders and administration site conditions
Common: Edema, thirst
Uncommon: Pyrexia (chills and fever), malaise, fatigue

Investigations
Uncommon: abnormalities in liver function tests, elevated serum creatinine

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkey Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone number: +90 800 314 00

08; fax: +90 312 218 35 99).

4.9 Overdose

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 can occur.
Respiratory depression and coma may be seen after nonsteroidal antiinflammatory medicine intake, but are rare.
In one case of naproxen sodium overdose, transient prolongation of the prothrombin time due to hypothrombinemia may have been due to selective inhibition of the synthesis of vitamin-K dependent clotting factors.
A few patients have experienced seizures, but it is not known whether these were naproxen-related or not. It is not known what dose of the medicine would be life-threatening.

Treatment:

Patients should be treated symptomatically as required. Within 1 hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within 1 hour of ingestion of a potentially life-threatening overdose.
Good urine output should be ensured.
Renal and liver function should be closely monitored.
Patients should be observed for at least 4 hours after ingestion of potentially toxic amounts.
Frequent or prolonged convulsions should be treated with intravenous diazepam.
Other measures may be indicated by the patient's clinical condition.
Hemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding. However, hemodialysis may still be appropriate in a patient with renal failure who has taken naproxen.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and anti-rheumatic agents
ATC code: M01AE02

Naproxen sodium is a nonsteroidal antiinflammatory medicine with antiinflammatory and analgesic activity. Like other nonsteroidal analgesic antiinflammatory medicines, Naproxen acts by inhibiting the cyclooxygenase (COX-1 and COX-2) enzymes that catalyze the prostaglandin synthesis, and hereby the prostaglandin synthesis.

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

5.2 Pharmacokinetic properties

Absorption:

Naproxen sodium is easily dissolved in water and is rapidly and completely absorbed from the gastrointestinal tract after oral administration. Following this rapid and complete absorption, the pain relief begins noticeably after 20 minutes. Peak plasma levels are reached within 1-2 hours and after 4-5 doses this peak level is steadied.

Distribution:
Naproxen has a half-life of 13 hours and at therapeutic levels, is greater than 99% albumin-bound.

Biotransformation:
Naproxen is extensively metabolized in the liver to 6-0-desmethyl naproxen.

Elimination:
Approximately 95% of the naproxen from any dose is excreted in the urine, primarily as naproxen, 6-0-desmethyl naproxen or their conjugates.

Characteristics in patients

Age and gender:
Since no pediatric studies with naproxen sodium have been performed, safety of naproxen sodium in children has not been established. And it should only be used juvenile rheumatoid arthritis in children over 5 years of age.

Renal insufficiency:
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. Naproxen-containing products are not recommended for use in patients with moderate to severe and severe renal impairment (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 24 mg/kg/day. Naproxen was not carcinogenic in rats.

Mutagenicity:
No mutagenicity was seen in *Salmonella typhimurium*, S*achharomyces cerevisisa*e and mouse lymphoma tests.

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

Teratogenicity:
Naproxen was not teratogenic when administered orally at dose of 20 mg/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 labor. These are known effects of this class of compounds and were demonstrated in pregnant rats with aspirin and indometacin.

Acute oral toxicity LD50: 248 mg/kg (in rats)
Oral LD50: 500 mg/kg (in rats)

Oral LD50: 1200 mg/kg (in mice)
Oral LD50: 4000 mg/kg (hamster)
Oral LD50> 1000 mg/kg (in dogs)

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose PH 101
Microcrystalline cellulose PH 102
Starch
Pregelatinized starch 1500
Polyvinyl pyrrolidone K25
Magnesium stearate

Film coating: (Opadry OY-D-7233 white)
Hypromellose
Titanium dioxide
Talc
Polyethylene glycol
Sodium lauryl sulphate

6.2 Incompatibilities

Not reported.

6.3 Shelf life

48 months.

6.4. Storage conditions

Should be stored at room temperature below 30ºC. Protect from light.

6.5 Type and nature of container

One side is transparent PVDC, the other is printed aluminum foil.
Each box contains 10 or 20 film tablets.

6.6 Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No: 1
34303 Küçükçekmece – Istanbul/TURKEY

8. MARKETING AUTHORIZATION NUMBER (S)

181/25

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization : 21.01.1997
Date of latest renewal : 20.03.2013

10. DATE OF REVISION OF THE TEXT

12.11.2021