

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Gerinap E.C. 250mg Gastro-resistant Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of Naproxen.

Excipients: Each tablet contains 8 mg lactose monohydrate.

For a full list of excipients see section 6.1.

3 PHARMACEUTICAL FORM

Gastro-resistant tablets.

White, circular, biconvex tablets.

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 rheumatoid arthritis in children over the age of five years.

In the management of dysmenorrhoea.

4.2 Posology and method of administration

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (*see section 4.4, Special warnings and precautions for use*).

Gerinap EC tablets should be swallowed whole and not broken or crushed.

Adults

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

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

For dysmenorrhoea the usual initial dose is 500mg and thereafter 250mg every 6 to 8 hours.

Elderly

NSAIDs should be used with particular caution in elderly patients who are more prone to adverse events. The lowest dose compatible with adequate safe clinical control should be employed. See also (*see section 4.4, Special warnings and precautions for use*)

Treatment should be reviewed at regular intervals and discontinued if no benefit is seen or intolerance occurs.

Children over the age of 5 years

Gerinap EC is effective in the treatment of juvenile rheumatoid arthritis in children over 5 years of age at a dose of 10mg/kg/day taken in two doses at 12 hour intervals. Gerinap EC tablets are not recommended for use for any other indication in children under 16 years of age.

Children under the age of 5 years

The safety of Gerinap EC tablets in children under 5 years of age has not been established and therefore use is not recommended.

4.3 Contraindications

- a) Use in patients with peptic ulcer disease, active peptic ulceration or intestinal inflammatory disease.
- b) Use in patients hypersensitive to naproxen or other non-steroidal anti-inflammatory agents including aspirin.
- c) Severe heart failure
- d) 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).

4.4 Special warnings and precautions for use

The use of Gerinap EC with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Undesirable effects may be reduced by using the lowest effective dose for the shortest possible duration necessary to control symptoms (*see section 4.2, Posology and method of administration and GI and 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 NSAID therapy.

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 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 events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (*see section 4.2, Posology and method of administration*)

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforations is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (*See section 4.3, Contraindications*), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (*see below and section 4.5, Interaction with other medicinal products and other forms of interactions*).

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, Interaction with other medicinal products and other forms of interactions*).

When GI bleeding or ulceration occurs in patients receiving Gerinap EC, the treatment should be withdrawn.

Gerinap E.C. tablets should be used with caution in patients with a history of gastrointestinal disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated (*See section 4.8, Undesirable effects*).

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

The use of 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 infertility, withdrawal of naproxen should be considered.

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, Undesirable effects*). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases with the first month of treatment. Gerinap EC should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Care should be taken in patients treated with any of the following drugs as interactions have been reported:

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (*see section 4.4, Special warnings and precautions for use*)

Anti-hypertensives: reduced anti-hypertensive effect.

Diuretics: reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Lithium: decreased elimination of lithium.

Methotrexate: decreased elimination of methotrexate.

Cyclosporin: increased risk of nephrotoxicity with NSAIDs.

Other NSAIDs: avoid concomitant use of two or more NSAIDs.

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (*see section 4.4, Special warnings and precautions for use*).

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (*see section 4.4, Special warnings and precautions for use*)

Aminoglycosides: reduction in renal function in susceptible individuals decreased elimination of aminoglycoside and increased plasma concentrations.

Probenecid: reduction in metabolism and elimination of NSAID and metabolites.

Oral hypoglycemic agents: inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia.

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 and hydratoins.

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.

Naproxen may interfere with some tests of 17-ketogenic steroids and assays of urinary 5-hydroxyindoleacetic acid, it is advised that naproxen therapy be temporarily discontinued for 48 hours before adrenal function and other affected tests.

The natriuretic effect of frusemide has been reported to be inhibited by some drugs of this class. Also the anti-hypersensitive effect of propranolol and other beta-blockers may be reduced.

4.6 Pregnancy and lactation

There is inadequate evidence of safety of the drug in human pregnancy. As with other drugs of this type naproxen delays parturition in animals but the relevance of this finding to human patients is not known. It also effects the human foetal cardiovascular system by causing closure of the ductus arteriosus.

Gerinap EC should not be used in pregnancy unless considered essential by the physician. Naproxen has been found in the milk of lactating mothers. The use of naproxen should therefore be avoided in patients who are breast feeding.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

Gastro-intestinal: The most commonly observed adverse events are gastrointestinal in nature. Petic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (*see section 4.4, Special warnings and precautions for use*). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, heamatemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4 – special warnings and precautions for use) have been reported following administration. Less frequently, gastritis has been observed.

Hypersensitivity/skin reactions: Rashes, urticaria, anaphylaxis, angio-oedema and eosinophilic pneumonitis. Erythema multiforme, photosensitivity reactions and alopecia. Rarely epidermolysis bullosa and porphyria cutanea tarda have been reported.

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

CNS: Headache, insomnia, lack of concentration and cognitive dysfunction.

Haematological: Agranulocytosis, thrombocytopenia, aplastic and haemolytic anaemia may occur rarely.

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

Other side effects reported rarely include vertigo, hearing impairment, tinnitus and visual disturbances. Jaundice, hepatitis, mild peripheral oedema, nephropathy, haematuria, vasculitis, aseptic meningitis and ulcerative stomatitis.

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, Special warnings and precautions for use*).

4.9 Overdose

Overdosage can be characterised by drowsiness, heartburn, indigestion, nausea or vomiting. The stomach may be emptied and usual supportive measures employed. It is not known what dose is life-threatening.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Naproxen is a non steroidal anti-inflammatory agent and also has analgesic and antipyretic activity in man. Naproxen reduces the synthesis of prostaglandins by inhibiting the cyclo-oxygenase enzyme. The exact mechanism of its anti-inflammatory action is not known.

5.2 Pharmacokinetic properties

Naproxen is completely absorbed following oral administration. Peak plasma concentrations are seen after about 2 hours. Absorption rate, but not extent, is diminished by concomitant administration with food or antacids.

Naproxen is highly protein bound (>99%) resulting in a volume of distribution of 0.91kg^{-1} .

Naproxen is extensively metabolised by the liver, and excretion is primarily by the kidneys. Less than 10% of a dose is excreted unchanged.

Plasma half life is 12 - 15 hours.

5.3 Preclinical safety data

Naproxen does not have mutagenic potential. There is no evidence of carcinogenicity in two year studies in rats. There is no evidence of teratogenicity in mice, rats or rabbits. Naproxen has been shown to delay parturition in animals and to affect the closure of the ductus arteriosus in the human foetal cardiovascular system.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize Starch
Povidone
Crospovidone
Talc
Colloidal Anhydrous Silica
Magnesium Stearate
Cellulose
Diethyl Phthalate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Polyvinylchloride (PVC)/aluminium foil blister packs containing 100 or 250 tablets.

Polypropylene tablet container with polyethylene cap containing 100 or 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Limited
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35/36 Baldoyle Industrial Estate
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8 MARKETING AUTHORISATION NUMBER

PA 0577/008/001

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