

1. NAME OF THE MEDICINAL PRODUCT

Nalgesin 220 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 220 mg naproxen sodium, which is equivalent to 200 mg naproxen.

Excipients with known effect:

- Sodium: 0.87 mmol (20.063 mg)/tablet

For the whole list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

The film-coated tablets are oval, slightly biconvex, pale gray blue film-coated tablets with metal shine.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Nalgesin 220 mg film-coated tablets are indicated in adults and children over 12 years of age for:

- short-term symptomatic treatment of mild to moderate pain (such as headache, toothache, menstrual pain, joint pain, muscle pain).

4.2 Posology and method of administration

Posology

Adults and children over 12 years.

The recommended dose for adults and children over 12 years of age is 1 film-coated tablet every 8–12 hours.

Alternatively, the initial dose is two film-coated tablets, followed by the ingestion of one additional film-coated tablet after 8–12 hours, if needed.

The maximum daily dose is 3 film-coated tablets (which corresponds to 660 mg of naproxenat sodium).

The duration of treatment is 5 days. If pain persists, as well as if the symptoms change, it is recommended to consult a physician.

Elderly patients

The lowest effective doses should be used (see section 4.4). The maximum dose for patients, older than 65 years, is 2 film-coated tablets per day, 1 tablet every 12 hours.

Patients with renal impairment

This medicinal product should be used with caution in patients with renal impairment (see section 4.4). The maximum dose for patients with renal impairment is 2 film-coated tablets per day, 1 tablet every 12 hours.

Patients with hepatic impairment

This medicinal product should be used with caution in patients with hepatic impairment (see section 4.4). The maximum dose for patients with hepatic impairment is 2 film-coated tablets per day, 1 tablet every 12 hours.

Paediatric population

The dosing for children over 12 years of age is the same as for adults.

Nalgesin should not be used in children from 2 to 12 years. The medicinal product is not appropriate for self-treatment as body-weight based dosing is not possible.

Nalgesin is contraindicated in children under 2 years of age (see section 4.3).

Method of administration

The tablets should be swallowed whole with sufficient amounts of liquid with or after meals.

For patients with a sensitive stomach, it is preferable to take the tablets during meals.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Hypersensitivity to acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs) that shows as of bronchial asthma, rhinitis and urticaria.

Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation, related to previous NSAID therapy.

Severe hepatic impairment.

Severe renal impairment.

Severe heart failure.

The last trimester of pregnancy (see section 4.6).

Children under 2 years of age.

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2. and GI and cardiovascular risks below).

The use of Nalgesin with concomitant NSAIDs including cyclo-oxygenase-2 selective inhibitors should be avoided.

The anti-inflammatory and antipyretic effects of naproxen sodium should be taken into account in infectious diseases because they may mask the signs of these diseases.

Taking Nalgesin and drinking alcoholic beverages at the same time may increase the risk of gastrointestinal bleeding.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (See section 4.2). Like all medications taken by elderly patients, naproxen sodium is recommended in the lowest effective doses.

Gastrointestinal effects

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime 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 (See section 4.3), 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 (See below and section 4.5).

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 ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin (See section 4.5).

When GI bleeding or ulceration occurs in patients receiving naproxen sodium, 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 their condition may be exacerbated (See section 4.8 – undesirable effects).

Cardiovascular and cerebrovascular effects

Caution (discussion with doctor or pharmacist) is required prior to starting treatment in patients with a history of hypertension and/or heart failure as fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of 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. There are insufficient data regarding the effects of low dose naproxen 600 mg/day to draw firm conclusions on possible thrombotic risks.

Skin and subcutaneous tissue reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs (see 4.8). Patients appear to be at highest risk of 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 sodium should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Precautions related to fertility

There is some evidence that drugs which inhibit cyclo-oxygenase/prostaglandin synthesis may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment.

Hepatic impairment

Caution should be used in patients with hepatic impairment (see sections 4.2 and 4.3). In chronic alcoholic liver disease and probably also in other forms of cirrhosis, the total plasma naproxen sodium concentrations are reduced while the plasma concentrations of unbound naproxen sodium are increased. Administration of the lowest effective doses is recommended.

Renal impairment

As naproxen sodium and its metabolites are eliminated primarily through the kidneys by glomerular filtration, naproxen sodium should be given with great caution to patients with renal insufficiency (see section 4.2). In patients with renal impairment, creatinine clearance should be determined and monitored during treatment. If creatinine clearance is less than 20 ml/min, treatment with naproxen sodium is not recommended (see section 4.3).

Paediatric population

Nalgesin should not be used in children from 2 to 12 years of age since body weight based dosing is not possible. The use in children under 2 years of age is contraindicated.

Nalgesin contents less than 1 mmol (23 mg) of sodium, that is like “sodium free”.

4.5 Interaction with other medicinal products and other forms of interaction

- Corticosteroids: Co-administration with NSAIDs may increase the risk of gastrointestinal ulceration or bleeding (See section 4.4).
- Anticoagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (See section 4.4).
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): There is an increased risk of gastrointestinal bleeding with concomitant administration with NSAIDs (See section 4.4).
- Acetylsalicylic acid: Clinical pharmacodynamic data suggest that concomitant naproxen usage for more than one day consecutively may inhibit the effect of low-dose acetylsalicylic acid on platelet activity and this inhibition may persist for up to several days after stopping naproxen therapy. The clinical relevance of this interaction is not known.
- Diuretics, ACE inhibitors and Angiotensin II Antagonists: NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. These interactions should be considered in patients taking naproxen sodium concomitantly with ACE inhibitors or angiotensin II antagonists. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.
- The concurrent use with acetylsalicylic acid and other NSAIDs, including COX-2 inhibitors is not recommended as it can increase the risk of adverse events.
- Concomitant treatment with medications containing the same active ingredient is not recommended.
- Since naproxen sodium is almost entirely bound to plasma proteins, caution should be used with co-administration of hydantoin derivatives or sulfonylurea derivatives as these medicinal products also bind to plasma proteins. Patients concomitantly treated with naproxen sodium and a hydantoin, sulphonamide or sulfonylurea should be observed for dose adjustment if necessary.
- Naproxen sodium may reduce the natriuretic effect of furosemide.
- Plasma lithium concentrations may increase during concomitant administration of lithium and naproxen sodium.
- Naproxen sodium reduces the tubular secretion of methotrexate; therefore, methotrexate toxicity may be enhanced during concurrent administration.
- If probenecid is administered concomitantly, the biological half-life of naproxen sodium is prolonged and its plasma concentrations increased.
- Co-administration of cyclosporine may increase the risk of renal impairment.
- Like other NSAIDs, naproxen sodium may increase the risk of renal impairment in patients taking ACE inhibitors concomitantly.
- *In vitro* studies have shown that concomitant use of naproxen sodium and zidovudine increases plasma zidovudine concentrations and might increase haematological toxicity.
- Like other NSAIDs, naproxen sodium can reduce the secretion of pemetrexed. Caution should be exercised when high doses of NSAIDs and pemetrexed are co-administered. In patients with mild to moderate renal impairment, NSAIDs should be avoided two days before and two days after administration of pemetrexed. If co-administration is necessary, toxicity should be closely monitored.
- The risk of experiencing gastrointestinal side effects when taking naproxen sodium is higher in people who regularly consume large amounts of alcohol and in people who have previously

abused alcohol. The simultaneous use of naproxen sodium and alcohol also increases the occurrence of gastrointestinal side effects.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%. The risk is believed to increase with dose and duration of therapy.

In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period (see section 5.3). From the 20th week of pregnancy onward, naproxen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, naproxen sodium should not be given unless clearly necessary. If naproxen sodium is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to naproxen for several days from gestational week 20 onward. Naproxen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension; see section 5.3);
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour (see section 5.3).

Consequently, naproxen sodium is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Breast-feeding

The use of Nalgesin is not recommended during breast-feeding.

Fertility

There is some evidence that drugs, which inhibit cyclo-oxygenase/prostaglandin synthesis, may cause impairment of female fertility by an effect on ovulation. This is reversible on withdrawal of treatment (see section 5.3).

4.7 Effects on ability to drive and use machines

Nalgesin normally has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions with naproxen are gastrointestinal in nature and include peptic ulcer, perforation or gastrointestinal bleeding, nausea, vomiting, diarrhoea, flatulence, constipation, abdominal pain and discomfort, stomatitis and exacerbation of Crohn's disease or colitis have also been reported. Edema, high blood pressure and heart failure have been reported in association with NSAIDs. Other commonly observed adverse reactions include headache, dizziness, lightheadedness, drowsiness, visual disturbances, palpitations, dyspnoea, thirst and increased sweating, as well as pruritus, skin rashes, ecchymoses and purpura.

Tabulated list of adverse reactions

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data)

	Common	Uncommon	Very rare	Not known
Blood and lymphatic system disorders		eosinophilia granulocytopenia leukopenia thrombocytopenia		
Nervous system disorders	headache dizziness drowsiness sleepiness	depression, abnormal dreams, inability to concentrate, insomnia, feeling of weakness		
Eye disorders	visual disturbances			
Ear and labyrinth disorders	tinnitus hearing disorders	hearing impairment		
Cardiac disorders	Oedema palpitations	congestive cardiac failure		
Respiratory, thoracic and mediastinal disorders	dyspnoea	eosinophilic pneumonitis		
Gastrointestinal disorders	nausea constipation abdominal pain dyspepsia diarrhoea stomatitis flatulence	gastrointestinal bleeding and/or perforation haematemesis melaena vomiting	ulcerative stomatitis relaps or aggravation of acute colitis or Crohn's disease	gastritis
Hepatobiliary disorders		abnormal liver function tests jaundice		
Skin and subcutaneous tissue disorders	pruritus rash ecchymoses purpura	alopecia photosensitive dermatitis	vesiculo-bullous rash including Stevens Johnson syndrome and toxic epidermal	pseudoporphyria

			necrolysis	
Musculo-skeletal disorders		muscle pain muscle weakness		
Renal and urinary disorders		glomerular nephritis hematuria interstitial nephritis nephrotic syndrome impaired renal function renal failure papillary necrosis of the kidneys elevated serum creatinine levels		
General disorders and administration site conditions	thirst sweating	Hypersensitivity reactions Menstrual irregularities Chills Fever		

Adverse reactions in which a causal relationship with sodium naproxen is unknown:

Blood and lymphatic system disorders

- aplastic anemia, hemolytic anemia

Immune system disorders

- allergic reactions (including facial oedema and angioedema)

Nervous system disorders

- aseptic meningitis, cognitive disorders, anxiety

Hepatobiliary disorders

- hepatitis, liver failure

Skin and subcutaneous tissue disorders

- erythema multiforme, photosensitivity reactions similar to porphyria cutanea tarda and epidermolysis bullosa, urticaria

Vascular disorders

- vasculitis, blue rash

General disorders and administration site conditions

- peripheral oedema, hyperglycemia, hypoglycemia.

Description of selected adverse reactions

Gastrointestinal disorders

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, particularly in the elderly may occur (see section 4.4). Nausea, vomiting, diarrhoea, constipation, abdominal distress, abdominal pain, melena, haematemesis, ulcerous stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported. Less frequently, gastritis has been observed.

Cardiac disorders

Oedema, hypertension and cardiac insufficiency have been reported with NSAID treatment. Clinical trial and epidemiological data suggest that use of 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) (see section 4.4).

Skin and subcutaneous tissue disorders

Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported very rare.

Renal disorders

The use of NSAIDs can cause acute renal failure, manifested by edema, sudden weight gain, and electrolyte disturbances. NSAID-induced renal failure is usually reversible within days to weeks after discontinuation of treatment.

In patients at increased risk of renal failure, renal function should be monitored. Naproxen should be discontinued in the event of proteinuria, increased blood urea nitrogen (BUN), creatinine, or potassium.

Paediatric population

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Signs and symptoms

After accidental or intentional ingestion of large quantities of naproxen sodium, gastrointestinal effects (e.g. abdominal pain, nausea, vomiting) and convulsions may occur. Dizziness, prolonged prothrombin time and consciousness disturbances may also occur.

Management

In acute poisoning, the ingested naproxen should be removed as quickly as possible, either by inducing vomiting or by gastric lavage. Supportive and symptomatic treatment should be continued. Activated charcoal should only be used if the ingestion has not been long.

There is no antidote, and hemodialysis is ineffective due to the high degree of protein binding.

Paediatric population

Symptoms of overdose and management are the same as in adults. The frequency of certain symptoms and signs may be different in children, for example rash and prolongation of blood clotting time occur more frequently in children than in adults. The frequency of effects on the central nervous system and on the gastrointestinal tract is the same for all ages, while other effects occur more frequently in adults.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroids, ATC code: M01AE02.

Mechanism of action

Main mechanism of action is inhibition of cyclo-oxygenase, an enzyme that is involved in the formation of prostaglandins. As a consequence, prostaglandin levels in various body fluids and tissues are reduced.

Pharmacodynamic effects

Naproxen sodium is a nonsteroidal anti-inflammatory agent with anti-inflammatory, analgesic and antipyretic properties. Most of the pharmacological effects of naproxen, as with other NSAIDs, are believed to be mediated either directly or indirectly by inhibition of prostaglandin (PG) synthesis. Like

other NSAIDs, naproxen sodium is a potent inhibitor of the secondary phase of human platelet aggregation *in vitro*.

Clinical efficacy and safety

Naproxen sodium, like all NSAIDs, can cause microbleeds and endoscopically confirmed lesions in the gastrointestinal tract. It has been found that it causes less of the latter than acetylsalicylic acid and indomethacin and more than diflunisal, etodolac, nabumetone and sulindac. Clinical studies have also confirmed a greater tolerance than aspirin and indomethacin, and there were no differences between naproxen sodium and other NSAIDs.

Like other NSAIDs, naproxen sodium inhibits platelet aggregation, but at therapeutic doses it has only a small effect on bleeding time.

Naproxen sodium does not affect normal renal function, there are only a few reports of adverse effects in patients with reduced renal function or heart failure.

Naproxen sodium does not have uricosuric effects.

Paediatric population

Clinical efficacy and safety for paediatric population under 2 years are not been proven.

5.2 Pharmacokinetic properties

Absorption

After oral administration, naproxen sodium is hydrolysed in acidic gastric juice. Microparticles of naproxen are released and then more rapidly dissolved in the small intestine. This results in a more rapid and complete absorption of naproxen; therefore, analgesically effective plasma levels are achieved rapidly. Peak plasma naproxen levels are reached around 1 hour after ingestion.

Although food diminishes the rate of absorption, it does not diminish its extent. Due to long half-life analgesic effect lasts up to 12 hours. The steady-state is achieved after up to 5 doses, i.e. within 2 to 3 days.

Distribution

At usual dosage, plasma naproxen levels range between 23 mg/l and 49 mg/l.

At concentrations of up to 50 mg/l, 99% of naproxen is bound to plasma proteins. At higher concentrations, the unbound fraction of the active substance is increased; at a concentration of 473 mg/l, 2.4% of unbound naproxen was measured. Due to the strong binding to plasma proteins, the volume of distribution is small and amounts to barely 10% of body weight.

Biotransformation

Approximately 70% of naproxen is excreted unmetabolised, 60% bound to glucuronic acid or other conjugates and 10% is free. The remaining 30% of naproxen is metabolised into ineffective 6-demethyl-naproxen.

Elimination

Approximately 95% of naproxen is excreted in the urine and 3% or less in the faeces.

The biological half-life of naproxen is 12 to 15 hours and does not depend on the dosing and plasma levels of naproxen. Creatinine clearance depends on plasma naproxen levels, probably due to increased unbound portion of the active substance at higher plasma levels.

Linearity/non-linearity

Plasma naproxen levels increase proportionally to the size of doses up to 500 mg. At larger doses, they are less proportional; due to the saturation of plasma protein binding of naproxen, creatinine clearance is also increased.

Pharmacokinetic/pharmacodynamic relationship

There are no data on studies examining the pharmacokinetic/pharmacodynamic relationship.

5.3 Preclinical safety data

Toxicological tests in various animal species by various routes of administration have shown low acute toxicity of naproxen. In chronic toxicity studies, naproxen had a toxicity profile typical of NSAIDs, causing gastrointestinal toxicity and, at high doses, renal damage.

Animal studies have shown no effect on fertility, but there is some evidence that prostaglandin synthesis inhibitors may reversibly reduce female fertility by affecting ovulation (see section 4.6). Due to inhibition of prostaglandin synthesis, administration of naproxen during late gestation may result in delayed parturition, as has been shown in studies in rats.

In animals, the use of prostaglandin synthesis inhibitors may increase pre- and post-implantation loss and embryo-foetal mortality. Inhibition of prostaglandin synthesis during the period of organogenesis can cause various malformations in animals, including cardiovascular malformations: premature closure of the ductus arteriosus can lead to congestive heart failure and persistent pulmonary hypertension in the newborn (see section 4.6).

No teratogenic effects have been observed with naproxen and there was no evidence of carcinogenic potential in a two-year study in rats. Naproxen was not mutagenic in mutagenicity tests.

Like many other NSAIDs structurally related to propanoic acid, naproxen is phototoxic, which can lead to damage to DNA molecules (*in vitro* tests).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Povidone
cellulose, microcrystalline
talc
magnesium stearate

Film coating

hypromellose
titanium dioxide
macrogol
indigo carmine
potassium aluminium silicate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original packaging material in order to protect from light.

6.5 Nature and contents of container

Blister pack (Al foil, PVC foil): 10 or 30 film-coated tablets (1 blister pack with 10 film-coated tablets) in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

KRKA, d. d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenija

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT