SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fenopron 300

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains as active ingredient, fenoprofen calcium equivalent to 300mg of fenoprofen.

3 PHARMACEUTICAL FORM

Film-coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

For the relief of mild/moderate pain.

4.2 Posology and method of administration

Undesirable effects may be minimised by using the shortest duration necessary to control symptoms (see section 4.4).

For oral administration to adults only, and not recommended for administration to children.

Dosage: 300-600mg three or four times per day. To be taken preferably with or after food.

Fenopron 300: Recommended initial dosage is 2 tablets three times per day then adjusted to the needs of the patient.

The maximum daily dose should not exceed 3g.

If fenoprofen is administered with meals the total amount absorbed is not affected although peak blood levels are delayed and diminished.

The elderly: There is no difference in the metabolism or pharmacokinetics of fenoprofen in the elderly. The elderly are at increased risk of the serious consequences of adverse reactions. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

4.3 Contraindications

Hypersensitivity to fenoprofen or to any of the excipients.
Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).
History of upper gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Fenoprofen should not be given to patients in whom aspirin, ibuprofen and other non-steroidal anti-inflammatory drugs induce any hypersensitivity reaction such as asthma, rhinitis, angioedema or urticaria, because cross-sensitivity to these drugs occurs in a high proportion of patients.

Patients with a history of significantly impaired renal function, severe hepatic or severe heart/cardiac failure (see section 4.4).

During the last trimester of pregnancy, (see section 4.6).

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the minimum effective dose for the shortest possible duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

The use of Fenopron with concomitant NSAIDs including cyclooxygenase 2 specific inhibitors should be avoided (see section 4.5).

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).

Respiratory disorders: Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

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 the 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). There are insufficient data to exclude such a risk for Fenopron.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Fenopron after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Cardiovascular, *Renal and Hepatic Impairment:* The administration of a NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3). Discontinuation of therapy is typically followed by recovery to the pre-treatment state.

Some patients have developed elevation of serum transaminase, LDH and alkaline phosphatase and it is recommended that fenoprofen be discontinued if any significant liver abnormalities occur. Borderline elevations of one or more liver function tests may occur in up to 15% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported. Patients in whom an abnormal liver test has occurred should be evaluated for evidence of more severe hepatic reactions. During long-term therapy, liver function tests should be monitored periodically. If fenoprofen is used in the presence of impaired liver function, it must be done under strict observation.

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events. Minor upper gastro-intestinal problems, such as dyspepsia, are common, usually developing early in therapy.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), 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).

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 gastrotoxicity, ulceration or bleeding, such as oral corticosteroids, or 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 Fenopron, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn’s disease) as these conditions may be exacerbated (see section 4.8).

SLE and mixed connective tissue disease: In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders, there may be an increased risk of aseptic meningitis (see section 4.8).

Impaired Female fertility: The use of Fenopron 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 Fenopron should be considered.

Dermatological: 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). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of reaction occurring in the majority of cases within the first month of treatment. Fenopron should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Genito-urinary: The most frequent reported problems have been episodes of dysuria, cystitis, haematuria, interstitial nephritis and nephrotic syndrome. This syndrome may be preceded by

the appearance of fever, rash, arthralgia, oliguria and uraemia, and may progress to anuria. Early recognition of the syndrome and withdrawal of the drug have been followed by rapid recovery. Patients who have had similar reactions with other non-steroidal anti-inflammatory drugs should not be given fenoprofen. Patients likely to have compromised renal function should be monitored periodically.

Patients with initial low haemoglobin values who are receiving long-term therapy with fenoprofen should have a haemoglobin determination at reasonable intervals.

Studies to date have not shown changes in the eyes attributable to the administration of fenoprofen. However, adverse ocular effects have been observed with other anti-inflammatory drugs, so eye examinations should be performed if visual disturbances occur in patients taking fenoprofen.

Since the safety of fenoprofen has not been established in patients with impaired hearing, these patients should have periodic tests of auditory function during chronic therapy.

Fenoprofen decreases platelet aggregation and may prolong bleeding time.

4.5 Interaction with other medicinal products and other forms of interaction

Other analgesics including cyclooxygenase-2 selective inhibitors*:* Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

Anti-hypertensives: Reduced anti-hypertensive effect.

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. Patients treated with fenoprofen may be resistant to the effects of loop diuretics.

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

Lithium: Decreased elimination of lithium.

Methotrexate: Decreased elimination of methotrexate.

Ciclosporin*:* Increased risk of nephrotoxicity.

Mifepristone: NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Corticosteroids: Increased risk of GI ulceration or bleeding (see section 4.4).

Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). In patients receiving coumarin-type anti-coagulants, the addition of fenoprofen could prolong the prothrombin time.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with Zidovudine. There is evidence of an increased risk of haemarthoses and haemotoma in HIV(+) haemophiliacs receiving concurrent treatment with Zidovudine and Ibuprofen.

Laboratory test interactions: Values of total and free triiodothyronine in patients receiving fenoprofen have been reported as falsely elevated. Thyroid stimulating hormones, total thyroxine and thyrotropin releasing hormone response are not affected.

Chronic administration of phenobarbitone may be associated with a decrease in plasma half-life of fenoprofen. Dosage adjustment of fenoprofen may be required.

In vitro studies have shown that fenoprofen may displace other drugs, for example, hydantoins, sulphonamides, or sulphonylureas, from their binding sites and this may lead to drug interaction. Theoretically, fenoprofen could likewise be displaced.

4.6 Pregnancy and lactation

Usage in 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 malformationwas 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. During the first and second trimester of pregnancy, Fenopron should not be given unless clearly necessary. If Fenopron 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.
During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension).
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis.

and the mother and the neonate, at the end of pregnancy, to:

- possible prolongationof bleeding time, an anti-aggregating effect which may occureven at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Fenopron is contraindicated during the third trimester of pregnancy.

Usage in nursing mothers: In limited studies so far available, NSAIDs appear in breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

See section 4.4 – Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Gastrointestinal: The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, dry mouth, metallic taste, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, pancreatitis, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed.

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs. They may consist of (a) non-specific allergic reactions and anaphylaxis (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angiodema and more rarely exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

Cardiovascular and cerebrovascular**:** Palpitations, tachycardia, atrial fibrillation, pulmonary oedema, hypertension, cardiac failure, ECG changes and supraventricular tachycardia have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that the 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).

Other adverse events reported less commonly include:

Renal: Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, papillary necrosis and renal failure. Episodes of dysuria, cystitis and haematuria, oliguria, azotaemia and anuria have occurred.

Hepatic: Abnormal liver function, hepatitis and jaundice. Increases in alkaline phosphatase, LDH and AST have been observed.

Neurological and special senses: Visual disturbances, optic neuritis, amblyopia, diplopia, headaches, paraesthesia, reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4), depression, confusion, hallucinations, tinnitus, hearing decrease, vertigo, dizziness, nervousness, malaise, fatigue, drowsiness, burning tongue, breast pain, personality change, lymphadenopathy, mastodynia, fever, upper respiratory infection and nasopharyngitis have been reported.

Haematological: Thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and haemolytic anaemia.

Dermatological: Photosensitivity, pruritus, rash, urticaria, anaphylaxis, Stevens-Johnson syndrome, angioneurotic oedema, increased sweating, exfoliative dermatitis; toxic epidermal necrolysis and alopecia have been reported.

4.9 Overdose

Symptoms of overdose appear within several hours and generally involve the gastrointestinal and central nervous systems. Symptoms include dyspepsia, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, fainting, occasionally convulsions, dizziness, headache, ataxia, tinnitus, tremor, drowsiness and confusion. Hyperpyrexia, tachycardia and hypotension may occur rarely following overdose. Respiratory depression and metabolic acidosis have also been reported following overdose with certain non-steroidal anti-inflammatory drugs. In cases of significant poisoning acute renal failure and liver damage are possible.

Treatment: Patients should be treated symptomatically as required. Within one hour of ingestion of a potentially toxic amount activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of a potentially toxic amount.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Fenoprofen calcium is a nonsteroidal, anti-inflammatory, antiarthritic drug that also possesses analgesic and antipyretic activities. Its exact mode of action is unknown, but it is thought that prostaglandin synthetase inhibition is involved.

5.2 Pharmacokinetic properties

Under fasting conditions, fenopron is rapidly absorbed, and peak plasma levels of 50mcg/l are achieved within 2 hours after oral administration of 600mg doses. Good dose proportionality was observed between 200mg and 600mg doses in fasting male volunteers. The plasma half-life is approximately 3 hours. About 90% of a single oral dose is eliminated within 24 hours as fenoprofen glucuronide and 4'-hydroxyfenoprofen glucuronide, the major urinary metabolites of fenoprofen. Fenoprofen is highly bound (99%) to albumin. The concomitant administration of antacid (containing both aluminium and magnesium hydroxide) does not interfere with absorption of fenopron.

5.3 Preclinical safety data

Reproduction studies in rats have shown fenoprofen calcium to be associated with prolonged labour and difficult parturition when given during late pregnancy, but no evidence of teratogenicity has been seen.

Fenoprofen shows anti-inflammatory effects in rodents by inhibiting the development of redness and oedema in acute inflammatory conditions and by

reducing soft-tissue swelling and bone damage associated with chronic inflammation. It exhibits analgesic activity in rodents by inhibiting the writhing response caused by the introduction of an irritant into the peritoneal cavities of mice and by elevating pain thresholds that are related to pressure in oedematous hindpaws in rats. In rats made febrile by the subcutaneous administration of brewer's yeast, fenoprofen produces antipyretic action.

In chronic studies in rats, high doses of fenoprofen calcium caused elevation of serum transaminase and hepatocellular hypertrophy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Hydrogen Phosphate
Maize Starch
Polacrilin Potassium
Magnesium Stearate
Stearic Acid Powder
Hydroxypropylmethylcellulose
Polyethylene Glycol 8000
Propylene Glycol
Titanium Dioxide
Sunset Yellow (E110)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25^{o}C.

6.5 Nature and contents of container

Snap-on. Screw-capped. High density polyethylene bottles of 100 tablets.

6.6 Special precautions for disposal

No special instructions

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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