

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NAPRIN

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains: Naproxen BP 500mg

Excipients with known effect: Each film-coated tablet contains Lactose Monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Naproxen is indicated for the treatment of rheumatoid arthritis, osteoarthritis (degenerative arthritis), ankylosing spondylitis, juvenile rheumatoid arthritis, acute gout, and acute musculoskeletal disorders (such as sprains, strains, direct trauma, lumbosacral pain, cervical spondylitis, tenosynovitis and fibrositis).

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:

Rheumatoid arthritis, osteoarthritis and ankylosing spondylitis: The usual dose is 500mg to 1g per day taken in two doses at 12-hour intervals or alternatively, as a single

administration.

In the following cases a loading dose of 750mg or 1g per day for the acute phase is recommended:

1. In patients reporting severe night-time pain and/or morning stiffness.
2. In patients being switched to naproxen from a high dose of another antirheumatic compound.
3. In osteoarthritis where pain is the predominant symptom.

Acute gout: The recommended dosage is 750mg at once, then 250mg every eight hours until the attack has passed.

Acute musculoskeletal disorders and dysmenorrhoea: The recommended dosage is 500mg initially followed by 250mg at 6 to 8 hours intervals as needed, with a maximum daily dose after the first day of 1250mg.

Elderly:

Studies indicate that although total plasma concentration of naproxen is unchanged, the unbound plasma fraction of naproxen is increased in older people. The implication of this finding for naproxen dosing is unknown. As with other drugs used in older people it is prudent to use the lowest effective dose and for the shortest duration possible as older people are more prone to adverse events. The patient should be monitored regularly for gastrointestinal bleeding during NSAID (non-steroidal anti-inflammatory drug) therapy. For the effect of reduced elimination in older people refer to Section 4.4.

Paediatric population (over 5 years)

For the treatment of juvenile rheumatoid arthritis: The usual dosage is 10mg per kg bodyweight per day taken in two doses at 12-hour intervals. Naproxen is not recommended for use in any other indication in children under 16 years of age.

Renal/hepatic impairment:

A lower dose should be considered in patients with renal or hepatic impairment. Naproxen is contra-indicated in patients with baseline creatinine clearance less than 30 ml/minute because accumulation of metabolites has been seen in patients with severe renal failure or those on dialysis (see section 4.3).

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Method of administration:

For oral administration; the tablets should be taken preferably with or after food and swallowed with a drink of water.

4.3 Contraindications

Hypersensitivity to naproxen, naproxen sodium, or to any of the excipients listed in section 6.1.

Active or history of peptic ulceration or active gastrointestinal bleeding (two or more distinct episodes of proven ulceration or bleeding).

History of gastrointestinal bleeding or perforation related to previous NSAIDs therapy.

Since the potential exists for cross-sensitivity reactions, naproxen should not be given to patients in whom aspirin, ibuprofen or other non-steroidal anti-inflammatory/analgesic drugs induce the syndrome of asthma, rhinitis, nasal polyps or urticaria. These reactions have the potential of being fatal. Severe anaphylactic-like reactions to naproxen have been reported in such patients.

Severe heart failure, hepatic failure and renal failure.

Naproxen is contraindicated during the last trimester of pregnancy (see section 4.6).

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). Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

Elderly

The elderly and/or debilitated patients are particularly susceptible to the adverse effects of NSAIDs especially gastrointestinal bleeding and perforation, which may be fatal. Prolonged use of NSAIDs in these patients is not recommended. Where prolonged therapy is required, patients should be reviewed regularly.

The antipyretic and anti-inflammatory activities of naproxen may reduce fever and inflammation, thereby diminishing their utility as diagnostic signs.

Respiratory disorders

Bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

Hepatic effects

As with other non-steroidal anti-inflammatory drugs, elevations of one or more liver function tests may occur. Hepatic abnormalities may be the result of hypersensitivity rather than direct toxicity. Severe hepatic reactions, including jaundice and hepatitis (some cases of hepatitis have been fatal) have been reported with this drug as with other non-steroidal anti-inflammatory drugs. Cross reactivity has been reported.

Naproxen decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

Although sodium retention has not been reported in metabolic studies, it is possible that patients with questionable or compromised cardiac function may be at a greater risk when

taking naproxen.

Gastrointestinal bleeding, ulceration and perforation

Gastrointestinal 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 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.

Care 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 antiplatelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving naproxen, 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 these conditions may be exacerbated (see section 4.8).

Renal effects

There have been reports of impaired renal function, renal failure, acute interstitial nephritis, haematuria proteinuria, renal papillary necrosis and occasionally nephritic syndrome associated with naproxen.

Renal failure linked to reduced prostaglandin production

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, angiotensin converting enzyme inhibitors, angiotensin-II receptor antagonists and the older people. Renal function should be monitored in these patients (see also section 4.3).

Use in patients with impaired renal function

As naproxen is eliminated to a large extent (95%) by urinary excretion via glomerular filtration, it should be used with great caution in patients with impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised and patients should be adequately hydrated. Naproxen is contraindicated in patients having a baseline creatinine clearance of less than 30 ml/minute (see section 4.3).

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of protein binding.

Certain patients, specifically those whose renal blood flow is compromised, such as in extracellular volume depletion, cirrhosis of the liver, sodium restriction, congestive heart failure, and pre-existing renal disease, should have renal function assessed before and during naproxen therapy. Some elderly people in whom impaired renal function may be expected, as well as patients using diuretics, may also fall within this category. A reduction in daily dosage should be considered to avoid the possibility of excessive accumulation of naproxen metabolites in these patients.

Use in patients with impaired liver function

Chronic alcoholic liver disease and probably also other forms of cirrhosis reduce the total plasma concentration of naproxen, but the plasma concentration of unbound naproxen is increased. The implication of this finding for naproxen dosing is unknown but it is prudent to use the lowest effective dose.

Haematological

Patients who have coagulation disorders or are receiving drug therapy that interferes with haemostasis should be carefully observed if naproxen-containing products are administered.

Patients at high risk of bleeding or those on full anti-coagulation therapy (e.g. dicoumarol derivatives) may be at increased risk of bleeding if given naproxen containing products concurrently.

Anaphylactic (anaphylactoid) reactions

Hypersensitivity reactions may occur in susceptible individuals. Anaphylactic (anaphylactoid) reactions may occur both in patients with and without a history of hypersensitivity or exposure to aspirin, other non-steroidal anti-inflammatory drugs or naproxen-containing products. They may also occur in individuals with a history of angio-oedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps.

Anaphylactoid reactions, like anaphylaxis, may have a fatal outcome.

Steroids

If steroid dosage is reduced or eliminated during therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of arthritis.

Ocular effects

Studies have not shown changes in the eye attributable to 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-containing products should have an ophthalmological examination.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention 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). Although data suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, some risk cannot be excluded.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with naproxen after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

Severe cutaneous adverse reactions (SCARs)

Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported post-marketing in association with naproxen treatment. If signs and symptoms suggestive of these reactions appear, naproxen should be withdrawn immediately. If the patient has developed SJS, or TEN or DRESS with the use of naproxen, treatment with naproxen must not be restarted and should be permanently discontinued.

Dermatological:

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 for these reactions early in the course of therapy: the onset of the reactions occurring in the majority of cases within the first month of treatment. Naproxen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Combination with other NSAIDs

The combination of naproxen-containing products and other NSAIDs, including cyclooxygenase-2 selective inhibitors, is not recommended, because of the cumulative risks of inducing serious NSAID-related adverse events.

Naproxen Tablets contains lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Naproxen Tablets contains sunset yellow (E110)

May cause allergic reactions.

Information on Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, i.e. is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

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

With food: Concomitant administration of food can delay the absorption of naproxen, but does not affect its extent.

Anti-coagulants: It is considered unsafe to take NSAIDs in combination with anticoagulants such as warfarin or heparin unless under direct medical supervision, as NSAIDs may enhance the effects of anti-coagulants (see section 4.4).

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risks of adverse effects (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.

Effect of high plasma protein binding of naproxen on other drugs: Due to the high plasma protein binding of naproxen, patients simultaneously receiving hydantoins, anticoagulants, other NSAIDs, aspirin or a highly protein bound sulfonamide should be observed for signs of over dosage of these drugs. Patients simultaneously receiving naproxen and a hydantoin, sulfonamide or sulfonylurea should be observed for adjustment of dose if required. No interactions have been observed in clinical studies with naproxen and anticoagulants or sulfonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal agents of this class.

Diuretics: Caution is advised when naproxen is co-administered with diuretics as there can be a decreased diuretic effect. The natriuretic effect of furosemide has been reported to be inhibited by some drugs of this class. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Lithium: Inhibition of renal lithium clearance leading to increases in plasma lithium concentrations has also been reported.

Anti-hypertensives: Naproxen and other non-steroidal anti-inflammatory drugs can reduce the anti-hypertensive effect of anti-hypertensives. Concomitant use of NSAIDs with ACE inhibitors or angiotensin-II receptor antagonists may increase the risk of renal impairment, especially in patients with pre-existing poor renal function (See Section 4.4).

Probenecid: Probenecid given concurrently increases naproxen plasma levels and extends its plasma half-life considerably.

Methotrexate: Caution is advised where methotrexate is administered concurrently because of possible enhancement of its toxicity, since naproxen, among other non-steroidal anti-inflammatory drugs, has been reported to reduce the tubular secretion of methotrexate in an animal model.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.

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

Mifepristone: NSAIDs should not be used for 8 to 12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone

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

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

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): There is an increased risk of gastrointestinal bleeding (see section 4.4) when anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.

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

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

Interference with laboratory tests: 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:

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. As with other drugs of this type, naproxen produces delay in parturition in animals and also affects the human foetal cardiovascular system (closure of ductus arteriosus). Use of naproxen in the last trimester of pregnancy is contraindicated (see section 4.3). 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 should not be given unless clearly necessary. If naproxen 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 (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (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.

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

Labour and delivery

Naproxen containing products are not recommended in labour and delivery because, through its prostaglandin synthesis inhibitory effect, naproxen may adversely affect foetal circulation and inhibit contractions, with an increased bleeding tendency in both mother and child.

Breast-feeding

Naproxen has been found in the milk of lactating women. The use of naproxen should be avoided in patients who are breast-feeding.

Fertility:

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

4.7 Effects on ability to drive and use machines

Some patients may experience drowsiness, dizziness, vertigo, insomnia, fatigue, visual disturbances or depression with the use of naproxen. If patients experience these or similar undesirable effects, they should not drive or operate machinery.

4.8 Undesirable effects

The following adverse events have been reported with NSAIDs and with naproxen.

Gastrointestinal disorders: The most commonly observed adverse events are gastrointestinal in nature. Heartburn, nausea, vomiting, constipation, diarrhoea, flatulence, dyspepsia, abdominal discomfort and epigastric distress. More serious reactions which may occur are gastrointestinal bleeding, which is sometimes fatal, particularly in the elderly (see section 4.4), inflammation, ulceration, perforation, and obstruction of the upper and lower gastrointestinal

tract, melaena, haematemesis, stomatitis, exacerbation of ulcerative colitis and Crohn's disease (see section 4.4), oesophagitis, gastritis and pancreatitis.

Blood and lymphatic system disorders: Neutropenia, thrombocytopenia, granulocytopenia including agranulocytosis, eosinophilia, leucopenia, aplastic anaemia and haemolytic anaemia.

Immune system disorders: Hypersensitivity reactions have been reported following treatment with NSAIDs in patients with, or without, a history of previous hypersensitivity reactions to NSAIDs. These may consist of (a) nonspecific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders including rashes of various types: pruritus, urticaria, purpura, angio-oedema and, more rarely, exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Metabolic and nutrition disorders: hyperkalaemia

Psychiatric disorders: Insomnia, dream abnormalities, depression, confusion and hallucinations.

Nervous system disorders: Convulsions, dizziness, headache, lightheadedness, drowsiness, paraesthesia, retrobulbar optic neuritis, inability to concentrate and cognitive dysfunction have been reported. Aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4).

Eye disorders: Visual disturbances, corneal opacity, papillitis and papilloedema.

Ear and labyrinth disorders: Tinnitus, hearing disturbances including impairment and vertigo.

Cardiac disorders: Oedema, palpitations, cardiac failure and congestive heart failure have been reported.

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) (see section 4.4).

Vascular disorders: Hypertension, vasculitis.

Respiratory, thoracic and mediastinal disorders: Dyspnoea, asthma, eosinophilic pneumonitis and pulmonary oedema.

Hepatobiliary disorders: Jaundice, fatal hepatitis and abnormal liver function tests.

Skin and subcutaneous tissue disorders: Skin rashes including fixed drug eruption, itching (pruritus), urticaria, ecchymoses, purpura, sweating.

Alopecia, erythema multiforme, Stevens Johnson syndrome, erythema nodosum, lichen planus, pustular reaction, SLE, epidermal necrolysis, very rarely toxic epidermal necrolysis, photosensitivity reactions (including cases in which skin resembles porphyria cutanea tarda “pseudoporphyria”) or epidermolysis bullosa-like reactions which may occur rarely.

If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued and the patient monitored.

Not known - Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4), fixed drug eruption

Musculoskeletal and connective tissue disorders: Myalgia and muscle weakness.

Renal and urinary disorders: Including, but not limited to, glomerular nephritis, interstitial nephritis, nephrotic syndrome, haematuria, raised serum creatinine, renal papillary necrosis and renal failure.

Reproductive system and breast disorders: Female infertility

General disorders and administration site conditions: Thirst, pyrexia, fatigue and malaise.

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 Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9 Overdose

Symptoms

Symptoms include headache, heartburn, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, drowsiness, dizziness, tinnitus, fainting. In cases of significant poisoning, acute renal failure and liver damage are possible.

Respiratory depression and coma may occur after the ingestion of NSAIDs but are rare.

In one case of naproxen overdose, transient-prolongation of the prothrombin time due to hypothrombinaemia 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 drug would be life-threatening.

Management

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one 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 four 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.

Haemodialysis does not decrease the plasma concentration of naproxen because of the high degree of its protein binding. However, haemodialysis 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 antirheumatic products, nonsteroids. ATC code: M01AE02

Naproxen is a non-steroidal anti-inflammatory analgesic compound with antipyretic properties as has been demonstrated in classical animal test systems. Naproxen exhibits its anti-inflammatory effect even in adrenalectomised animals, indicating that its action is not mediated through the pituitary-adrenal axis.

Naproxen inhibits prostaglandin synthetase (as do other NSAIDs). As with other NSAIDs, however, the exact mechanism of its anti-inflammatory action is not known.

5.2 Pharmacokinetic properties

Naproxen is completely absorbed from the gastro-intestinal tract, and peak plasma levels are reached in 2 to 4 hours. Naproxen is present in the blood mainly as unchanged drug,

extensively bound to plasma proteins. The plasma half-life is between 12 and 15 hours, enabling a steady state to be achieved within 3 days of initiation of therapy on a twice daily dose regimen. The degree of absorption is not significantly affected by either foods or most antacids.

Excretion is almost entirely via the urine, mainly as conjugated naproxen, with some unchanged drug. Metabolism in children is similar to that in adults. Chronic alcoholic liver disease reduces the total plasma concentration of naproxen but the concentration of unbound naproxen increases. In the elderly, the unbound plasma concentration of naproxen is increased although total plasma concentration is unchanged.

5.3 Preclinical safety data

Carcinogenicity

Naproxen was administered with food to Sprague-Dawley rats for 24 months at doses of 8, 16 and 24mg/kg/day. Naproxen was not carcinogenic in rats.

Mutagenicity

Mutagenicity was not seen in *Salmonella typhimurium* (5 cell lines), *Sachharomyces cerevisisae* (1 cell line) and mouse lymphoma tests.

Fertility

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

Teratogenicity

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

Perinatal/Postnatal Reproduction

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose BP
Crospovidone BP
Maize Starch BP
Purified Water BP
Croscarmellose Sodium BP

Colloidal Anhydrous Silica BP
Magnesium Stearate BP
Purified Talc

6.2 Incompatibilities

Not Known

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store in a cool dry place below 30°C

Keep all medicines out of reach of children

6.5 Nature and contents of container

Alu-Alu blister pack of 10 Tablets. Such 3 blisters are packed into printed carton along with pack insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

UNIJULES LIFE SCIENCES LIMITED

B# 35 & 36, MIDC Industrial Area,

Kalmeshwar, Nagpur-441501

India

Manufactured at –

RAINBOW LIFE SCIENCES PVT. LTD.

Manufactured At

Plot No. 357, G.I.D.C., Sachin,

Surat - 394210 Gujarat, India.

Tel: +91-22-41713600

Fax: +91-22-41713631

Email: info@rainbowlifesciences.com

8. MARKETING AUTHORISATION NUMBER(S) –

H2022/CTD7340/14438

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION--

APRIL 2022

10. DATE OF REVISION OF THE TEXT

December 2027