SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Naproxen "Grünenthal" 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 500 mg naproxen.

For a complete list of the other ingredients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

4. CLINICAL PARTICULARS

4.1. Indications

Symptomatic treatment of pain and inflammation in
- Acute arthritis (including gout)
- Chronic arthritis, in particular rheumatoid arthritis
- Ankylosing spondylitis and other inflammatory rheumatic spinal diseases
- Irritation in arthritis and spondylarthritis
- Fibrositis
- Painful swelling or inflammation after injury.

4.2. Dosage, Mode and Duration of Administration

Single and Daily Dosage

Dosage in adults
Depending on the nature and severity of the disease (see below), the recommended daily dosage for adults is 500-1250 mg naproxen, divided into 1-3 single doses. A single dose of 1000 mg naproxen should not be exceeded.

Unless otherwise prescribed, the following dosage is recommended:

Rheumatic diseases
The daily dose is generally 1-1½ Naproxen "Grünenthal" 500 mg film-coated tablets (equivalent to 500–750 mg naproxen).

At the beginning of treatment, in acute flares, or when switching from another high-dosed anti-inflammatory agent to Naproxen "Grünenthal" 500 mg film-coated tablets, a dose of 1½ Naproxen "Grünenthal" 500 mg film-coated tablets (equivalent to 750 mg naproxen) daily is recommended, divided into two single doses (one Naproxen "Grünenthal" 500 mg film-coated tablet in the morning, half a tablet in the evening or vice versa) or in a single dose (either mornings or evenings).

In isolated cases the daily dose can be raised to two Naproxen "Grünenthal" 500 mg film-coated tablets (equivalent to 1000 mg naproxen).

The maintenance dose is one Naproxen "Grünenthal" 500 mg film-coated tablet (equivalent to 500 mg naproxen daily), which can be divided into two single doses (mornings and evenings) of half a Naproxen "Grünenthal" 500 mg film-coated tablet or in one (either mornings or evenings).

Acute gout
Treatment starts with a single dose of 1½ Naproxen "Grünenthal" 500 mg film-coated tablets (equivalent to 750 mg naproxen), then half a Naproxen "Grünenthal" 500 mg film-coated tablet (equivalent to 250 mg naproxen) every eight hours until the symptoms have subsided.

Posttraumatic swelling and pain
Treatment starts with a single dose of one Naproxen "Grünenthal" 500 mg film-coated tablet (equivalent to 500 mg naproxen) taken in one and then half a Naproxen "Grünenthal" 500 mg film-coated tablet (equivalent to 250 mg naproxen) every 6-8 hours.

Naproxen "Grünenthal" 500 mg film-coated tablets are not suitable for children or adolescents because the amount of the active substance is too high.

Mode and duration of administration
Naproxen "Grünenthal" 500 mg film-coated tablets should be swallowed whole preferably before a meal with plenty of liquid (in the event of acute symptoms, also on an empty stomach). Intake with meals may delay absorption.

The physician is to decide on the duration of the treatment.

In rheumatic diseases long-term administration of Naproxen "Grünenthal" 500 mg film-coated tablets may be necessary.

Side-effects may be reduced by giving the lowest effective dose over the shortest period necessary to manage the symptoms (see section 4.4).

In primary dysmenorrhoea and after insertion of an intra-uterine pessary the duration of treatment depends on the symptoms. However, Naproxen "Grünenthal" 500 mg film-coated tablets should only be taken for a few days. If the complaints persist, a physician should be consulted.

Special Patient Groups

Elderly patients
Special dose adjustment is not necessary. In view of the possible side-effect profile elderly patients should be monitored with special care (see section 4.4).

Impaired renal function
In patients with slightly to moderately impaired renal function it is not necessary to reduce the dose (for patients with severe renal insufficiency see sections 4.3 and 5.2).

Impaired hepatic function
In patients with slightly to moderately impaired hepatic function it is not necessary to reduce the dose. (For patients with severely impaired hepatic function see sections 4.3 and 5.2.)

4.3. Contraindications

Naproxen "Grünenthal" 500 mg film-coated tablets must not be used in
- known hypersensitivity to the active substance naproxen or one of the other components of the medicinal product;
- history of reactions of bronchospasms, asthma, rhinitis or urticaria after administration of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs;
- unexplained dyshaematopoiesis;
- existing or previous recurrence of peptic ulcers or haemorrhage (at least two distinctive episodes of proven ulceration or haemorrhage);
- history of gastrointestinal haemorrhage or perforation in connection with previous treatment with non-steroidal anti-inflammatory drugs (NSAID);
- cerebrovascular or other active haemorrhage;
- severe hepatic or renal function disorders;
- severe cardiac insufficiency;
- pregnancy, in the last three months (see section 4.6).

Children and adolescents must not take Naproxen "Grünenthal" 500 mg film-coated tablets on account of the high content of the active ingredient.

4.4. Special Precautions and Warnings

Gastrointestinal safety

Naproxen "Grünenthal" 500 mg film-coated tablets should not be combined with NSAIDs, incl. selective cyclo-oxygenase-2 inhibitors.

Side-effects may be reduced by giving the lowest effective dose over the shortest period necessary to manage the symptoms (see section 4.2 and gastrointestinal and cardiovascular risks below).

Elderly patients
In elderly patients the incidence of adverse events during NSAID treatment is higher, in particular gastrointestinal haemorrhage and perforation, in some cases with a fatal outcome (see section 4.2).

Gastrointestinal haemorrhage, ulcers and perforation
Gastrointestinal haemorrhage, ulcers or perforation, in some cases with a fatal outcome, have been reported with all NSAIDs. They occurred at any time during therapy with or without any warning signs or a history of severe gastrointestinal events.

The risk of gastrointestinal haemorrhage, ulceration or perforation is higher with increasing doses of the NSAID, in patients with a history of ulcers, in particular with complications of haemorrhage or perforation (see section 4.3), and in elderly or debilitated patients. These patients should start with the lowest available dose.

In these patients and those requiring concomitant treatment with low-dosed acetylalicylic acid (ASA) or other drugs that may increase the gastrointestinal risk (see section 4.5), combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered (see below and section 4.5).

Patients with a history of gastrointestinal toxicity, in particular in old age, should report any unusual abdominal symptoms (in particular gastrointestinal haemorrhage), especially at the start of treatment.

Care should be taken in patients concomitantly taking drugs that may increase the risk of ulcers or haemorrhage, e.g. oral corticosteroids, anticoagulants such as warfarin, selective serotonin re-uptake inhibitors or thrombocyte aggregation inhibitors such as ASA (see section 4.5).

If gastrointestinal haemorrhage or ulcers occur during treatment with Naproxen "Grünenthal" 500 mg film-coated tablets, treatment is to be terminated.

In patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) NSAIDs should only be used with care, as the patient's condition may deteriorate (see section 4.8).

<u>Cardiovascular and cerebrovascular effects</u>

Suitable monitoring and counselling of patients with a history of hypertension and/or mild to moderate cardiac decompensation are necessary, fluid accumulation and oedema have been reported in connection with NSAID therapy.

Clinical studies and epidemiological data suggest that the use of coxibs and some NSAIDs (in particular in high doses and on long-term treatment) may be associated with a slightly increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke). Although data suggest that the use of naproxen (1000 mg daily) may be associated with a lower risk, such an effect cannot be ruled out.

Patients with refractory hypertension, cardiac insufficiency, ischaemic heart disease, peripheral arterial and/or cerebrovascular disease should only be treated with naproxen after careful consideration of the benefit/risk ratio. Such considerations should also be made before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Dermal reactions

During NSAID treatment there have been very rare reports of severe dermal reactions, in some cases with a fatal outcome, including exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome) (see section 4.8). The risk of such reactions appears to be highest at the start of treatment, as in the majority of cases these reactions occurred in the first month of treatment. At the first sign of rash, mucosal lesions or other signs of hypersensitivity Naproxen "Grünenthal" 500 mg film-coated tablets should be withdrawn.

Other Points

Naproxen "Grünenthal" 500 mg film-coated tablets should only be given after careful consideration of the benefit/risk ratio in
- acquired porphyria
- systemic lupus erythematosus (SLE) and mixed connective tissue disease (see section 4.8).

Particularly careful medical supervision is necessary in
- patients with a history of gastrointestinal disorders or chronic intestinal inflammation (ulcerative colitis, Crohn's disease);
- hypertension or cardiac insufficiency;
- impaired renal function;
- liver function disorders;
- immediately after major surgery.
- patients suffering from hay-fever, nasal polyps or chronic obstructive respiratory tract diseases, as they have an increased risk of allergic reactions. These may be in the form of asthma attacks ("analgesic asthma"), angioneurotic oedema or urticaria;
- special care is also necessary in patients who are allergic to other substances, because there is also an increased risk of allergic reactions on administration of Naproxen "Grünenthal" 500 mg film-coated tablets.
- concomitant administration of more than 15 mg methotrexate per week.

Severe acute hypersensitivity reactions (e.g. anaphylactic shock) are very rare. On the first signs of a hypersensitivity reaction after administration of Naproxen "Grünenthal" 500 mg film-coated tablets treatment must be terminated. The appropriate medical steps must be taken by experts.

Long-term administration of analgesics may give rise to headache that must not be treated by increasing the dose.

In general, habitual intake of analgesics, in particular combined with several analgesic substances, may lead to permanent renal damage with the risk of kidney failure (analgesic nephropathy).

Patients experiencing visual disorders during treatment with naproxen should undergo an ophthalmological examination.

Concomitant use of NSAIDs and alcohol may intensify substance-related side-effects, particularly those affecting the gastrointestinal tract or central nervous system.

As regards female fertility see section 4.6.

Naproxen, the active substance of Naproxen "Grünenthal" 500 mg film-coated tablets, may transiently inhibit blood platelet function (thrombocyte aggregation). Therefore patients with coagulation disorders should be carefully monitored.

On the concomitant administration of Naproxen "Grünenthal" 500 mg film-coated tablets and lithium preparations (drugs for the treatment of psychological diseases) or certain diuretics (potassium-sparing diuretics), lithium and potassium concentrations in the blood must be checked (see 4.5).

On long-term administration of Naproxen "Grünenthal" 500 mg film-coated tablets, liver values, renal function and the blood picture must be checked at regular intervals.

4.5. Interactions with Other Medicinal Products and Other Forms of Interaction

On concomitant administration of Naproxen "Grünenthal" 500 mg film-coated tablets with preparations containing digoxin, phenytoin or lithium the serum levels of these medicines may increase. Serum lithium levels must be checked.

Naproxen "Grünenthal" 500 mg film-coated tablets may attenuate the effect of diuretics and antihypertensive agents.

Naproxen "Grünenthal" 500 mg film-coated tablets may attenuate the effect of ACE inhibitors. On concomitant administration the risk of renal function disorders may be raised.

The concomitant administration of Naproxen "Grünenthal" 500 mg film-coated tablets and potassium-sparing diuretics may induce hyperkalaemia. Therefore blood potassium values must be checked.

The concomitant administration of Naproxen "Grünenthal" 500 mg film-coated tablets and acetylsalicylic acid or other non-steroidal anti-inflammatory drugs, thrombocyte aggregation inhibitors, selective serotonin re-uptake inhibitors and glucocorticoids increases the risk of gastrointestinal ulcers and gastrointestinal haemorrhage (see 4.4).

The administration of Naproxen "Grünenthal" 500 mg film-coated tablets within 24 hours before or after methotrexate may raise the concentration of methotrexate in the blood and increase its toxic effects.

Non-steroidal anti-inflammatory agents (such as naproxen) may increase the nephrotoxicity of ciclosporin.

Medicines containing probenecid or sulfinpyrazone may delay the excretion of naproxen.

The administration of antacids may reduce the absorption of Naproxen "Grünenthal" 500 mg film-coated tablets.

NSAIDs may intensify the effect of anticoagulants such as warfarin (see 4.4). On concomitant treatment coagulation values should be checked.

Clinical studies have so far not shown any interactions between naproxen and oral antidiabetics. Nevertheless, your blood sugar levels should be checked if you take these drugs at the same time.

Note on laboratory tests
Naproxen "Grünenthal" 500 mg film-coated tablets may influence platelet aggregation and prolong bleeding time. This effect should be taken into account when determining the bleeding time.

4.6. Pregnancy and Lactation

Pregnancy

Inhibition of prostaglandin synthesis may have negative effects on pregnancy and/or embryo-foetal development. Data from epidemiological studies indicate an increased risk of miscarriage, cardiac anomalies and gastroschisis after administration of prostaglandin synthesis inhibitors in the early phases of pregnancy. Presumably the risk increases with the dose and duration of treatment.

Animal studies have shown that the administration of a prostaglandin synthesis inhibitor increases pre- and postimplantation loss and embryo-foetal mortality. There have also been reports of increased incidences of various anomalies, including cardiovascular anomalies, in animals given prostaglandin synthesis inhibitors during the organogenetic phase.

In the first six months of pregnancy naproxen should only be given if absolutely necessary. If naproxen is given to a woman who is trying to become pregnant or during the first six months of pregnancy, the dose should be kept as low as possible and the duration of treatment as short as possible.

During the last three months of pregnancy all prostaglandin synthesis inhibitors may:
- expose the foetus to the following risks:
    - cardiopulmonary toxicity (with premature occlusion of the ductus arteriosus and pulmonary hypertension);
    - renal function disorders leading to renal failure and oligohydramnios;
- expose the mother and child to the following risks at the end of pregnancy:
    - possible prolongation of the bleeding time, an effect inhibiting thrombocyte aggregation, which may occur even with very low doses;
    - inhibition of uterine contractions resulting in delayed or prolonged delivery.

Therefore naproxen is contraindicated in the last three months of pregnancy.

Naproxen "Grünenthal" 500 mg film-coated tablets should not be used during puerperium on account of delayed uterine devolution and intensified postpartum haemorrhage.

Lactation

Small amounts of naproxen pass into the breast milk. As a precaution Naproxen "Grünenthal" 500 mg film-coated tablets should not be taken during lactation.

Fertility

As with other medicinal products that are known to inhibit cyclo-oxygenase/prostaglandin synthesis, Naproxen "Grünenthal" 500 mg film-coated tablets may affect fertility, and therefore treatment in women who wish to become pregnant is not recommended. In women who have difficulty in becoming pregnant or have undergone infertility examinations, discontinuation of Naproxen "Grünenthal" 500 mg film-coated tablets should be considered.

4.7. Effects on Ability to Drive and Operate Machinery

Central nervous side-effects such as fatigue and dizziness may occur during treatment with high doses of Naproxen "Grünenthal" 500 mg film-coated tablets, and therefore reaction time may be altered in isolated cases and the ability to drive and/or operate machinery may be affected. This applies particularly in conjunction with alcohol.

Once-only or short-term use of Naproxen "Grünenthal" 500 mg film-coated tablets as an analgesic does not require any special precautions.

4.8. Side-effects

The following terms are used to assess the incidence of side-effects:

Very common *≥ 10% of those treated*	***Common*** *< 10%, but ≥ 1% of those treated*
Uncommon *< 1%, but ≥ 0.1% of those treated*	***Rare*** *< 0.1%, but ≥ 0.01% of those treated*
Very rare *< 0.01% of those treated or incidence unknown*	

With the following adverse drug reactions it must be taken into account that they are mainly dose-dependent and vary interindividually.

The most common side-effects are those affecting the digestive tract. Peptic ulcers, perforation or haemorrhage, in some cases fatal, may occur, particularly in elderly patients (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, digestion problems, abdominal pain, tarry stools, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported after use. Gastritis has been observed less frequently.

In particular the risk of gastrointestinal haemorrhage depends on the dose and duration of treatment.

Oedema, hypertension and cardiac insufficiency have been reported in connection with NSAID treatment.

Clinical studies and epidemiological data suggest that the use of some NSAIDs (in particular in high doses and on long-term treatment) is associated with a slightly increased risk of arterial thrombotic events (e.g. myocardial infarction or stroke) (see section 4.4).

<u>Cardiac diseases</u>

Very rare
- Cardiac insufficiency
- Hypertension

<u>Diseases of the blood and lymphatic system</u>
Uncommon
- Blood picture disorders.

Very rare
- Dyshaematopoiesis (aplastic anaemia, leukopenia, thrombocytopenia, pancytoenia, agranulocytosis). Prodromal symptoms may be fever, sore throat, superficial oral lesions, influenza-like symptoms, severe lassitude, nasal and dermal haemorrhage. On long-term treatment the blood picture should be regularly checked.
- Haemolytic anaemia.

Diseases of the nervous system
Common
- Headache, dizziness, insomnia, agitation, irritability or fatigue.

Ocular diseases
Common
- Visual disorders

Diseases of the ears and labyrinth
Common
- Auditory disorders, tinnitus

Gastrointestinal diseases
Very common
- Gastrointestinal complaints, e.g. nausea, vomiting, heartburn, stomach ache, bloating, constipation or diarrhoea, and minor loss of gastrointestinal blood, which may cause anaemia in isolated cases.

Common
- Gastrointestinal ulcers (possibly with haemorrhage and perforation).

Uncommon
- Haematemesis, melaena or bloody diarrhoea, lower abdominal complaints (e.g. haemorrhagic colitis or exacerbation of Crohn's disease/ulcerative colitis), stomatitis, oesophageal lesions.

  In the event of these symptoms the patient is to be instructed to discontinue the medicinal product and consult a physician immediately.

Diseases of the kidneys and urinary tract
Common
- Peripheral oedema, particularly in patients with hypertension.

Uncommon
- Reduced urine excretion.
- Acute renal failure, nephrotic syndrome or interstitial nephritis.

Very rare
- Renal damage (papillary necrosis), in particular on long-term treatment, hyperuricaemia.

Renal function should be checked regularly.

Diseases of the skin and subcutaneous tissues
Uncommon
- Increased photosensitivity (including blister formation), alopecia (mostly reversible).

Very rare
- Bullous dermal reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (Lyell syndrome).

Infections and parasitic diseases

There have been very rare reports of a deterioration in infectious diseases (e.g. development of necrotising fasciitis) in a temporal connection with the systemic administration of non-steroidal anti-inflammatory agents.

This may possibly be connected with the mechanism of action of non-steroidal anti-inflammatory agents.

If during administration of Naproxen "Grünenthal" 500 mg film-coated tablets signs of an infection recur or deteriorate, the patient should be requested to consult a physician immediately, who must check whether anti-infective/antibiotic treatment is indicated.

Very rare
- Symptoms of aseptic meningitis with severe headache, nausea, vomiting, fever, stiff neck or disorientation.

  Patients with auto-immune diseases (SLE, mixed connective tissue disease) seem to be predisposed.

Diseases of the immune system
Common
- Hypersensitivity reactions with exanthema, pruritus, purpura or ecchymosis.

Very rare
- Severe hypersensitivity reactions (e.g. angioneurotic syndrome). Signs of these may be swollen face, tongue and throat (oedema), dyspnoea, tachycardia, severe cardiovascular disorders up to life-threatening shock.

  On the occurrence of these manifestations immediate medical assistance is required.

Respiratory tract
Uncommon
- Asthma attacks (possibly with hypotension), bronchospasms, eosinophilic pneumonia.

Hepatic and biliary diseases
Uncommon
- Liver function disorders.

Very rare
- Liver damage, particularly on long-term treatment.

4.9. Overdose

Symptoms of an overdose
The symptoms of an overdose include central nervous disorders with headache, dizziness, muzziness, unconsciousness, abdominal pain, nausea and vomiting. Also gastrointestinal haemorrhage and liver and kidney function disorders are possible. Hypotension, respiratory depression and cyanosis may also occur.

Treatment of an overdose
There is no specific antidote. Treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

ATC code M01A E02.

Naproxen is a non-steroidal anti-inflammatory/analgesic agent which has proved to be effective by inhibiting prostaglandin synthesis in the usual animal experimental inflammation models. In humans, naproxen reduces inflammatory pain, swelling and fever.

5.2. Pharmacokinetic Properties

After oral administration a fraction of naproxen is already absorbed in the stomach and finally completely absorbed from the small intestine. After an oral dose of 250 mg naproxen in a normal-release formulation maximum plasma levels of about 35-40 µg/ml are reached after a mean of 2-4 hours. The necessary therapeutically effective plasma concentration is probably 15 µg/ml. The distribution volume is about 0.09 l/kg.

Plasma protein binding is about 99%.

Naproxen passes the placental barrier and is also secreted into the breast-milk.

After hepatic metabolism elimination is mainly renal. The extent of biliary excretion is not known.

After i.v. administration of 100 mg naproxen about 10% of the dose is excreted unchanged and about 60% is excreted via the kidneys in a conjugated form as glucuronide.

About 28% is demethylated to inactive 6-O-desmethylnaproxen, 5% appears unchanged and 22% in a conjugated form in the urine; only 0.1 - 3% is recovered in the faeces.

The elimination half-life in healthy volunteers and patients with kidney disease is 10-18 hours. However in some cases the elimination half-life is subject to considerable variations in progressive renal function disorders. Patients with impaired renal function tend to have lower plasma concentrations than persons with healthy kidneys. In pronounced impairment of kidney function (creatinine clearance 1-10 ml/min) the AUC (area under the plasma concentration curve) is reduced by about 50%.

In patients with restricted liver function clearance of the non-protein-bound fraction of naproxen is reduced by about 60%, the elimination half-life prolonged, and the plasma concentration raised compared to persons with healthy livers.

Absolute bioavailability after oral administration is greater than 90%.

5.3. Preclinical Safety Data

Acute toxicity
Acute toxicity tests in various animal species have shown no specific sensitivity. For symptoms of intoxication see 4.9.

Chronic toxicity
Subchronic and chronic toxicity tests with naproxen have been carried out on mice, rats, rabbits, dogs, mini-pigs and monkeys with daily oral administration for two weeks to 24 months. In the toxic dosage range gastrointestinal ulceration occurred. Kidney damage in the form of crystalline deposits in the renal tubules occurred in some animal species with an extremely high dosage.

Mutagenic and tumorigenic potential
The mutagenic potential has not been investigated in detail; tests carried out so far have been negative.
A long-term study in rats showed no evidence of a tumorigenic potential of naproxen.

Reproduction toxicity
Tests in three animal species (rats, mice, rabbits) showed no evidence of a teratogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of the Other Ingredients

Croscarmellose sodium, povidone K 90, magnesium stearate (Ph. Eur.), hypromellose, macrogol 400, macrogol 6000, propylene glycol, polysorbate 80, titanium dioxide (E 171), ferric oxide or hydroxide (E 172).

6.2. Incompatibilities

None known so far.

6.3. Shelf-life

The shelf-life is five years.

6.4. Special Precautions for Storage

None.

6.5. Nature and Contents of the Container

20 film-coated tablets (N1)
50 film-coated tablets (N2)
100 film-coated tablets (N3)

6.6. Special Precautions for Disposal and Other Handling Instructions

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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Tel. 0241 - 569-1 111
Fax 0241 - 569-1 112

8. MARKETING AUTHORISATION NUMBER(S)

13523.00.00

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/02/1994

10. DATE OF INFORMATION

March 2007

11. SALE RESTRICTIONS

Prescription-only.