SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ipaflex 200 mg mjuka kapslar

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 220 mg naproxen sodium equivalent to 200 mg naproxen.

Excipients with known effect:

Propylene glycol (E 1520)	17.7 mg
Sorbitol (E 420)	76.8 mg
Soya lecithin	trace amounts

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule
Blue, transparent soft gelatin capsule approximately 20 to 22 mm long and 8 to 10 mm wide.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Ipaflex are indicated for short-term symptomatic treatment of mild to moderate pain.

4.2 Posology and method of administration

Posology

Use the lowest effective dose for the shortest duration.

Adults and children from 12 years of age:

- General: 1 capsule every 8 to 12 hours.
- An initial dose of 2 capsules may optionally be taken followed by another capsule 12 hours later if symptoms persist.
- Do not take more than 3 capsules per 24 hours.

Method of administration

Ipaflex are taken un-chewed with plenty of liquid and preferably before meals.

Patients with a sensitive stomach are recommended to take Ipaflex, preferably after meals with plenty of water or milk.

If Ipaflex are required for more than 5 days, or if symptoms worsen, a doctor should be consulted.

Elderly people from 65 years of age:

Dosage should not exceed 2 capsules per day in two single doses. In patients with mild or moderate cardiac impairment, a dose reduction may be required.

Renal impairment
Ipaflex should be given at the lowest effective dose (maximum 2 capsules per day) in patients with mild renal impairment and renal function should be carefully monitored. Ipaflex should be avoided, if possible, in patients with moderate renal impairment and is contraindicated in severe renal impairment (see section 4.3 and 4.4).

Hepatic impairment
Ipaflex should be used with caution in patients with impaired hepatic function (maximum 2 capsules per day). Ipaflex should be avoided, if possible, in patients with severe hepatic impairment or cirrhotic liver disease (see section 4.3 and 4.4).

Paediatric population
Ipaflex are contraindicated in children below 12 years of age, as the dose of naproxen is too high (see section 4.3).

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1
- Patients who have had an allergic reaction (e.g. bronchospasm, asthma, rhinitis, urticaria or angioedema) in response to administration of acetylsalicylic acid or another non-steroidal anti-inflammatory drug (NSAIDs).
- Patients who are allergic to peanut or soya as this product may contain traces of soya lecithin
- Cerebrovascular haemorrhages or other active haemorrhages.
- Active or prior repeated occurrence of gastric ulcer/bleeding (two or more evident episodes of proven ulceration or bleeding).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- Unclarified blood formation disturbances
- Severe renal failure (creatinine clearance < 30 ml/min)
- Severe hepatic failure
- Severe heart failure
- Third trimester of pregnancy
- Children below the age of 12 years

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 gastrointestinal and cardiovascular risks below).

A doctor should be consulted if pain persists, recurs or deteriorates.

Gastrointestinal (GI) safety
NSAIDs, including naproxen, can cause severe or serious gastrointestinal adverse events including gastrointestinal bleeding, ulceration and perforation, which can be fatal. This can occur at any time, with or without warning symptoms. The risk of such reactions increases with increasing doses and may not be related to prior occurrence of severe gastrointestinal side effects. The risk of severe gastrointestinal undesirable effects is elevated in debilitated patients.

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 which may be fatal (see section 4.2 and 4.3), with alcohol use and in the elderly.

Combination treatment with protective products (for example misoprostol or proton pump inhibitors) should be considered in these patients as well as in patients who concomitantly need low doses of acetylsalicylic acid or other medicinal products that probably increase the gastro-intestinal risk (see section 4.5). These patients should report any unusual abdominal symptom (especially bleeding), especially at the start of treatment.

Caution is needed in patients who are concomitantly treated with medicinal products, which may increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors, other NSAIDs including cyclooxygenase-2 inhibitors and products that counteract the platelet aggregation, such as acetylsalicylic acid.

When gastro-intestinal bleeding or ulceration occurs in patients who are receiving naproxen, the treatment should be discontinued.

NSAIDs should be used with caution in patients with a history of gastro-intestinal diseases (ulcerative colitis, Crohn's disease) as these conditions may worsen (see section 4.8).

Pain due to gastrointestinal disorders is not an indication for naproxen.

A doctor should be consulted if gastrointestinal symptoms, such as pyrosis, gastric pain or haemorrhage occur while using naproxen.

Cardiovascular and cerebrovascular safety

Caution should be exercised in patients with a history of hypertension and/or heart failure (consult with doctor or pharmacist) prior to treatment. Fluid retention, hypertension and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of coxibs and some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data available on the effects of low-dose naproxen (220 mg – 660 mg naproxen sodium per day) in order to draw firm conclusions on the possible risk of thrombosis.

Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

Naproxen can temporarily inhibit blood platelet function (blood platelet aggregation). Patients with coagulation disorders should therefore be carefully monitored.

Severe cutaneous adverse reactions (SCARs)

Severe skin reactions, of which some fatal, including exfoliative dermatitis, Stevens-Johnson's syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported very rarely in connection with the use of NSAIDs (see section 4.8). Patients appear to have the greatest risk of these reactions at the beginning of the treatment: in the majority of the cases the reaction started within the first month of treatment. Treatment with naproxen should be discontinued with the

first symptoms of a skin rash, mucosal lesions or any other sign of hypersensitivity and medical help sought straight away. If the patient has developed SJS, or TEN or DRESS with the use of Ipaflex, treatment with Ipaflex must not be restarted and should be permanently discontinued.

Other information

Naproxen should only be used after careful consideration in patients with congenital disorder of porphyrin metabolism (e.g. acute intermittent porphyria).

Patients with systemic lupus erythematosus or mixed connective tissue disease appear to be at increased risk of aseptic meningitis.

Caution should be exercised in elderly patients and in those with hepatic and renal impairment.

- Anaphylactoid reactions generally occur in patients know to be hypersensitive to naproxen, acetylsalicylic acid or other prostaglandin synthetase inhibitors. They may also occur in patients without previous exposure or known hypersensitivity to these medicinal products. Treatment must be discontinued at the first signs of a hypersensitivity reaction following ingestion of naproxen. Depending on the symptoms, any clinical measures required must be initiated by specialists.
- Through concomitant intake of alcohol, active substance-related undesirable effects, particularly those that concern the gastrointestinal tract or the central nervous system, may be increased with use of NSAIDs.
- The anti-inflammatory, analgesic and antipyretic activities of naproxen may mask certain symptoms of infection and fever. It should therefore be used with caution in patients with infections and is not recommended in case of varicella due to potential exacerbation of the varicella.
- Do not use for more than 5 days without consulting a doctor.
- Long-term use of any pain medication for headache may worsen the existing headache. If this situation occurs or is suspected, a doctor should be consulted and the treatment discontinued. In patients who have frequent or daily headaches, despite (or as a result of) the regular use of analgesics, the diagnosis of Medication Overuse Headache should be considered.
- The habitual use of painkillers, especially that of several painkilling drugs in combination, may quite generally lead to permanent kidney damage with the associated risk of kidney failure (analgesic nephropathy).

Excipients with known effect

This medicine contains propylene glycol and sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

This medicine contains less than 1 mmol sodium (23 mg) in each capsule, that is to say essentially ‘Sodium Free’.

4.5 Interaction with other medicinal products and other forms of interaction

Naproxen (like other NSAIDs) should only be used with caution together with the following medicinal products:

The following combinations should be avoided with naproxen

Other NSAIDs including salicylates:
The concomitant use of two or more NSAIDs can lead to an increased risk of gastrointestinal ulcers and bleeding because of a synergistic effect. Concomitant use of naproxen with other NSAIDs should therefore be avoided (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.

Warfarin
NSAIDs inhibit thrombocyte aggregation and damage the lining of the gastrointestinal tract, which would increase the risk of gastrointestinal bleeding in patients taking anticoagulants. Recent epidemiological studies indicate that the risk of bleeding gastrointestinal ulcers is especially high during concomitant use of NSAIDs and warfarin. Concomitant use should therefore be avoided. It has recently been shown that this interaction may also have a metabolic component, in that NSAIDs and warfarin are metabolised by the same enzyme, CYP 2 C9. NSAIDs inhibit the metabolism of anticoagulants *in vitro.* The interaction potential is greatest for phenylbutazone followed by diclofenac and ibuprofen. Other drugs have not been investigated.

Methotrexate (high dose)
Organic acids such as NSAIDs may reduce the clearance of methotrexate as a result of the tubular secretion of methotrexate being inhibited, and some metabolic interaction with reduced clearance of methotrexate may also occur as a result. During high-dose treatment using methotrexate concomitant prescription of NSAIDs should therefore always be avoided.

Ticlopidine
NSAIDs should not be combined with ticlopidine due to the additional inhibition of thrombocyte function.

The following combinations with naproxen may require dosage adjustment or specific monitoring of the patient

Lithium:
The concomitant use of naproxen with lithium preparations may increase serum levels of these medicinal products. A check of serum-lithium level is not as a rule required on correct use (maximum over 5 days). Because of lithium's very low therapeutic index, the combination of lithium and NSAIDs should be avoided unless frequent monitoring of serum lithium levels can be implemented and any reductions can be made to the lithium dose.

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 inhibitors or angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be

adequately hydrated and regular monitoring of renal parameters should be considered following initiation of combination therapy. The concomitant administration of naproxen and potassium-sparing diuretics may lead to hyperkalaemia.

Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Anticoagulants:
NSAIDs may enhance the effects of anticoagulants, such as warfarin, increasing the risk of gastrointestinal bleeding (see section 4.4).

Methotrexate (low dose):
Caution should be exercised if both NSAIDs and methotrexate are given within the space of 24 hours, as the plasma levels of methotrexate may increase and cause increased toxicity. The risk of a potential interaction between NSAIDs and methotrexate must therefore be considered even at low dosages of methotrexate. Patients with impaired renal function may be a risk group for this interaction. Renal function should therefore be monitored during combination therapy.

Ciclosporin:
The risk of nephrotoxic effect caused by ciclosporin is increased by the co-administration of certain NSAIDs. Renal function must therefore be carefully monitored during concomitant treatment.

Tacrolimus:
Concomitant administration of NSAIDs with tacrolimus may increase the risk of nephrotoxicity due to decreased synthesis of prostacyclin in the kidneys. Renal function must therefore be carefully monitored during concomitant treatment.

Probenecid:
Concurrent probenecid use increases plasma naproxen levels and considerably prolongs the plasma half-life.

Clopidogrel:
Experimental studies have found that clopidrogrel increases naproxen-induced gastrointestinal blood loss (see section 4.4). This is likely to apply to all NSAIDs.

The clinical significance of the following combinations with naproxen has not yet been established:

Antacids, cholestyramine or food may delay the absorption of naproxen without the absorbed quantity decreasing.

Interactions with laboratory assays:
Administration of naproxen should be discontinued temporarily (48 hours) prior to adrenal function tests, as interference with certain reactions to 17-ketogenic steroids may occur. Naproxen may interfere with some assays of urinary 5-hydroxy-indoleacetic acid.

4.6 Fertility, pregnancy and lactation

Fertility

There have been some indications that products that inhibit the cyclo-oxygenase/ prostaglandin synthesis reduce the fertility of women by influencing ovulation. This is reversible by discontinuing the treatment.

Pregnancy
There are insufficient data available from animal studies to assess any potential harmful effect.

Inhibition of the prostaglandin synthesis may adversely affect pregnancy and/or embryonal/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformations and gastroschisis after use of prostaglandin synthesis inhibitors in the early stages of the pregnancy. The absolute risk of cardiovascular malformation was increased from less than 1% to approximately 1.5%. The risk is believed to increase with dose and duration of treatment. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased incidence of pre- and post-implantation losses 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.

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 trimesters of pregnancy, Ipaflex should not be given unless clearly necessary, and if used, 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 Ipaflex for several days from gestational week 20 onward. Ipaflex should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of the pregnancy all prostaglandin synthesis inhibitors can expose the foetus to:
-Cardiopulmonary toxicity (premature constriction/closing of the ductus arteriosus and pulmonary hypertension);
-Renal dysfunction (see above);

The mother and the neonate, at the end of pregnancy, may experience:
- Prolongation of bleeding time, an anti-aggregation effect on the thrombocytes that may occur even at very low doses.
-Inhibition of the contraction of the uterus resulting in a delayed or prolonged delivery.

Naproxen is contraindicated in the third trimester (see section 4.3).

Breast feeding
Naproxen is found in human milk. Ipaflex should therefore not be used by breast-feeding women.

4.7 Effects on ability to drive and use machines

Side effects, such as tiredness and dizziness, can occur when using Ipaflex. As a result, the ability to react may be altered in individual cases and the ability to take part actively in road traffic and use machines may be impaired. This particularly applies in interaction with alcohol.

4.8 Undesirable effects

The reported frequencies of undesirable effects are based on the following categories:

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)

The listing of undesirable effects below comprises all side effects reported during treatment with naproxen, including those reported during high-dose long-term therapy in rheumatism patients. Reported frequencies beyond very rare reports refer to short-term use of daily doses up to a maximum of 750 mg naproxen for oral formulations (= 3 capsules).

With the following adverse drug reactions, it must be accounted for that they are predominantly dose-dependent and vary inter-individually.

System organ class	**Incidence**	**Reported adverse event**
Infections and infestations [1]	Very Rare	Aseptic meningitis (Symptoms include severe headache, nausea, vomiting, fever, stiff neck or clouding of consciousness). Exacerbation of infection-related inflammations (e.g. development of necrotising fasciitis)
Blood and lymphatic system disorders	Very Rare	Anaemia including aplastic anaemia, leukopenia, thrombocytopenia, pancytopenia, agranulocytosis, haemolytic anaemia. Early signs may include: fever, sore throat, superficial wounds in the mouth, flu-like symptoms, pronounced fatigue, nosebleeds and skin bleeding.
Immune system disorders	Uncommon	Hypersensitivity Description of selected adverse reactions: exanthema, pruritus, purpura, ecchymoses, urticaria, angioedema
	Very Rare	Asthma

[1] If signs of an infection occur newly or get worse during use of this product, the patient is therefore recommended to consult a doctor immediately. It should be ascertained whether there is an indication for an anti-infective/antibiotic therapy.

		Asthma attacks (possibly with drop in blood pressure), bronchospasm, eosinophilic pneumonia Severe general hypersensitivity reactions. Signs may include: swelling of the face, tongue and larynx, breathlessness, tachycardia, blood pressure drop to the point of life-threatening shock.
Psychiatric disorders	Uncommon	Sleeplessness, agitation, irritability, tiredness.
	Very Rare	Depression, dream abnormalities, inability to concentrate.
Nervous system disorders	Common	Headache and dizziness
	Very Rare	Cognitive dysfunction, convulsions
Eye disorders	Uncommon	Visual disturbances.
	Very Rare	Eye swelling, eye oedema Corneal opacity, papillitis, papilloedema, retrobulbar optic neuritis.
Ear and labyrinth disorders	Very Rare	Tinnitus, hearing disorder.
Cardiac disorders	Very Rare	Tachycardia, palpitations, heart failure.
Vascular disorders	Very Rare	Hypertension, vasculitis.
Respiratory, thoracic and mediastinal disorders	Very Rare	Dyspnoea, asthma.
Gastrointestinal disorders	Common	Dyspepsia, nausea, pyrosis, abdominal pain.
	Uncommon	Abdominal fullness, obstipation, diarrhea, vomiting, gastrointestinal ulcers, sometimes with bleeding (hematemesis and/or melaena) and perforation.
	Rare	Gastrointestinal bleeding.

	Very Rare	Stomatitis, oesophagitis, pancreatitis, colitis, aphthous ulcers.
Hepatobiliary disorders	Very Rare	Increased liver enzymes, hepatitis (including fatal outcomes), and jaundice
Skin and subcutaneous tissue disorders	Rare	Photosensitivity
	Very Rare	Alopecia, sweating, pseudoporphyria, erythema multiforme, bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell's syndrome), lichen planus, erythema nodosum, SLE (systemic lupus erythematosus).
	Not known	Fixed drug eruption, Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)
Renal and urinary disorders	Uncommon	Reduced urinary output, formation of oedemas.
	Very Rare	Papillary necrosis, hyperuricaemia, nephrotic syndrome, interstitial nephritis, renal failure, haematuria, proteinuria.
Investigations	Very Rare	Serum creatinine increased, hyperkalemia

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, and exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.
Oedema, hypertension and cardiac insufficiency have been reported in association with NSAID therapy.

Clinical studies and epidemiological data suggest that the 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).

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.*

4.9 Overdose

Symptoms

Symptoms of overdose may include central nervous disturbances including headache, dizziness, light-headedness, unconsciousness and abdominal pain and abdominal discomfort, pyrosis, dyspepsia, nausea, vomiting, gastrointestinal bleeding. Transient change in hepatic function, hypoprothrombinaemia, renal dysfunction, metabolic acidosis, apnoea and disorientation. A few patients have experienced seizures, but it remained unclear whether these were caused by treatment with naproxen. Hypotension acute renal failure, respiratory depression and coma may occur.

Management

A specific antidote does not exist. Patients should be treated symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroids

ATC code: M01AE02

Naproxen sodium is an NSAID (nonsteroidal anti-inflammatory drug). It is a non-narcotic analgesic with predominantly anti-inflammatory and antipyretic effects. Its mechanism of action is not fully understood, however, it inhibits prostaglandin synthetase similar to other NSAIDs. Furthermore, naproxen inhibits platelet function reversibly.

Clinical evidence demonstrates that when 220 mg of naproxen sodium is taken the pain-relieving effects can last for up to 12 hours

5.2 Pharmacokinetic properties

Naproxen sodium readily dissolves in water and following oral administration, it is rapidly and fully absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 1-2 hours after ingestion after fasting. Naproxen has a plasma elimination half-life of about 12 to 17 hours. At the therapeutic dose, more than 99% is bound to serum albumin. Approximately 95% of the naproxen sodium dose is excreted in the urine as unchanged naproxen, 6-0-desmethylnaproxen and its conjugates.

5.3 Preclinical safety data

Unremarkable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Core:

Macrogol
Lactic acid
Propylene glycol (E 1520)
Povidone

Capsule shell Ingredients:

Gelatin
Sorbitol liquid, partially dehydrated (E 420)
Glycerol
Purified water
Patent blue V (E131)

The capsules may contain trace amounts of soya lecithin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C
Store in the original package in order to protect from moisture.
Do not refrigerate

6.5 Nature and contents of container

PVC / PE / PVDC aluminium blisters containing 10 or 20 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

< To be completed nationally>

8. MARKETING AUTHORISATION NUMBER

< To be completed nationally>

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

< To be completed nationally>

10. DATE OF REVISION OF THE TEXT

23-Sep-2024