SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NAPRIUS 500 mg Tablets
NAPRIUS 500 mg Granules for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

500 mg Tablets
Each tablet contains:
- Naproxen 500 mg

500 mg Granules for oral suspension
Each sachet contains:
- Naproxen 500 mg

For the complete list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Tablets, Granules for oral suspension

4. CLINICAL INFORMATION

4.1. Therapeutic Indications

Analgesic, antipyretic, long-acting anti-inflammatory and therefore it founds application in the treatment of arthritis and polyarthritis, rheumatoid arthritis, gouty arthropathy, ankylosing spondylitis, neuralgia, myalgia.

4.2. Posology and method of administration

The side effects can be minimized with the use of the lowest effective dose for the shortest possible duration of treatment necessary to control the symptoms (see section 4.4).

Adults:

The initial dose of NAPRIUS is 500-1000 mg/day, divided into two doses, at 12 hours interval.
Therefore according to the intesity of symptoms and respons of patient, a dose of 250 or 500mg is administered, so in the morning at breakfast, as in the evening at dinner.
The maximum dose of 1000mg/day is indicated especially in patients with severe pain during night and/or morning stiffness, in bouts of rheumatoid arthritis, in patients previously treated unsuccessfully with other antirheumatic drugs at high-dose and in osteoarthritis, when the pain is the predominant symptom.
Once obtained the remission of symptoms, the dose may be reduced to 750-500mg or even less, in two divided doses at 12 hours interval.
When from subdivision a different measure of dose results (for example 500 + 250 mg), the greater one should be given in the morning or evening, depending on the prevalence of symptoms during the day or night.
In acute gout attacks, it is recommended a loading dose of 500 mg followed by 250 mg every 8 hours during the first 24 hours, then passing to maintenance doses of 250 mg twice a day for 6-7 days.
The granules contained in the sachets suitably dissolved in water, allow a more rapid absorption of the active substance and play a more ready analgesic action, moreover thay are more suitable for patients with swallowing difficulties and/or digestive disorders.

4.3. Contraindications

History of gastrointestinal bleeding or perforation related to previous active treatements or history of bleeding/recurrent peptic ulcer (two or more distinct episodes of proven ulceration or bleeding).
The product should not be administered in cases of gastroduodenal ulcer and peptic ulcer in place, in ulcerative colitis.
Severe heart failure.
Hypersensitivity to the active substance or to any of the excipients.
Because of the possibility of cross-sensitivity, Naprius is contraindicated in patients in whom acetylsalicylic acid and/or other NSAIDs induce symptoms of allergies, such as asthma, urticaria, rhinitis, anaphylactic or anaphylactoid reactions.
Use of this product is not foreseen in children, unless, in the judgment of the physician in cases of absolute necessity.
The product is contraindicated also during pregnancy and lactation.

4.4. Special warnings and precautions for use

Special warnings:
Patients whose activities require alertness should use caution if they would note dizziness, drowsiness or dizziness, or depression during therapy with naproxen.
Precautions for use:
Undesirable effects may be minimized by using the lowest effective dose for the shortest duration of treatment necessary to control symptoms (see section 4.2 and below paragraphs about GI and cardiovascular risks).

Cardiovascular and cerebrovascular effects
An appropriate monitoring and instructions are required for patients with a history of hypertension and/or from mild to moderate congestive heart failure, as in association with treatment with NSAIDs fluid retention and edema 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).
Although some data suggest that the use of naproxen (1000 mg /day) may be associated with a lower risk, some risks can not be excluded.
Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease should be treated with naproxen only after careful evaluation. Similar considerations should be made before initiating a long-term treatment in patients with risk factors for cardiovascular events (for example hypertension, hyperlipidemia, diabetes mellitus, smoking).
The use of NAPRIUS should be avoided with concomitant NSAIDs and COX-2 selective inhibitors.
Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and gastrointestinal perforation which may be fatal (see section 4.3).
Gastrointestinal bleeding, ulceration and perforation: during treatment with all NSAIDs at any time, with or without warning symptoms or a previous history of serious GI events, GI bleeding, ulceration or perforation, which can be fatal, were reported.
In the elderly and in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), the risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses. These patients should start treatment with the lowest available dose. Concomitant use of protective agents (misoprostol or proton pump inhibitors) should be considered for these patients and also for patients requiring concomitant low dose of aspirin, or other drugs that may increase the risk of gastrointestinal events (see below and section 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) 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 anti-platelet agents such as aspirin (see section 4.5).
When GI bleeding or ulceration occurs in patients receiving NAPRIUS, treatment should be discontinued.
NSAIDs should be administered with caution in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as these conditions may be exacerbated (see section 4.8).
Caution should be exercised in patients with a history of hypertension and/or heart failure because, in association with NSAID therapy, fluid retention and edema have been reported.
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). In the early stages of therapy, patients appear to be at highest risk of the onset of the reaction occurring in the majority of cases within the first month of treatment. NAPRIUS should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of hypersensitivity.
The use of NAPRIUS, as with all medications inhibiting the synthesis of prostaglandins and cyclooxygenase is not recommended in women who intend to become pregnant.
The administration of NAPRIUS should be discontinued in women who have fertility problems or undergoing fertility tests.
In some patients receiving naproxen were found occasionally even serious gastrointestinal bleeding and peptic ulcer.
Such events are rare, but patients with acute inflammatory diseases in place of the gastrointestinal tract or medical history or who have complained gastrointestinal disorders as a result of other antirheumatic drugs, the treatment should be carried out only under strict medical supervision.
A similar caution should be exercised in treating patients with greatly reduced functionality of heart, liver or kidney.
In such patients regular monitoring of clinical and laboratory parameters should be monitored, especially in the case of prolonged treatment.
In particular, chronic treatment with NAPRIUS is not recommended in patients with creatinine clearance below 20 ml/minute. Patients with hepatic impairment should be treated with the lowest effective dose.
Like other NSAIDs, naproxen should be used with caution in patients with allergic reactions in place or at anamnesis as it can cause bronchospasm, asthma and other allergic reactions.
Having detected ocular changes during animal studies with NSAIDs, it is recommended in case of prolonged treatment, to make periodic ophthalmologic controls.
NAPRIUS may decrease platelet aggregation and prolong bleeding time.

4.5. Interactions with other medicinal products and other forms of interaction

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
Anticoagulants: NSAIDs may enhance the effects of anticoagulants, such as warfarin (see section 4.4).
Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).
It was reported a decrease in natriuretic effect of furosemide after co-administration with some NSAIDs.
The association of these drugs with lithium leads to a decrease of renal clearance and consequent increase in the plasma concentration of the latter.
NAPRIUS, like other NSAIDs, may reduce the antihypertensive effect of propranolol and other beta-blockers.
Probenecid, given simultaneously with NAPRIUS, increases its plasma levels and significantly increases its half-life.
Combination with methotrexate should be used with caution since, in animal models, it has been reported that naproxen reduces the tubular secretion of methotrexate.

Naproxen should not be used simultaneously to its salt (naproxen sodium) or vice versa as they both circulate in the blood in anionic form.
It is not recommended concomitant use with acetylsalicylic acid or other NSAIDs.
NAPRIUS can be used simultaneously to gold salts and/or corticosteroids.

Since interactions were observed between NSAIDs and drugs highly bound to proteins, such as hydantoin, sulfa drugs and anticoagulants, barbiturates, patients receiving concomitantly NAPRIUS and these drugs should be observed in order to exclude the effects of overdose.
In patients treated with other NSAIDs and coumarin anticoagulants, increase in prothrombin time and decreased platelet aggregation were observed.
It is suggested that therapy with NAPRIUS should be temporarily suspended 48 hours before doing adrenal function tests since NAPRIUS may interfere with some tests for steroids 17-ketogens.
Similarly NAPRIUS may interfere with some tests for urinary 5-hydroxyindoleacetic acid. Avoid taking alcohol.
Naproxen may decrease the effectiveness of intrauterine devices.
It is not recommended the use of non-steroidal anti-inflammatory drugs concomitantly with quinolones.

Acetylsalicilic 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. Pregnancy and lactation

Pregnancy
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development. Results of 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 of cardiac malformations increased from less than 1% to about 1.5%. It was found that the risk increases with dose and duration of therapy. In animals, administration of inhibitors of prostaglandin synthesis has shown to cause an increase in the loss of pre- and post-implantation, and embryo-fetal mortality. Furthermore, an increased incidence of various malformations, including cardiovascular, has been reported in animals to which inhibitors of prostaglandin synthesis were administered during the organogenesis period.

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

the mother and newborn, at the end of pregnancy, to:
- possible prolongation of bleeding time, and antiplatelet effects which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labor.

The use of the drug close to delivery may result in the delay of birth; in addition, the drug can cause, when administered during this period, changes in haemodynamics of the small circle of the baby with serious consequences for breathing.
The product is contraindicated during pregnancy and lactation.

4.7. Effects on ability to drive and use machinery

Patients whose activities require alertness should use caution if they would notice dizziness, drowsiness or dizziness, or depression during therapy with naproxen.

4.8. Undesirable effects

Gastrointestinal: The most commonly observed adverse events are of gastrointestinal nature. You may experience peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly (see section 4.4).

After administration of NAPRIUS have been reported: nausea, vomiting, diarrhea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4).

Less frequently, gastritis has been observed.

In association with NSAIDs treatment, edema, hypertension and heart failure have been reported.

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) (see Section 4.4).

Bullous reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis (very rarely).

Among the gastrointestinal effects, the most commonly observed ones include: nausea, vomiting, abdominal and epigastric pain, gastric pyrosis, dyspepsia, constipation, diarrhea, stomatitis.

Occasionally you may experience GI bleeding, peptic ulcers and colitis.

At level of Central Nervous System may occur, headache, drowsiness, insomnia, and difficulty in concentrating. At level of skin were observed rash, itching, bruising, urticaria, angioedema. Have been reported rarely hypersensitivity reactions to naproxen and naproxen sodium, eosinophilic pneumonia, erythema multiforme, Stevens-Johnson syndrome, epidermo-necrolysis, photosensitivity reactions, bronchospasm, laryngeal edema.

The cardiovascular effects reported are tachycardia, dyspnea, peripheral edema and mild heart failure.

Occasionally there have been alterations in the hematopoietic system such as thrombocytopenia, granulocytopenia, aplastic or hemolytic anemia.

They may also experience hearing and vision problems, ear buzzing, dizziness, jaundice, severe hepatitis, renal impairment, haematuria, ulcerative stomatitis, aseptic meningitis, vasculitis, thirst, abnormal liver function tests.

Have been reported rarely: alopecia, seizures, hyperkalemia.

As with other NSAIDs, anaphylactic or severe anaphylactoid reactions in patients with or without previous exposure to drugs of this class can occur.

4.9. Overdosage

Overdose symptoms may occur as lethargy, gastric pyrosis, indigestion, nausea or vomiting.

If of a large amount of naproxen is ingested, accidental or voluntary, you must perform gastric emptying and implement the normal measures required in these cases.

Researches on animal indicate that the prompt administration of an adequate amount of activated carbon significantly reduces the absorption of the drug.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamics properties

- Pharmacotherapeutic Group: Anti-inflammatory, anti-rheumatic drugs. ATC Code: M01AE02
- Pharmacodynamic effects:
  Anti-inflammatory - Analgesic and Antipyretic.

5.2. Pharmacokinetics properties

- Absorption:

After oral administration, naproxen is completely re-absorbed.
The profile of concentrations after intake of the product shows that plasma concentrations increase with the increase of doses (proportionality to the dose of 500mg), achieve therapeutically significant levels quickly with a half-life of about 12-15 hours.
The steady-state is reached after 4-5 administrations.

- Distribution:
  The binding to plasmatic proteins is higher than 99%.
  Naproxen reaches therapeutically significant levels either in the liquid and in the synovial membrane.
  Naproxen crosses placental barrier.
- Biotransformation:
  About 30% is transformed at hepatic level into the 6-demethyl-naproxen metabolite (demetyilated naproxen), practically inactive.
- Excretion:
  Naproxen is excreted through urine, partially immodified (about 10%) and partially coniugated with glucuronic acid.
  Demetyilated naproxen is excreted as free and coniugated forms.

5.3. Safety preclinical data

Preclinical data show absence of risks for humans on the basis of safety pharmacology conventional studies, repeated administrations toxicity, genotoxicity and carcinogenic potential.
No further information are available about preclinical data, in addition to those already reported in this Summary of Product Characteristics. (see section 4.6).

6. PHARMACEUTICAL INFORMATION

6.1. List of excipients

Tablets:
Lactose, Maize starch, Polyvinylpyrrolidone, Magnesium stearate.

Granules for olra suspension:
Mannite, Sodium chloride, Ammonium glycyrrhizinate, Mint flavor, Mint anise flavor, Sodium dioctylsulphosuccinate, Sucrose, Polyvinylpyrrolidone.

- **Additional notes:**

Tablets

- The product contains 4.68g of lactose. When administered according to the recommended posology, each dose gives till 156 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficit, or glucose-galctose malabsoprtion, must not take this medicine.

Granules for oral suspension

- The product contains 65g of sucrose. When administered according to the recommended posology, each dose gives till 3.250g of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galctose malabsoprtion, or o da sucrase isomaltase insufficency, must not take this medicine.

6.2. Incompatibilities

Not known.

6.3. Shelf-life

5 years, in unopened package.

6.4. Special precautions for conservation

No special precautions for conservation.

6.5. Nature and content of package

Aluminium and PVC, containing tablets.
Heat-sealed sachets, made of Aluminium and PVC, containing granules for oral suspension.
500 mg Tablets- 30 Tablets
500 mg Granules for oral suspension - 20 sachets

6.6. Special precautions for disposal and handling

No special instructions.

7. MARKETING AUTHORIZATION HOLDER

AESCULAPIUS FARMACEUTICI S.r.l. - Via Cefalonia, 70 - 25124 BRESCIA.

8. MARKETING AUTHORIZATION NUMBER

500 mg Tablets - 30 tablets	M.A. no. 024667139
500 mg Granules for oral suspension - 20 sachets	M.A. no. 024667154

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

Renewal date: June 2010

10. DATE OF REVISION OF THE TEXT

September 2018