SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

BIO-NAPROXEN 250 Tablets

BIO-NAPROXEN 500 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BIO-NAPROXEN 250 tablet contains 250 mg of naproxen.

Each BIO-NAPROXEN 500 tablet contains 500 mg of naproxen.

Contains sugar: lactose (BIO-NAPROXEN 250 contains 78,40 mg/tablet lactose & BIO-NAPROXEN 500 contains 156,80 mg/tablet lactose).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets

BIO-NAPROXEN 250: Round, yellow, biconvex tablets with score line on one side and plain on other side.

BIO-NAPROXEN 500: Yellow, capsule-shaped, biconvex tablet coded with NPX 500 on one side and break line on reverse.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. BIO-NAPROXEN may also be used in the treatment of acute gout, mild to moderate pain, associated with primary dysmenorrhoea, bursitis and acute tendonitis.

4.2 Posology and method of administration

BIO-NAPROXEN should not be used in children under the age of 16 years.

Adults

Rheumatoid arthritis, osteo-arthritis and ankylosing spondylitis: 250 to 375 mg twice daily with food.

Acute gout: An initial dose of 750 mg with meals, followed by 250 mg every 8 hours until the attack has subsided.

Mild to moderate pain associated with primary dysmenorrhoea, bursitis and acute tendonitis: An initial dose of 500 mg followed by 250 mg every 6 to 8 hours with food.

Use the lowest effective dose for the shortest possible duration of treatment.

4.3. Contraindications

- Hypersensitivity or allergic reactions to medicines containing naproxen or naproxen sodium, aspirin or other non-steroidal anti-inflammatory agents.
- Patients in whom aspirin or other non-steroidal anti-inflammatory / analgesic medicines 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.
- BIO-NAPROXEN should not be used in pregnant women or mothers breastfeeding their infants.
- Heart failure.
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs.
- Active or history of recurrent ulcer/haemorrhage/perforations.
- Porphyria.
- Children: BIO-NAPROXEN is not recommended for use in children under the age of 16 years.

- Severe renal function impairment: BIO-NAPROXEN is not recommended in patients with baseline creatinine clearance of less than 20 ml/minute because accumulation of naproxen metabolites has been seen in such patients (see section 4.4).

4.4 Special warnings and precautions for use

BIO-NAPROXEN should be used with special care in patients with gastrointestinal bleeding, with a history of bronchospasm (asthma), with impaired renal or liver function and elderly patients or patients with cardiovascular disease.

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 cardiovascular risks below).

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 BIO-NAPROXEN therapy. In view of BIO-NAPROXEN's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patient.

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 BIO-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 disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Gastrointestinal bleeding, ulceration and perforation

GI bleeding, ulceration or perforation, which can be fatal, has been reported with BIO-NAPROXEN 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 BIO-NAPROXEN doses
- in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3)
- in the elderly
- when used with alcohol
- in smoking

These patients should commence BIO-NAPROXEN treatment on the lowest dose available. Combination therapy with protective medicine (e.g., misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other medicines likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, particularly the 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 antiplatelet medicine such as aspirin (see section 4.5). When GI bleeding or ulceration occurs in patients receiving BIO-NAPROXEN, the treatment should be withdrawn.

BIO-NAPROXEN should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as these condition may be exacerbated (see section 4.8). The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing dose and duration of BIO-NAPROXEN treatment, in patients with a history of ulcers, and the elderly.

When gastrointestinal bleeding or ulceration occurs in patients receiving BIO-NAPROXEN, treatment with BIO-NAPROXEN should be stopped.

Cardiovascular, renal and hepatic impairment

The administration of BIO-NAPROXEN 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 and the elderly. Renal function should be monitored in these patients (see also section 4.3).

Impaired renal function

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

BIO-NAPROXEN should be used with caution in patients with impaired renal function or a history of kidney disease, especially if long-term usage is considered as BIO-NAPROXEN is an inhibitor of prostaglandin synthesis.

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of naproxen as contained in BIO-NAPROXEN at higher than recommended doses. Presenting signs and symptoms included reduced level of consciousness and generalised weakness. Naproxen i.e., BIO-NAPROXEN induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

Caution should be taken in patients with conditions leading to a reduction in blood volume and/or renal blood flow where renal prostaglandins play a supportive role in the maintenance of renal perfusion. In these patients administration of BIO-NAPROXEN may lead to a dose-dependent reduction in renal prostaglandin formation and may cause overt renal decompensation or failure. Patients with the greatest risk of developing this reaction are those with impaired renal function, hypovolaemia, heart failure, liver dysfunction, salt depletion, those taking diuretics and the elderly. Discontinuation of BIO-NAPROXEN is generally followed by recovery to the pre-treatment state.

BIO-NAPROXEN should be used with great caution where there is impairment of renal function as it is eliminated to a large extent (95 %) via glomeral filtration; the monitoring of serum creatinine and/or creatinine clearance should be conducted in these patients.

BIO-NAPROXEN should be used with great caution in these patients and the close monitoring of serum creatinine and/or creatinine clearance is recommended. BIO-NAPROXEN is not recommended in patients having baseline creatinine clearance of less than 20 ml/min. BIO-NAPROXEN is not recommended in patients with baseline creatinine clearance of less than 20 ml/min because accumulation of naproxen metabolites has been seen in these patients (see section 4.3).

Certain patients, specifically those whose renal blood flow is compromised, because of 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 BIO-NAPROXEN therapy. Some elderly patients 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 BIO-NAPROXEN metabolites in these patients.

Impaired liver function

Elevations of one or more liver function tests may occur. Hepatic abnormalities could 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. Cross-reactivity has been reported.

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 BIO-NAPROXEN dosing is unknown but it is prudent to use the lowest effective dose. BIO-NAPROXEN should be used with caution in patients with a history of, or in those with impaired liver function.

Haematological

BIO-NAPROXEN decreases platelet aggregation and prolongs bleeding time. This effect should be brought into consideration when bleeding times are determined. Patients who suffer from coagulation disorders or are receiving medicine therapy that interferes with haemostasis should be carefully monitored if BIO-NAPROXEN is administered.

Patients at high risk of bleeding, and those on full anticoagulation therapy, may be at increased risk of bleeding if given BIO-NAPROXEN concurrently.

As it causes an increased bleeding tendency it should be given with caution to patients receiving coumarin anti-coagulants such as warfarin, and to patients with bleeding disorders and cardiovascular disease. BIO-NAPROXEN may interfere with some tests for 17-ketogenic steroids.

Elderly

The elderly has an increased frequency of adverse reactions to NSAIDs including BIO-NAPROXEN, especially gastrointestinal perforation, ulceration, and bleeding (PUBs) which may be fatal (see section 4.2). Elderly or debilitated patients may be at a greater risk of experiencing undesirable effects than younger patients. In elderly patients the clearance is reduced. Use of the lowest possible dose is recommended.

Respiratory disorders

Caution is required if BIO-NAPROXEN is administered to patients suffering from, or with a previous history of, bronchial asthma since BIO-NAPROXEN have been reported to precipitate bronchospasm in such patients.

Systemic lupus erythematosus (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).

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 BIO-NAPROXEN (see section 4.8). Patients appear to be at highest risk for 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. BIO-NAPROXEN should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as BIO-NAPROXEN. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue BIO-NAPROXEN and evaluate the patient immediately.

Impaired female fertility

The use of BIO-NAPROXEN may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of fertility, withdrawal of naproxen should be considered.

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 medicines or naproxen-containing products such as BIO-NAPROXEN. They

may also occur in individuals with a history of angioedema, bronchospastic reactivity (e.g. asthma), rhinitis and nasal polyps.

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

Because of the possibility of cross-sensitivity due to structural relationships which exist among non-steroidal, anti-inflammatory medicines, acute allergic reactions are more likely to occur in patients who have exhibited previous allergic reactions to these compounds.

Naproxen, in common with other NSAIDs, decreases platelet aggregation and prolongs bleeding time. This effect should be brought into consideration when bleeding times are determined. Patients who have coagulation disorders or who are receiving medicine therapy that affects with haemostasis should be carefully observed when given BIO-NAPROXEN (see section 4.5).

Patients who have exhibited aspirin hypersensitivity in the past (usually as the angioedema/asthma syndrome) may exhibit the same phenomenon with BIO-NAPROXEN. Bronchospasm may be precipitated in such patients and in patients suffering from, or with a history of bronchial asthma or allergic disease (see section 4.3).

Patients on full anticoagulation therapy (e.g., heparin or warfarin), may be at an increased risk of bleeding if given BIO-NAPROXEN concurrently. Therefore, the benefits should be weighed against these risks.

Mild peripheral oedema has been observed in a few patients receiving BIO-NAPROXEN. Although sodium retention has not been reported in metabolic studies, it is possible that patients with questionable or compromised function may be at a greater risk when taking BIO-NAPROXEN.

Steroids

If the corticosteroid dosage is reduced or eliminated during BIO-NAPROXEN therapy, the corticosteroid dosage must be reduced gradually and the patient must be monitored closely for any evidence of adverse effects, including adrenal insufficiency and worsening of symptoms of arthritis.

Ocular effects

Studies have not shown changes in the eye attributable to BIO-NAPROXEN administration. In rare cases, adverse ocular disorders including papillitis, retrobulbar optic neuritis and papilloedema have been reported in users of NSAIDs including BIO-NAPROXEN, although a cause-and-effect relationship cannot be established; accordingly, patients who develop visual disturbances during treatment with BIO-NAPROXEN should have an ophthalmological examination.

Combination with other NSAIDs

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

The use of BIO-NAPROXEN with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

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

Interference in tests

BIO-NAPROXEN therapy should be temporarily withdrawn 48 hours before adrenal function tests are performed as it may artifactually interfere with some tests for 17-ketogenic steroids. Similarly, naproxen may interfere with some assays of urinary 5-hydroxyindoleacetic acid.

Sporadic abnormalities in laboratory tests (e.g., liver function test) have occurred in patients on BIO-NAPROXEN therapy, but no definite trend was seen in any test indicating toxicity.

Medication Overuse Headache (MOH)

After long term treatment with analgesics, headache may develop or aggravate. Headache caused by overuse of analgesics (MOH - medication-overuse headache) should be suspected in patients who have frequent or daily headaches despite (or because of) regular use of analgesics. Patients with medication overuse headache should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

Pregnancy

Regular use of NSAIDs such as BIO-NAPROXEN during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

The administration of Nonsteroidal anti-inflammatory drugs (NSAID's) around 20 weeks or later in pregnant patients may cause serious kidney problems in an unborn baby. This may lead to low levels of amniotic fluid because around 20 weeks of pregnancy the unborn baby's kidneys produces amniotic fluid. Amniotic fluid provides a protective cushion and helps the lungs, digestive system, and muscles of the unborn baby to develop (see section 4.3).

Medicines that inhibit prostaglandin synthesis, like BIO-NAPROXEN, may adversely affect pregnancy and/or the embryo or foetal's development. The risk is believed to increase with an increased dose and/or duration of therapy.

It is recommended to avoid the administration of BIO-NAPROXEN in pregnant woman at 20 weeks or later (see section 4.3). Unless specifically advised by a healthcare professional to administer BIO-NAPROXEN between 20 and 30 weeks, the dose should be kept as low and the duration of treatment as short as possible, ultrasound monitoring of amniotic fluid is recommended if BIO-NAPROXEN treatment extends beyond 48 hours.

BIO-NAPROXEN may cause renal dysfunction, which may progress to renal failure with oligohydroamniosis, and in some cases neonatal renal impairment. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. Oligohydramnios may be reversible with treatment. Discontinuation and possible prolongation of bleeding time due to the anti-aggregating effect which may occur even at very low doses of BIO-NAPROXEN.

BIO-NAPROXEN contains lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take BIO-NAPROXEN.

4.5 Interaction with other medicines and other forms of interaction

Naproxen is highly protein-bound hence patients receiving hydantoins, anticoagulants or a highly protein-bound sulfonamide should be closely monitored for signs of overdosage of this medicine. No interactions have been observed in clinical studies with naproxen or sulfonylureas, but caution is nevertheless advised since interaction has been seen with other non-steroidal medicines of this class.

NSAIDs: use of two or more NSAIDs concomitantly could result in an increase in side effects. NSAIDs, including BIO-NAPROXEN, have been reported to increase steady state plasma lithium levels by inhibition of renal lithium clearance. Decreased elimination of lithium. It is recommended that these levels are monitored whenever initiating, adjusting or discontinuing naproxen.

Anti-hypertensives: Reduced anti-hypertensive effect. Concomitant administration of BIO-NAPROXEN with beta blockers may reduce their antihypertensive effect and may increase the risk of renal impairment associated with the use of ACE inhibitors or angiotensin II receptor antagonists.

Probenecid: during concurrent administration caution is advised as it increases naproxen plasma levels and extends its half-life considerably.

Decreased elimination of methotrexate: Caution is advice when methotrexate is administered concurrently, due to the possible enhancement of its toxicity as BIO-NAPROXEN, like other NSAIDs has been reported to reduce tubular secretion of methotrexate in an animal model.

Furosemide: The natriuretic effect of furosemide has been reported to be inhibited by some medicine of this class.

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 8-12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

Corticosteroids: As with all NSAIDs, caution should be taken when co-administered with corticosteroids because of the increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs as this may increase the risk of adverse effects (see section 4.4).

Acetylsalicylic acid: Clinical pharmacodynamic data suggest that concomitant BIO-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 BIO-NAPROXEN therapy. The clinical relevance of this interaction is not known.

Diuretics: NSAIDs may reduce the effect of diuretics and antihypertensive medicinal products. The risk of acute renal insufficiency, which is usually reversible, may be increased in some patients with compromised renal function (e.g., dehydrated patients or elderly patients) when angiotensin II receptor antagonists are combined with NSAIDs. 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. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Anti-coagulants: BIO-NAPROXEN may enhance the effects of anti-coagulants such as warfarin (see section 4.4).

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

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

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

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

Bisphosphonates: concomitant use of bisphosphonates and NSAIDs may increase the risk of gastric mucosal damage.

Antacids or cholestyramine: the concurrent administration with BIO-NAPROXEN can delay the absorption of BIO-NAPROXEN. BIO-NAPROXEN should be taken at least one hour before or four to six hours after cholestyramine.

Food: concomitant administration can delay the absorption of BIO-NAPROXEN but does not affect the extent thereof.

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

Cardiac glycosides: increased plasma concentrations of digoxin have been reported.

ACE inhibitors and potassium-sparing diuretics: concomitant administration may increase the risk of hyperkalaemia.

Thyroid function tests: BIO-NAPROXEN may interfere with thyroid function tests by lowering serum thyroid hormone concentrations.

Adrenal function tests: it is advised that BIO-NAPROXEN therapy should be temporarily discontinued 48 hours before these tests are performed. BIO-NAPROXEN may artifactually interfere with some tests for 17-ketogenic steroids. BIO-NAPROXEN may similarly interfere with some urinary assays of 5-hydroxyindoleacetic acid (5-HIAA).

Aspirin: Plasma concentrations of BIO-NAPROXEN are significantly decreased by concomitant administration of therapeutic doses of aspirin.

Thiazide diuretics, beta-adrenergic antagonists, prazosin and captopril: BIO-NAPROXEN may reduce the diuretic, natriuretic and anti-hypertensive effects of these medicines, due to the inhibition of synthesis of renal prostaglandins.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety and efficacy of BIO-NAPROXEN in pregnancy and lactation has not yet been established.

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 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.

During the first and second trimester of pregnancy, BIO-NAPROXEN should not be given unless clearly necessary. If BIO-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.

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-hydramniosis;
- 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 BIO-NAPROXEN is contraindicated during the last trimester of pregnancy.

Breastfeeding

BIO-NAPROXEN crosses the placenta and has been found in the milk of lactating mothers.

In limited studies so far available, BIO-NAPROXEN can appear in breast milk in very low concentrations.

BIO-NAPROXEN should be avoided when breastfeeding.

Fertility

If BIO-NAPROXEN is administered to woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and the duration of treatment as short as possible.

See section 4.4 for use regarding female fertility.

4.7 Effects on the ability to drive and use machines

Undesirable effects such as drowsiness, dizziness, fatigue and visual disturbances are possible after taking BIO-NAPROXEN. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

System organ class	Frequent	Less frequent	Frequency not known
Blood and lymphatic system disorders		Haemolytic anaemia, granulocytopenia, thrombocytopenia, agranulocytosis.	Leukopenia, neutropenia, eosinophilia, anaemias including aplastic anaemia.
Immune system disorders		Allergic and hypersensitivity reactions anaphylaxis including fever, asthma, rashes, hepatotoxicity, anaphylactoid reaction.	Laryngeal oedema, serum sickness-like reaction, lymphadenopathy, Patients who have exhibited aspirin hypersensitivity in the past (usually as the angio-oedema/asthma syndrome) may exhibit the same phenomenon with Bio-Naproxen.

Metabolism and nutrition disorders		Hyperkalaemia.	Hypokalaemia***
Psychiatric disorders		Depression, Cognitive dysfunction, insomnia, inability to concentrate, dream abnormalities.	Hallucinations.
Nervous system disorders	Confusion, dizziness, drowsiness, headache, light-headedness	Convulsions, aseptic meningitis*	Malaise, nervousness, headache, vertigo, paraesthesia, exacerbation of Parkinson's Disease.
Eye disorders	Visual disturbances		Blurred vision and other ocular reactions, corneal opacity, papillitis, retrobulbar, optic neuritis and papilloedema.
Ear and labyrinth disorders	Hearing disturbance, tinnitus.	Hearing impairment.	
Cardiac disorders	Oedema.	Palpitations.	Cardiac failure, angioneurotic oedema, congestive heart failure, pericarditis.
Vascular disorders		Vasculitis, arterial thrombotic events e.g. myocardial infarction or stroke (see 4.4).	Hypertension.

Respiratory, thoracic and mediastinal disorders		Aggravated asthma, eosinophilic, pneumonitis.	Dyspnoea, bronchospasm, rhinitis, pulmonary oedema, haemoptysis.
Gastrointestinal disorders		Pancreatitis.	Thirst, peptic ulcers, perforation or gastrointestinal bleeding**, sometimes fatal. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4), gastritis, colitis, oesophagitis, non-peptic gastrointestinal ulceration, abdominal discomfort.
Hepato-biliary disorders		Hepatitis (some cases of hepatitis have been fatal), jaundice.	Abnormalities of liver function tests.
Skin and subcutaneous tissue disorders	Ecchymoses, itching (pruritus), purpura, skin eruptions, sweating, skin rash.	Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, erythema multiforme, urticaria,	Erythema nodosum, fixed drug eruption, lichen planus, pustular reaction, SLE, angio-oedema, epidermal necrosis, exfoliative and bullous dermatoses, Drug Reaction

		alopecia, photosensitivity reactions, including cases of porphyria cutanea tarda or epidermolysis bullous. If skin fragility, blistering or other symptoms suggestive of pseudoporphyria occur, treatment should be discontinued immediately, and the patient closely monitored.	with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4).
Musculoskeletal and connective tissue disorders		Myalgia, muscle weakness.	
Renal and urinary disorders		Glomerular nephritis, haematuria, interstitial nephritis, nephritic syndrome, renal papillary necrosis.	Impairment of renal function, hyperkalaemia, renal disease, reversible renal failure, renal tubular acidosis***, raised serum creatinine and fluid retention may occur, nephropathy.

Reproductive system and breast disorders		Unexplained vaginal bleeding and/or heavy menstrual bleeding.	Impaired female fertility (see 4.4).
General disorders and administration site disorders	Fatigue.		Mild peripheral oedema, pyrexia (chills and fever).

*especially in patients with existing auto-immune disorders, such as system lupus erythematosus, mixed connective tissue disease, with symptoms such as stiff neck headache, nausea, vomiting, fever and disorientation.

** sometimes fatal, particularly in the elderly, may occur (See section 4.4).

***Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of naproxen at higher than recommended doses.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

Headache, vomiting, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, dizziness, drowsiness, epigastric pain, abdominal discomfort, heartburn, indigestion, nausea, tinnitus, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible. Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

BIO-NAPROXEN may be absorbed rapidly, and high blood levels could be reached quickly.

Treatment

Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

3.1 Antirheumatics (anti-inflammatory agent)

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroidal anti-inflammatory drugs (NSAIDs).

ATC code: M01AE02

Naproxen is a non-steroidal anti-inflammatory medicine (NSAID) with analgesic and antipyretic properties.

Mechanism of action

Naproxen reduces the synthesis of prostaglandins primarily by inhibiting the enzyme cyclo-oxygenase. Naproxen has been shown to have anti-inflammatory activity in a number of experimental models. Naproxen inhibits prostaglandin E_2 synthesis in vitro by human rheumatoid synovial microsomes. It also inhibits prostaglandin E_2 production by phytohemagglutinin-stimulated peripheral blood mononuclear cells. At 10^{-4} M ($23mg.1^{-1}$) naproxen inhibits neutral protease activity derived from human polymorphonuclear

leucocytes. Naproxen also inhibits in vitro the activity of cathepsin-β and other hydrolytic enzymes derived from lysosomes. Naproxen is a potent in inhibitor of leucocyte migration and produces effects comparable to those of colchicine.

5.2 Pharmacokinetic properties

Absorption

Naproxen is readily absorbed from the gastrointestinal tract.

Distribution

Peak plasma levels being reached 2 to 4 hours after ingestion. Plasma concentrations of naproxen increase proportionally with dose up to about 500 mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. At therapeutic concentrations naproxen is more than 99 % bound to plasma proteins and has a plasma half-life of about 13 hours.

Elimination

Approximately 95 % of a dose is excreted in the urine as Naproxen and 6-O-desmethyl naproxen and their conjugates. Less than 3 % of a dose has been recovered in the faeces. Naproxen crosses the placenta and is excreted in breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose

Preglatinised starch

Sodium starch glycolate

Quinoline yellow lake 19248

Polysorbate 80

Povidone

Purified talc

Magnesium stearate

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Bio-Naproxen 250:

Polypropylene container with polyethylene closures: 36 months

HDPE container 30 tablets: 48 months

Amber PVC/PVDC Aluminium foil blister strips: 36 months

Polyethylene zip lock pouch (patient ready pack): 36 months

Bio-Naproxen 500:

Polypropylene container with polyethylene closures: 36 months

HDPE container 30 tablets: 36 months

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of the container

BIO-NAPROXEN 250 and BIO-NAPROXEN 500 can be packed in the following containers:

White opaque, polypropylene securitainer containing 30 and 250 tablets.

Screw cap white, opaque HDPE container containing 30 and 250 tablets.

Amber PVC/PVDC blister containing 56 or 14 tablets per carton.

White, opaque, polyethylene zip lock patient ready pack (for state use only), containing 28 or 56 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

BIOTECH LABORATORIES (PTY) LTD

Ground Floor, Block K West, Central Park

400 16th Road

Randjespark

Midrand, 1685

8. REGISTRATION NUMBERS

BIO-NAPROXEN 250: W/3.1/0436

BIO-NAPROXEN 500: W/3.1/0437

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTORISATION

Date of registration: 28 March 1990

10. DATE OF THE REVISION OF THE TEXT

30 September 2024