Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Naproxen E.C. 375 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains Naproxen Ph. Eur. 375 mg.

3 PHARMACEUTICAL FORM

Gastro-resistant tablet

Naproxen E.C. 375mg Tablets: White, circular, biconvex, coated tablet embossed with the identifying marking “N375”. Diameter 11mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the management of various arthritides, such as rheumatoid arthritis, osteoarthritis, spondylitis, gout, etc., and of musculoskeletal disorders. For the management of juvenile polyarthritis and rheumatoid arthritis in children over the age of five years.

4.2 Posology and method of adminstration

For oral administration. Tablets should be swallowed whole and not broken or crushed.

Adults:

The usual dose is 250 mg twice daily, with a maximum daily dose of 1000 mg.

In the case of gout a dose of 750 mg may be required as an initial dose given once, with 250 mg every eight hours thereafter for a maximum of 72 hours. Subsequently use may be made of the usual regimen if necessary.

Children over the age of 5 years:

The usual total daily dose is 10 mg/kg b.w. in divided doses every 12 hours.

The safety of the drug in children under the age of 5 years has not been demonstrated and its use therefore cannot be recommended in this group.

4.3 Contraindications

1. Use in patients with peptic ulcer disease, active peptic ulceration or intestinal inflammatory disease.

2. Use in patients hypersensitive to naproxen or other non-steroidal anti-inflammatory agents including aspirin.

3. Use in children under 16 years of age except for juvenile rheumatoid arthritis.

4.4 Special warnings and special precautions for use

1. The product should only be used with great caution in patients with a history of, or existent, gastrointestinal disease, or in those with impaired liver function.

2. The product will prolong bleeding time and decrease platelet aggregation.

3. Because of its occasional tendency to induce fluid retention, use of the drug requires careful observation for this feature in persons with incipient or existent congestive failure.

4. Naproxen is mainly excreted through the kidney by glomerular filtration. It should only be used with caution in patients with renal dysfunction particularly if long term dosage is under consideration. Such patients with pre-existent renal dysfunction should have regular monitoring of serum creatinine or creatinine clearance. Prolonged use should be avoided in patients with a creatinine clearance - less than 20 ml/min.

5. Certain patients in whom renal blood flow is compromised such as in extracellular fluid volume depletion, cirrhosis of the liver, sodium retention, congestive heart failure, renal disease should have renal function assessed before and during therapy. Elderly patients in whom renal function is often impaired would also be included in this group. Consideration should be given to a reduction in daily dosage.

4.5 Interaction with other medicinal products and other forms of interaction

1. The product is highly bound to plasma protein so that caution should be exercised in use in patients concomitantly receiving other drugs strongly protein bound such as anticoagulants, sulphonamides, hydantoins.

2. Patients with established aspirin hypersensitivity may react similarly to naproxen. This is particularly of concern in those with asthma in whom bronchospasm may be precipitated.

3. Naproxen may interfere with some tests of 17-ketogenic steroids.

4.6 Pregnancy and lactation

Naproxen should not be used in pregnancy unless considered essential by the physician. There is no evidence of teratogenic effect in animal studies. The drug appears in the milk during lactation.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Side effects include rash, gastrointestinal upset, headache, tinnitus and vertigo. Jaundice with hepatitis, thrombocytopenia, aplastic and haemolytic anaemia have been reported rarely.

4.9 Overdose

Significant overdosage of the drug may be characterised by drowsiness, heartburn, indigestion, nausea or vomiting. A few patients have experienced seizures, but it was not determined whether these were naproxen-related or not. It is not known what dose of the drug would be life-threatening.

Should a patient ingest a large amount of Naproxen EC accidentally or purposefully, the stomach may be emptied and the usual supportive measures employed. Animal studies indicate that the prompt administration of activated charcoal in adequate amounts would tend to reduce markedly the absorption of the drug.

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

However, haemodialysis may still be appropriate in a patient with renal failure who has taken naproxen.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Naproxen is a non-steroidal anti-inflammatory agent, with analgesic and antipyretic properties. It exhibits its anti-inflammatory effect even in adrenalectomised animals, indicating that its action is not mediated through the pituitary-adrenal axis. It inhibits prostaglandin synthetase, as do other non-steroidal, anti-inflammatory agents. As with other agents, the exact mechanism of its anti-inflammatory action is not known.

5.2 Pharmacokinetic properties

Naproxen is readily absorbed from the gastro-intestinal tract, metabolised in the liver and excreted mainly in the urine with a half-life of 12 to 15 hours. At therapeutic levels, naproxen is greater than 99% protein bound. Plasma concentrations of naproxen increase proportionally up to about 500 mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. Naproxen has a plasma elimination half-life of about 13 hours. Approximately 95% of a dose is excreted in urine as naproxen and 6-O-desmethylnaproxen and their conjugates, the remainder being excreted via the faeces. Naproxen diffuses into synovial fluid; it crosses the placenta and is excreted in breast milk in small amounts.

5.3 Preclinical safety data

No evidence of tumorigenicity was found after a two-year study performed in rats at doses of 8, 16, and 24 mg/kg/day. The maximum dose was 0.28 times the systemic exposure to humans at the recommended dose.
Reproduction studies have been performed in rats at 20 mg/kg/day, rabbits at 20 mg/kg/day, and mice at 170 mg/kg/day with no evidence of impaired fertility or harm to the foetus due to the drug.
The oral LD50 of naproxen is 543 mg/kg in rats, 1234 mg/kg in mice, 4110 mg/kg in hamsters and greater than 1000 mg/kg in dogs.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Magnesium Stearate
Microcrystalline Cellulose
Povidone
Sodium Starch Glycollate

Enteric coating
Cellulose Acetate Phthalate
Castor Oil
Talc (micronised)

6.2 Incompatibilities

None Known.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Amber glass bottle with tamper evident polyethylene cap, polypropylene securitainer with tamper evident polyethylene cap, or PVC/Aluminium foil blister pack.

Pack sizes 30, 50, 100 or 250 tablets.

6.6 Instructions for use and handling

No special instructions.

7 MARKETING AUTHORISATION HOLDER

Olinka (UK) Limited,
38/40 Chamberlayne Road,
London, NW10 3JE,
England.

8 MARKETING AUTHORISATION NUMBER

PA 476/7/6

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th December 1991
Date of last renewal: 16th December 2001

10 DATE OF REVISION OF THE TEXT

December 2001