SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Naproxennatrium Aurobindo 220 mg, zachte capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains Naproxen sodium 220 mg equivalent to 200 mg naproxen

Excipients with known effect:
Sorbitol, 65.3 mg per capsule, soft
Lecithin originating from soya oil

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Capsules, soft.

Blue transparent soft gelatin capsule containing 220 mg of naproxen sodium per capsule. Approximately 20 to 22 mm in length and 8 to 10 mm in width.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of minor and moderate pain, such as:
- Headache,
- toothache,
- muscle pain,
- arthralgia,
- back pain,
- painful menstruation
- minor pain associated with the cold.
- Reducing fever.

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 children from 12 years of age and above:
- General: Take 1 capsule every 8 to 12 hours.
An initial dose of 2 capsules may be taken and, if the complaints persist, followed by one capsule after 12 hours.
Maximal daily dose is 3 capsules per 24 hours.
Eldery from 65 years old:
Not more than 2 capsules per 24 hours.

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

Hepatic impairment
Naproxen should be used with caution in patients with impaired hepatic function. Naproxen should be avoided if possible in patients with severe hepatic impairment or cirrhotic liver disease (see section 4.3 and 4.4).

Method of administration
<Invented Name> is administered orally, preferably immediately after meals with plenty of water or milk.
- Not to be used longer than 10 consecutive days without consulting a doctor.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients who have had an allergic reaction such as asthma, rhinitis or urticaria, when using acetylsalicylic acid or other prostaglandin synthetase inhibitors (NSAIDs).
- Active or history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
- Ulcerations of the gastrointestinal tract, gastritis congestiva or gastritis atrophica.
- Gastrointestinal bleeding or other bleeding such as cerebrovascular bleeding.
- Haemorrhagic diathesis or treatment with anticoagulants.
- Severe renal impairment (creatinine clearance < 30 ml/min).
- Severe hepatic impairment
- Severe heart failure.
- Pregnancy in the third trimester (See section 4.6 Pregnancy and lactation).

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 gastro-intestinal and cardiovascular risks below).
- A doctor should be consulted if pain and / or fever persist, recur or worsen.

- When gastrointestinal complaints such as heartburn, stomach pain or bleeding occur while using<Invented Name>, a doctor should be consulted.
- In patients with a history of hypertension and / or heart failure, caution is advised (consultation with doctor or pharmacist) prior to treatment. Fluid retention, hypertension and oedema have been reported in association with therapy with NSAIDs.
- Caution is needed in elderly and in patients with impaired liver function.
- Naproxen should be used with great caution in patients with impaired renal function; in these patients the renal function should be carefully monitored.
- The antipyretic, analgesic and anti-inflammatory activities of <Invented Name> , may mask certain symptoms of infection. Caution is therefore advised in its application in patients with infection.
- Patients with gastrointestinal tract disorders and blood coagulation problems may use <Invented Name> only under medical supervision.
- Pain due to gastrointestinal disorders is not an indication for <Invented Name>.
- Anaphylactoid reactions usually occur in patients with a known hypersensitivity to <Invented Name>, acetylsalicylic acid or other prostaglandin synthetase inhibiting agents. However, they can also occur in patients without previous exposure to or known hypersensitivity to these agents.
- All patients may at any time during the treatment demonstrate gastrointestinal tract events. The risk of such events increases with increasing doses. The risk of severe gastrointestinal side effects is increased in debilitated patients. In these patients, the lowest dose should be used.
- The use of <Invented Name> with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Elderly patients

Elderly patients more frequently experience side effects of NSAIDs, in particular gastro-intestinal bleeding and perforation, which can be fatal (see section 4.2).

- **Cardiovascular and cerebrovascular events.**

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, some risk cannot be excluded. There are insufficient data available on the effects of low doses of naproxen <220 mg - 660 mg of naproxen per day> to draw definitive conclusions about the potential risk of thrombosis.

Gastro-intestinal bleeding, ulceration and perforation:

- Gastro-intestinal bleeding, ulceration and perforation, which can be fatal, have been reported with the use of all NSAIDs at any time during the treatment, with or without warning symptoms or the prior occurrence of severe gastro-intestinal side effects.
- The risk of gastro-intestinal bleeding, ulceration and perforation is greater with higher doses, the prior occurrence of ulceration, in particular if complicated by bleeding and perforation (see section 4.3) and in elderly patients. These patients should start the treatment with the lowest available dosage. Combination treatment with protective products (for example misoprostol or proton pump inhibitors) should be considered in these patients as well as in patients who concomitantly need low doses of acetylsalicylic acid or other medicinal products that probably increase the gastro-intestinal risk (see section 4.5).

- Patients who had a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptom (especially bleeding), especially at the start of treatment. Caution is needed in patients who are concomitantly treated with medicinal products, which may increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors and products that counteract the platelet aggregation, such as acetylsalicylic acid.
- When gastro-intestinal bleeding or ulceration occurs in patients who are receiving <Invented Name>, the treatment should be discontinued.
- NSAIDs should be used with caution in patients with a history of gastro-intestinal diseases (ulcerative colitis, Crohn's disease) as these conditions can worsen (see section 4.8).

Severe cutaneous adverse reactions (SCARs)
Severe skin reactions, including exfoliative dermatitis, 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 <Invented Name> treatment. Patients appear to have the greatest risk of these reactions at the beginning of the treatment: in the majority of the cases the reaction started within the first month of treatment. If signs and symptoms suggestive of these reactions appear, <Invented Name> should be withdrawn immediately. If the patient has developed SJS, or TEN or DRESS with the use of <Invented Name>, treatment with <Invented Name> must not be restarted and should be permanently discontinued.

Impaired female fertility
There have been some indications that products that inhibit the cyclo-oxygenase/ prostaglandin synthesis reduce the fertility of women by having an effect on the ovulation. This is reversible by discontinuing the treatment.

Excipients

This medicine contains sorbitol. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

<Invented Name> contains lecithin originating from soya oil. If you are allergic to peanut or soya do not use this medicinal product.

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

A doctor or pharmacist should be consulted, if in addition to <Invented Name> also any other medicines are regularly used.

As a result of the strong binding of naproxen to plasma proteins, the dose of phenytoin and highly protein bound sulfonamides (such as sulfadoxine) must be reduced during concomitant use of

prostaglandin synthetase inhibitors, such as naproxen. Only exceptionally high doses of naproxen can cause the release and overdose symptoms of thiopental and hydantoins.

Naproxen may increase the effects of oral anticoagulants and heparin (increased risk of bleeding due to inhibition of platelet aggregation). Anticoagulants: NSAIDs can increase the effect of anticoagulants, such as warfarin (see section 4.4).
It should be taken into account that the effects of sulfonylurea compounds (oral antidiabetics) may be strengthened due to repression of plasma proteins.

Corticosteroids: increased risk of gastro-intestinal ulceration and bleeding (see section 4.4).

Platelet aggregation inhibitors and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastro-intestinal bleeding (see section 4.4).

The natriuretic effect of furosemide has been reported to be inhibited by several drugs of this class. Inhibition of lithium clearance leading to increases in plasma lithium concentrations has also been reported.

<Invented Name> and other NSAIDs may reduce the antihypertensive effect of beta-blockers.
Concomitantly used probenecid increases naproxen plasma levels and extends its plasma half-life considerably.

Severe increase in the toxicity of methotrexate was observed in combined therapy with naproxen. The mechanism of this interaction has not been clearly established, it has been suggested that a reduction in renal clearance of methotrexate may play a role. Combined naproxen-methotrexate therapy should be avoided.

As other prostaglandin synthetase inhibitors, naproxen sodium may increase the risk of renal impairment associated with the use of ACE-inhibitors.

Prostaglandin synthetase inhibitors such as naproxen may cause an increased nephrotoxicity of cyclosporine due to its effect on renal prostaglandins. The combination with other prostaglandin synthetase inhibitors is not recommended, because of the toxicity of the combination therapy and the lack of evidence of therapeutic benefit.

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

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 section 4.3).

Breast-feeding

Naproxen has been found in the milk of lactating women. Therefore, lactating women should not use <Invented Name>.

Fertility

There are indications that inhibitors of cyclooxygenase/prostaglandin synthesis decrease the fertility of women by an effect on the ovulation, which is reversible by ceasing the treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Side effects, such as drowsiness, dizziness, and insomnia can occur when using <Invented Name>. As a result,

the ability to react may be altered in individual cases and the ability to take part actively in road traffic and using machines may be impaired.

4.8 Undesirable effects

The most common side effects are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleedings, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, blood in the stool, heamatemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported after administration. Gastritis was less frequently observed.

The following frequencies are taken as a basis when evaluating side effects: 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) and not known frequency (cannot be estimated from the available data).

Blood and lymphatic system disorders:
Very rare: Aplastic anemia, haemolytic anemia, Granulocytopenia such as agranulocytosis, thrombocytopenia

Immune system disorders:
Rare: Anaphylactic reactions to naproxen and naproxen sodium preparation. Anaphylactic reactions have been reported in patients with, and without, proven hypersensitivity to acetylsalicylic acid, other NSAIDs and to <Invented Name>.

Metabolism and nutrition disorders:
Rare: Hyperkalaemia
Not known frequency: Gout

Psychiatric disorders:
Uncommon: Impaired concentration, insomnia, cognitive dysfunction

Nervous system disorders:
Common: Cephalea, dizziness, drowsiness, light-headedness
Very rare: Convulsions, aseptic meningitis

Eye Disorders:
Common: Visual disturbances

Ear and Labyrinth disorders:
Common: Tinnitus
Rare: Hearing impairment

Cardiac disorders:
Very rare: Tachiycardia, Oedema, hypertension and heart failure

Vascular disorders:

Rare: Vasculitis

Respiratory, thoracic and mediastinal disorders:
Rare: Eosinophilic pneumonitis
Very rare: Dyspnoea, asthma

Gastrointestinal disorders:
Very common: epigastric or abdominal distress
Common: Nausea, dyspepsia, heartburn
Uncommon: Vomiting, diarrhoea, constipation, gastrointestinal bleeding and / or perforations
Rare: Ulcerative stomatitis, haematemesis
Very rare: colitis
Not known frequency: Non-peptic gastrointestinal ulceration, peptic syndrome

Hepatobiliary disorders:
Very rare: Fatal hepatitis, jaundice

Skin and subcutaneous tissue disorders:
Uncommon: Photosensitive reactions, rash, pruritus
Very rare: Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necolysis, alopecia, photosensitive reactions where the skin looks like porphyria cutanea tarda or epidermolysis bullosa
Not known frequency: Angioedema, Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4), fixed drug eruption

Renal and urinary disorders:
Very rare: Haematuria, glomerular nephritis, interstitial nephritis, renal papillary necrosis, nephrotic syndrome
Not known frequency: Renal impairment

Reproductive system and breast disorders:
Not known frequency: Impaired female fertility (see section 4.6)

General disorders and administration site conditions:
Not known frequency: Mild peripheral oedema

Oedema, hypertension and heart failure have been reported in association with NSAID treatment.

Clinical trial data and epidemiological data suggest that use of some NSAIDs, especially at high doses and in long term treatment may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke)(see section 4.4).

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Symptoms of overdose may include: nausea, vomiting, stomach pain, drowsiness (coma at very serious intoxications), dizziness, disorientation, diarrhoea, gastrointestinal bleeding, hypernatremia, convulsions (rarely), effects on liver and kidneys, hypotension, respiratory depression, cyanoses and metabolic acidosis.

Treatment
Treatment consists initially of avoiding absorption by giving activated charcoal. With large amounts, gastric lavage is indicated only within one hour after intake of naproxen. Further treatment is supportive and symptomatic.
Haemodialysis does not reduce the plasma concentration of <Invented Name>, due to the high protein binding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory and antirheumatic products, non-steroids, propionic acid derivatives, ATC code: M01A E02.

Naproxen sodium is an NSAID (a non-steroidal, anti-inflammatory drug). It is a non-narcotic analgesic with mostly an anti-inflammatory and antipyretic effect. As with other NSAIDs, it works by inhibiting prostaglandin synthetase. The exact mechanism of the anti-inflammatory and analgesic effect is not known.

5.2 Pharmacokinetic properties

Naproxen sodium is easily soluble in water and when taken orally, is rapidly and completely absorbed from the gastrointestinal tract. After intake on an empty stomach, peak plasma levels are achieved after 1-2 hours. An average elimination half-life of naproxen is in the magnitude of 13 to 17 hours. In therapeutic doses more than 99% is bound to serum albumin. Ca. 95% of a naproxen sodium dose is excreted in the urine as unchanged naproxen, 6-O-desmethylnaproxen and its conjugates. With increasing dosage the urinary excretion is faster than could be expected based on linear processes.

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 seet 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 does 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

Macrogol 600
Lactic acid
Propylene glycol
Povidone K-30
Capsule shell:
Gelatin
Sorbitol, liquid, partially dehydrated
Glycerol
Purified water
Patent blue V (E131)
Processing aids:
Triglyceride
Isopropyl alcohol
Lecithin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate.

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Blister formed of PVDC/PE/PVC//Alu packed into carton.
Pack sizes of 3, 10, 12, 20 or 24 capsules in blister.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma BV
Baarnsche Dijk 1
3741 LN Baarn

8. MARKETING AUTHORISATION NUMBER

RVG 118864

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

Datum van eerste verlening van de vergunning: 28 september 2017

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 4.2 t/m 4.5, 4.7 t/m 4.9, 5.2: 12 december 2024