Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naproxen sodium Krka 550 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 550 mg naproxen sodium, which is equivalent to 500 mg naproxen.

Excipient with known effect:
sodium 2,17 mmol (50 mg) per tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

The tablets are oval, slightly biconvex, one-side scored blue film-coated tablets. Dimension: 18 x 8 mm

The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Naproxen sodium Krka is used for
- treatment of mild to moderate pain,
- symptomatic treatment of rheumatoid arthritis, osteoarthritis, acute gout attacks and ankylosing spondylitis,
- relief of primary dysmenorrhoea symptoms,
- symptomatic treatment of acute migraine headaches,
- symptomatic treatment of primary and secondary menorrhagia associated with insertion of IUD.

4.2 Posology and method of administration

Posology

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

Adults and adolescents aged 16 years and over

The usual daily dose for pain relief ranges from 550 mg to 1100 mg naproxen sodium. The recommended initial dose is 550 mg, followed by 275 mg every 6 to 8 hours, depending on the severity of the process. When administered for prolonged periods of time, the dose should be adjusted depending on the patient's clinical response.

Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis
The recommended daily dose is1100 mg of naproxen sodium, divided into a morning and an evening dose. Alternatively a single daily dose of 550-1100 mg of naproxen sodium can be taken in the morning or evening.

Acute gout attacks
The recommended initial dose is 825 mg of naproxen sodium, followed by 275 mg of naproxen sodium every 8 hours until the attack diminish.

Dysmenorrhoea
The recommended initial dose is 550 mg of naproxen sodium taken as a single dose, followed by 275 mg of naproxen sodium every 6-8 hours if necessary.

Migraine headaches
The recommended initial dose is 825 mg of naproxen sodium taken as a single dose at the first symptoms, followed by 275 mg of naproxen sodium after half an hour.

Menorrhagia
The recommended first day daily dose is 825-1375 mg of naproxen sodium, divided into two doses, followed by a daily dose of 550-1100 mg of naproxen sodium for a maximum period of four days.

Special populations

Elderly
The dose should be reduced in elderly patients (see section 4.4) and the lowest effective dose should be used for the shortest possible duration.

Patients with renal and/or hepatic insufficiency
In patients with mild or moderate renal or hepatic failure the dose should be reduced (see section 4.4) and the lowest effective dose should be used for the shortest possible duration.

This medicinal product is not recommended in patients with a baseline creatinine clearance lower than 30 ml/min, since an accumulation of naproxen metabolites has been observed in patients with severe kidney failure and patients in dialysis (see section 4.4).

Paediatric population
Naproxen sodium Krka tablets are not recommended for use in children and adolescents under 16 years of age.

Method of administration

This medicinal product is administered orally.
The tablets should be swollen whole with some liquid and preferably during or after meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
History of bronchospasm, asthma, rhinitis or urticaria associated with acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAID).
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 heart failure.
The last trimester of pregnancy (see section 4.6).
It should not be administered to patients with ulcerative colitis.
It should not be administered to patients who suffer from severe liver or kidney failure.
It should not be administered to patients who are taking other non-steroidal anti-inflammatory drugs.

4.4 Special warnings and precautions for use

Paediatric population
Naproxen sodium Krka tablets are not recommended for use in children and adolescents under 16 years of age. There are no data on the safety and efficacy of naproxen sodium in children under the age of 2.

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

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (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) especially 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 Krka, 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 is required in patients with a history of hypertension and/or heart failure as fluid retention 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 risks cannot be excluded.

As a result, patients with uncontrolled hypertension, congestive heart failure, established coronary heart disease, peripheral artery disease and/or cerebrovascular disease should only receive treatment with Naproxen sodium Krka if the physician decides that the benefit/risk ratio for the patient is favourable. This same assessment should be performed before starting a long-term treatment in patients with known cardiovascular risk factors (e.g., hypertension, hyperlipidaemia, diabetes mellitus and smoking).

Skin 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 section 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 Krka should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Elderly
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal. Clearance decreases with age. Therefore, in this patient group, it is appropriate to reduce the dose to the lowest limit of the recommended dosage range (see section 4.2).

Anaphylactic reactions
Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur in patients with or without a history of hypersensitivity or exposure to acetylsalicylic acid, other NSAIDs or products whose ingredients include naproxen. They may also occur in patients with a history of angio-oedema, bronchospastic reactivity (e.g., asthma), rhinitis or nasal polyps. These reactions may be life-threatening.
Bronchospasm may be triggered in patients with history of this disease or in patients suffering from asthma, an allergic disease or hypersensitivity to aspirin.

Renal effects
Cases of abnormal kidney function, kidney failure, acute interstitial nephritis, haematuria, proteinuria, papillary necrosis and occasionally nephrotic syndrome have been reported in association with the use of naproxen (see section 4.8).

Like other NSAIDs, Naproxen sodium Krka should be used with caution in patients with kidney dysfunction or a history of kidney disease, since it inhibits the synthesis of prostaglandins. Likewise, caution should be exercised in disorders that cause a decrease in blood volume and/or kidney blood flow in which renal prostaglandins help to maintain renal perfusion. In such patients, the administration of Naproxen sodium Krka or other NSAIDs may cause a dose-dependent reduction in renal

prostaglandin synthesis and thus trigger decompensation or manifest kidney failure. Patients with a greater risk of experiencing this reaction are those with kidney failure, hypovolaemia, heart failure, liver failure or saline depletion, as well as those treated with diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists and elderly patients. In general, the baseline condition is restored after Naproxen sodium Krka is withdrawn. In such patients, Naproxen sodium Krka must be used with a great deal of caution, and it is advisable to monitor serum creatinine concentration and/or creatinine clearance and ensure that patients are adequately hydrated. The possibility of reducing the daily dose should be assessed to prevent too many naproxen sodium metabolites from accumulating.

Naproxen sodium Krka is not recommended in patients with a baseline creatinine clearance lower than 30 ml/min, since an accumulation of naproxen sodium metabolites has been observed in them.

Given that naproxen sodium and its metabolites are largely (95%) excreted in urine through glomerular filtration, it is recommended that Naproxen sodium Krka be used with a great deal of caution in patients with significantly reduced kidney function. Serum creatinine and/or creatinine clearance should be monitored in such cases.

Haemodialysis does not decrease the concentration of naproxen in plasma, due to its high degree of plasma protein binding.

In some patients, especially those with decreased kidney blood flow (reduced extracellular volume, liver cirrhosis, sodium-free diet, congestive heart failure and pre-existing kidney diseases), kidney function must be assessed before and during treatment with Naproxen sodium Krka. This category should include elderly patients and those treated with diuretics in whom kidney failure may be presumed. In such cases, it is recommended that the daily dose of Naproxen sodium Krka be decreased to prevent an excessive accumulation of naproxen sodium metabolites.

Hepatic effects
Like other NSAIDs, naproxen may increase some liver function test values. Liver abnormalities may be due more to hypersensitivity than to a direct toxic effect. As with other NSAIDs, severe liver reactions have been reported, including jaundice and hepatitis (some cases of hepatitis have been fatal), with naproxen sodium. Cross-reactivity has also been observed (see section 4.8).

In addition, the fact that non-steroidal anti-inflammatory drugs may cause an increase in liver function parameters must be considered.

In patients with liver disease due to chronic alcoholism, and probably other forms of liver cirrhosis, it is recommended that the minimum effective dose be administered, since in these cases a decrease in the total concentration of naproxen sodium in plasma, linked to an increase in its unbound fraction, has been observed, although the role that this may play is unknown.

Haematological effects
Naproxen sodium reduces platelet aggregation and prolongs bleeding time. This effect must be borne in mind when bleeding times are determined.

Treatment with naproxen sodium requires close monitoring of patients with clotting disorders or in treatment with haemostasis-altering drugs. Patients with a high risk of bleeding or undergoing total anticoagulant treatment (e.g., dicoumarol derivatives) may run a greater risk of bleeding if they are administered naproxen sodium concomitantly.

Antipyretic effects
Given naproxen antipyretic and anti-inflammatory action, fever and inflammation may partially lose their diagnostic utility.

Ocular effects
The studies performed have not revealed ophthalmological changes that may be attributed to the administration of naproxen sodium. On rare occasions, serious ophthalmological disorders such as papillitis, retrobulbar neuritis and papilloedema have been reported in patients treated with NSAIDs, including naproxen sodium, although a causal relationship has not been established. Therefore, in cases of vision disorders during treatment with Naproxen sodium Krka, an ophthalmological examination should be performed.

Combination with other NSAIDs
The combined use of Naproxen sodium Krka and other NSAIDs is not recommended, given the increased risks of causing severe adverse reactions associated with NSAIDs.

The concomitant administration of Naproxen sodium Krka with other NSAIDs, including selective cyclooxygenase-2 inhibitors (Coxibs), should be avoided. Adverse reactions can be reduced if the lowest effective dose is used for the shortest possible time to manage symptoms (see section 4.2).

Important information about some of the ingredients of Naproxen sodium Krka
This medicinal product contains 2.17 mmol (or 50.00 mg) sodium in the 550 mg strength tablets. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interactions

Anticoagulants
NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Acetylsalicylic acid
Clinical pharmacodynamic data suggest that concomitant usage of naproxen and acetylsalicylic acid 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.

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).

Corticosteroids
Co-administration with NSAIDs may increase the risk of gastrointestinal ulceration or bleeding (see section 4.4)

Antacids or cholestyramine
The concomitant administration of antacids or cholestyramine may delay the absorption of naproxen, but does not affect the degree of absorption. Concomitant ingestion of food may delay the absorption of naproxen, but does not affect the degree of absorption.

Hydantoin derivatives or sulfonylurea derivatives
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 and a hydantoin, sulphonamide or sulphonylurea should be observed for dose adjustment if necessary.

Probenecid
If probenecidis administered concomitantly, the biological half-life of naproxen sodium is prolonged and its plasma concentrations increased.

Methotrexate
Naproxen sodium reduces the tubular secretion of methotrexate; therefore, methotrexate toxicity may be enhanced during concurrent administration.

Furosemide
Naproxen sodium may reduce the natriuretic effect of furosemide.

Lithium
Plasma lithium concentrations increase during concomitant administration of lithium and naproxen sodium.

Beta-blockers, ACE inhibitors and Angiotensin Receptor Antagonists
Naproxen may decrease the antihypertensive effect of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists (ARAs).
Like other NSAIDs, naproxen sodium may increase the risk of kidney failure associated with its use with ACE inhibitors or ARAs, especially in patients with a history of poor kidney function (see section 4).

Steroids
If steroid administration is reduced or withdrawn during treatment with naproxen, the decrease in the steroid dose must be slow and patients must be closely monitored to detect any sign of side effects, including kidney failure or an exacerbation of arthritis symptoms.

Naproxen decreases platelet aggregation and prolongs bleeding time. This effect must be considered when bleeding time is determined.

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

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. 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.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis
- 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

Consequently, naproxen sodium is contraindicated during the third trimester of pregnancy.

The use of this medicinal product is not recommended in labour, since due to its inhibitory effect on prostaglandin synthesis, it may negatively affect foetal circulation and inhibit uterine contractions, thereby increasing the risk of uterine haemorrhage.

Breast-feeding:
The naproxen anion has been detected in the milk of breastfeeding mothers at a concentration of approximately 1% of the plasma concentration. Considering the possible side effects of prostaglandin inhibitors on newborns, its administration to breastfeeding mothers is not recommended.

Fertility:
There is some evidence that drugs, which inhibit cyclo-oxygenase/prostaglandin synthesis, may cause impairment of female fertility by an effect on ovulation.

4.7 Effects on ability to drive and use machines

Some patients experience somnolence, dizziness, vertigo, insomnia or depression during treatment with this medicinal product. Patients who experience these or other similar effects must be cautious when engaging in activities that require a great deal of attentiveness.

It must be used with caution in patients whose occupation requires attentiveness and who have noticed vertigo or visual abnormalities during treatment with this drug.

4.8 Undesirable effects

Undesirable effects that may occur during treatment with naproxen sodium are classified into the following groups in order of frequency:
- 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)

Gastrointestinal disorders

The most commonly observed adverse reactions are gastrointestinal in nature. Inflammation, bleeding (in some cases fatal, especially in elderly patients), peptic ulcers, perforation and obstruction of the upper or lower gastrointestinal tract may occur (see section 4.4). Cases of oesophagitis, gastritis, pancreatitis, stomatitis, exacerbation of ulcerative colitis and Crohn's disease have been reported (see section 4.4). There have also been cases of heartburn, dyspepsia, abdominal pain, nausea, vomiting, diarrhoea, flatulence, constipation, haematemesis and melaena.

Frequency of undesirable effects listed by individual organ systems:

	Rare	**Very rare**
Blood and lymphatic system disorders		agranulocytosis, aplastic anaemia, eosinophilia, haemolytic anaemia, leukopenia, thrombocytopenia
Immune system disorders		anaphylactoid reactions
Metabolism and nutrition disorders		hyperkalaemia
Psychiatric disorders		depression, sleep abnormalities, insomnia
Nervous system disorders		dizziness, somnolence, headache, feeling of dizziness, retrobulbar optic neuritis, seizures, cognitive dysfunction, difficulty concentrating
Eye disorders		vision disorders, corneal opacity, papillitis, papilloedema
Ear and labyrinth disorders		hearing loss, hearing impairment, tinnitus, vertigo
Cardiac disorders		palpitations, reported association between heart failure and treatment with NSAIDs, congestive heart failure
Vascular disorders		reported oedema and hypertension associated with treatment with NSAIDs, vasculitis*
Respiratory, thoracic and mediastinal disorders		asthma, eosinophilic pneumonia, dyspnoea, pulmonary oedema.
Hepatobiliary disorders	liver damage	hepatitis (some cases of hepatitis have been fatal), jaundice.
Skin and subcutaneous tissue disorders		ecchymosis, pruritus, purpura, skin rash, sweating, alopecia, epidermal necrolysis, erythema multiforme, bullous disorders (including Stevens–Johnson syndrome and toxic epidermal necrolysis), erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, systemic lupus erythematosus, urticaria and photosensitivity reactions (including rare cases in which the skin takes on an appearance of porphyria cutanea tarda [pseudoporphyria] or of epidermolysis bullosa and angioneurotic oedema)**
Musculoskeletal and connective tissue disorders		myalgia, muscle weakness
Renal and urinary disorders		haematuria, interstitial nephritis, nephrotic syndrome, kidney disease, kidney failure, renal papillary necrosis
Reproductive system and breast disorders		female infertility
General disorders and administration site conditions		oedema, thirst, pyrexia (chills and fever), general malaise
Investigations		abnormal liver function test values, high serum creatinine

*Data from clinical trials and epidemiological studies suggest that the use of some NSAIDs (especially in high doses and in long-term treatments) may be associated with a moderate increase in the risk of atherothrombotic events (for example, myocardial infarction or stroke). Although the data suggest that the use of naproxen (1000 mg/day) may be associated with a lower risk, the risk cannot be ruled out.

**If skin fragility, blistering or other symptoms indicative of pseudoporphyria occur, treatment should be suspended and the patient should be monitored

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
The symptoms of naproxen overdose include: dizziness, somnolence, epigastric pain, abdominal discomfort, indigestion, nausea, transient liver function disorders, hypoprothrombinaemia, kidney dysfunction, metabolic acidosis, apnoea, disorientation and vomiting. Given that naproxen sodium is rapidly absorbed, it should be considered that high blood levels of naproxen may be reached in a short time. Some patients have experienced seizures, but the relationship that this may have to the medicinal product is unknown.

Gastrointestinal bleeding may occur. Hypertension, acute kidney failure, respiratory depression or coma may occur after ingestion of NSAIDs, but this is rare.

Anaphylactic reactions with therapeutic ingestion of NSAIDs have been reported, and may occur following an overdose.

Treatment
Patients' symptoms should be treated, and support measures should be implemented following overdose with NSAIDs. There are no specific antidotes. Prevention to avoid greater absorption (e.g., activated charcoal) may be indicated in patients cared for within 4 hours of ingestion with symptoms or following a significant overdose. Forced diuresis, alkalinisation of urine, haemodialysis and haemoperfusion may not be useful due to the high protein binding.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antiinflammatory and antirheumatic products, non-steroids, propionic acid derivates, ATC code: M01AE02.

Mechanism of action
Naproxen sodiumis a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic action. Naproxen sodium is a propionic acid derivative chemically related to the arylacetic acid group. Naproxen sodium is a white to yellowish-white crystalline solid that is easily soluble in water at a neutral pH.

Its anti-inflammatory effect has been confirmed even in adrenalectomised animals, which indicates that its action is not mediated through the pituitary–adrenal axis.

Like other non-steroidal anti-inflammatory agents, naproxen inhibits prostaglandin synthetase, although the exact mechanism of anti-inflammatory action is unknown for this type of product.

5.2 Pharmacokinetic properties

Absorption
Naproxen sodiumis easily soluble in water. It is practically completely absorbed. Absorption takes place in the gastrointestinal tract and maximum plasma levels are reached after 1-2 hours. Concomitant ingestion of food may delay the absorption of naproxen, but does not affect the degree of absorption.

Distribution
Naproxen has a volume of distribution of 0.16 l/kg, and at therapeutic levels it binds to serum albumin at a rate of more than 99%. In doses exceeding 500 mg/day, proportionality is lost as a result of an increase in clearance caused by saturation of protein binding at high doses. However, the concentration of unbound naproxen continues to increase in proportion to the dose.

A state of equilibrium is reached after 3-4 days.

Naproxen penetrates the synovial fluid, crosses the placenta and is detectable in the milk of breastfeeding mothers at a concentration of approximately 1% of the plasma concentration.

Biotransformation
Naproxen is extensively metabolised by the liver to 6-O-desmethylnaproxen.

Elimination
Approximately 95% of the dose of naproxen sodium is excreted unchanged in urine (< 1%), as 6-O-desmethylnaproxen (< 1%) or its conjugates (66%-92%). The speed of excretion of the metabolites and conjugates almost entirely matches the speed of disappearance of the drug from plasma. Only 3% or less is excreted in faeces.

Naproxen clearance is approximately 0.13 ml/min/kg. Its elimination half-life is approximately 14 hours regardless of chemical form or formulation.

Pharmacokinetics in special situations:

Renal failure
Given that both naproxen and its metabolites are largely eliminated by the kidneys, accumulation may occur in cases of renal failure. Naproxen elimination is reduced in patients with severe renal failure. In patients with severe renal failure (creatinine clearance < 10 ml/min) there is greater naproxen clearance than estimated, based only on the degree of kidney dysfunction.

Children
The pharmacokinetic profile of naproxen in children aged 5-16 years is similar to that recorded in adults, even when clearance tends to be greater in children. No trials on the pharmacokinetics of naproxen have been conducted in children under the age of 5.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

In animals, the administration of a prostaglandin synthesis inhibitor has shown an increase in pre- and post-implantation losses and embryo-foetal mortality. Furthermore, an increase in the incidence of various malformations, including cardiovascular malformations, has been reported in animals that received a prostaglandin synthesis inhibitor during the organogenesis period.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
povidone K30
cellulose, microcrystalline
talc
magnesium stearate

Film coating
hypromellose
titanium dioxide (E171)
macrogol 8000
indigo carmine (E132)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Blister pack (Alu foil, PVC foil): 10 x 1, 16 x 1, 30 x 1, 40 x 1 and 60 x 1 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.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Krka d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/090/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19th January 2018

10 DATE OF REVISION OF THE TEXT

February 2019