SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Larafen* CR Capsules 200mg.

Ketoprofen Controlled Release Capsules 200mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Ketoprofen BP 200mg.

Excipient(s) with known effect

Sucrose

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatine capsule with an opaque pink cap and transparent body containing white to whitish pellets. Each capsule is embossed with "KET 200 CR" on the body

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Larafen* CR is an analgesic, anti-inflammatory and antipyretic; recommended for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and other musculoskeletal conditions including bursitis, capsulitis, synovitis, tendinitis, fibrositis and low back pain. It is also useful to relieve the pain of sciatica, acute gout and dysmenorrhoea.

4.2 Posology and method of administration

The lowest effective dose should be used for the shortest duration necessary to relieve symptoms (see section 4.4).

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

Adults:

One 200mg Larafen CR Capsule to be taken orally once daily with a little

food.

The maximum daily dose is 200mg. The balance of risks and benefits should be carefully considered before commencing treatment with 200mg daily, and higher doses are not recommended (see also section 4.4).

Patients with impaired renal function and the elderly:

It is advisable to reduce the initial dosage and maintain such patients on the minimal effective dose. Individual adjustment may be considered, only after good individual tolerance has been ascertained (see section 5).

Elderly:

The elderly are at increased risk of serious adverse reactions from NSAIDs. If a NSAID is considered necessary, it is generally advisable in the elderly to begin ketoprofen therapy at the lower end of the dose range and to maintain such patients on the lowest effective dosage. The patient should be monitored for GI bleeding during NSAID therapy.

Patients with impaired hepatic function:

These patients should be carefully monitored and kept at the minimal effective daily dosage (see section 4.3 and 5).

Children:

The safety and effectiveness of ketoprofen capsules have not been established. There are no recommendations for the use of Larafen CR in children.

Method of administration:

Oral. Larafen CR capsules should always be prescribed "To be taken with or after food" to minimise gastric intolerance

4.3 Contraindications

Larafen CR are contraindicated in the following cases:

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

• Active peptic ulcer, or any history of gastrointestinal bleeding, ulceration or perforation.

• Haemorrhagic diathesis.

• Patients who have previously shown hypersensitivity reactions such as bronchospasm, asthma attacks, rhinitis, angioedema, urticaria or other allergic-type reactions to ketoprofen, ibuprofen, aspirin or any other non-steroidal anti-inflammatory drugs.

• Severe, rarely fatal, anaphylactic reactions have been reported in such patients (see section 4.8).

• Severe heart failure, hepatic failure/insufficiency and renal failure/insufficiency (see section 4.4).

• During the third trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

The use of Larafen CR with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

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

Masking of symptoms of underlying infections

Larafen CR capsules can mask symptoms of infection, which may lead to delayed initiation of appropriate treatment and thereby worsening the outcome of the infection. This has been observed in bacterial community acquired pneumonia and bacterial complications to varicella. When Larafen CR capsules are administered for fever or pain relief in relation to infection, monitoring of infection is advised. In non-hospital settings, the patient should consult a doctor if symptoms persist or worsen.

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.

Some epidemiological evidence suggests that ketoprofen may be associated with a high risk of serious gastrointestinal toxicity, relative to some other NSAIDs, especially at high doses (see also sections 4.2 and 4.3).

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 patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5). Ketoprofen should not be used in patients with any history of peptic ulceration (see section 4.3).

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

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.

As with other drugs in the same therapeutic category, patients should be advised to

take ketoprofen with food, to minimise gastric intolerance.

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).

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

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. 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 within the first month of treatment. Ketoprofen should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Cardiovascular, Renal and Hepatic impairment:

The administration of an NSAID may cause a dose dependent reduction in renal blood flow caused by prostaglandin inhibition and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, heart failure, liver dysfunction, cirrhosis, nephrosis, in patients receiving diuretic therapy, in patients with chronic renal impairment, particularly if the patient is elderly. In these patients, administration of ketoprofen may induce a reduction in renal blood flow caused by prostaglandin inhibition and lead to renal decomposition (see section 4.3). At start of the treatment renal function should be monitored in these patients (see also section 4.3).

NSAIDs have been reported to cause nephrotoxicity in various forms and this can lead to interstitial nephritis, nephrotic syndrome and renal failure. Renal function must be carefully monitored.

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil fumarate and with risk factors for renal dysfunction. If tenofovir disoproxil fumarate is co-administered with an NSAID, renal function should be monitored adequately.

Hyperkalaemia may occur in patients with underlying diabetes, renal disorders, and/or receiving concomitant treatment with hyperkalaemia promoting agents (see section 4.5). Caution should be exercised when treating such patients and they must be monitored when receiving ketoprofen.

In patients with abnormal liver function tests or with a history of liver disease, transaminase levels should be evaluated periodically, particularly during long-term therapy. Rare cases of jaundice and hepatitis have been described with ketoprofen.

Cardiovascular and cerebrovascular effects

<u>Precautions:</u>

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 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 ketoprofen.

As with all NSAIDs, careful consideration should be given when treating patients with existing uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease, as well as before initiating long-term treatment in patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

An increased risk for arterial thrombotic events has been reported in patients treated with non-aspirin NSAIDs (e.g. parecoxib and valdecoxib) for perioperative pain in the setting of coronary artery bypass surgery (CABG). This effect has not been observed with ketoprofen.

Visual disturbances

If visual disturbances, such a blurred vision, occur treatment should be discontinued.

Infectious disease

As with other NSAIDs, in the presence of an infectious disease, it should be noted that the anti-inflammatory, analgesic and the antipyretic properties of ketoprofen may mask the usual signs of infection progression such as fever.

Respiratory disorders

Patients with asthma combined with chronic rhinitis, chronic sinusitis, and/or nasal polyposis have a higher risk of allergy to aspirin and/or NSAIDs than the rest of the population. Administration of this medicinal product can cause asthma attacks or bronchospasm particularly in subjects allergic to aspirin or NSAIDs (see section 4.3).

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 Ketoprofen, as with other NSAIDs, may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or who are undergoing investigation of infertility, withdrawal of ketoprofen should be considered.

Excipients:

Patients with rare hereditary problems of fructose intolerance, glucose- galactose

malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended medicinal product associations

Other analgesics/NSAIDs (including cyclooxygenase-2 selective inhibitors) and high dose salicylates:

Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects, particularly gastrointestinal ulceration and bleeding (see section 4.4).

Anticoagulants, Sulphonamides and Hydantoins:

Increased risk of bleeding (see section 4.4).

- Heparin
- Vitamin K antagonists (such as warfarin)
- Platelet aggregation inhibitors (such as ticlopidine, clopidogrel)
- Thrombin inhibitors (such as dabigatran)
- Direct factor Xa inhibitors (such as apixaban, rivaroxaban, edoxaban)

Ketoprofen, is highly protein bound, and therefore, it might be expected to displace other protein bound drugs e.g. anticoagulants, sulphonamides and hydantoins such as phenytoin. Patients must be monitored closely for change in dosage requirements when giving ketoprofen to patients already receiving other highly protein bound drugs.

NSAIDs may enhance the effects of anti-coagulants, such as warfarin and heparin, platelet aggregation inhibitors (i.e. ticlopidine, clopidogrel) (see section 4.4).

Increased risk of bleeding (see section 4.4).

If co-administration is unavoidable, patient should be closely monitored.

Lithium:

Risk of elevation of lithium plasma levels sometimes reaching toxic levels due to decreased elimination of lithium. Where necessary, plasma lithium levels should be closely monitored and the lithium dosage levels adjusted during and after NSAID therapy.

Methotrexate

Serious interactions have been recorded after the use of high dose methotrexate with NSAIDs, including ketoprofen, due to decreased elimination of methotrexate.

- *At doses greater than 15 mg/week:* Increased risk of haematologic toxicity of methotrexate, particularly if administered at high doses (>15 mg/week), possibly related to displacement of protein-bound methotrexate and to its decreased renal clearance.

- *At doses lower than 15 mg/week:* During the first weeks of combination treatment, full blood count should be monitored weekly. If there is any alteration of the renal function or if the patient is elderly, monitoring should be done more frequently.

Medicinal product associations requiring precaution for use

Diuretics: Reduced diuretic effect. Diuretics can increase the risk of nephrotoxicity of NSAIDs. These properties should be kept in mind when treating patients with compromised cardiac function or hypertension, to avoid a possible worsening of these conditions. Patients and particularly dehydrated patients taking diuretics are at a greater risk of developing renal failure secondary to a decrease in renal blood flow caused by prostaglandin inhibition. Such patients should be rehydrated before initiating co-administration therapy and renal function monitored when the treatment is started (see section 4.4).

ACE inhibitors and Angiotensin II antagonists

In patients with compromised renal function (e.g. dehydrated patients or elderly patients, the co- administration of an ACE inhibitor or Angiotensin II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure.

Corticosteroids: Increased risk of gastrointestinal ulceration and bleeding (see section 4.4).

Pentoxifylline: There is an increased risk of bleeding. More frequent clinical monitoring and monitoring of bleeding time is required.

Tenofovir: Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.

Nicorandil: In patients concomitantly receiving Nicorandil and NSAIDs, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and haemorrhage (see section 4.4).

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

ketoprofen and digoxin has not been demonstrated. However, caution is advised, in particular in patients with renal impairment, since NSAIDs may reduce renal function and decrease renal clearance of cardiac glycosides.

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.

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

Aminoglycosides: Reduction in renal function in susceptible individuals, decreased elimination of aminoglycosides and increased plasma concentrations have been reported.

Oral Hypoglycaemic Agents: Inhibition of metabolism of sulfonylurea drugs, prolonged half-life and increased risk of hypoglycaemia is known to occur with oral hypoglycaemic agents.

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

Medicinal product associations to be taken into account

Antihypertensive agents (beta-blockers, angiotensin converting enzyme inhibitors, diuretics: Risk of reduced anti-hypertensive effect (inhibition of vasodilator prostaglandins by NSAIDs)

Thrombolytics: Increased risk of bleeding.

Probenecid: Concomitant administration of probenecid may markedly reduce the plasma clearance of ketoprofen.

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

Ciclosporin: Increased risk of nephrotoxicity particularly in elderly subjects.

Medicinal products and therapeutic categories that can promote hyperkalaemia (i.e. potassium salts, potassium-sparing diuretics, ACE inhibitors and angiotensin II antagonists, NSAIDs, heparins (low molecular-weight or unfractioned), cyclosporin, tacrolimus and trimethoprim).

The risk of hyperkalaemia can be enhanced when the drugs mentioned above are administered concomitantly (see section 4.4)

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus, particularly in elderly subjects.

4.6 Fertility, Pregnancy and Breast-feeding

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern.

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 malformation was 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. From the 20th week of pregnancy onward, Ketoprofen use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, ketoprofen should not be given unless clearly necessary. If ketoprofen 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. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Ketoprofen for several days from gestational week 20 onward. Ketoprofen should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

In view of the known effects during the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose

- the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension)

- renal dysfunction (see above)

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

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.

- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, ketoprofen is contraindicated during the third trimester of pregnancy (see section 4.3 and 5.3).

The onset of labour may be delayed and the duration increased with an increased bleeding tendency in both mother and child (see section 4.3). NSAIDs should also not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the foetus.

Breast-feeding

No data are available on the excretion of ketoprofen in human milk. Ketoprofen is not recommended in nursing mothers.

Fertility

See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

Patient should be warned about the potential undesirable effects such as dizziness or convulsions, drowsiness, fatigue, nausea, confusion, visual disturbances, somnolence and headaches are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

Classification of expected frequencies:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

The following adverse reactions have been reported with Ketoprofen in adults:

Blood and the lymphatic system disorders:

Rare: haemorrhagic anaemia, anaemia due to bleeding

Not known: agranulocytosis, thrombocytopenia, bone marrow failure, aplastic anaemia, haemolytic anaemia, neutropenia, leucopenia

Immune system disorders:

Rare: anaphylactic reactions/anaphylaxis (including shock)

Not Known: non-specific allergic reactions,

Psychiatric disorders:

Not known: depression, hallucinations, confusion, mood altered, insomnia

Nervous system disorders:

Uncommon: headache, dizziness, somnolence

Rare: paraesthesia

Not known: convulsions, dysgeusia, vertigo, malaise, drowsiness, 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)

Eye disorders:

Rare: visual disturbances such as blurred vision (see section 4.4)

Not known: optic neuritis

Ear and labyrinth disorders:

Rare: tinnitus

Cardiac disorders:

Not known: cardiac failure has been reported in association with NSAID treatment, exacerbation of heart failure, oedema

Vascular disorders

Not known: hypertension, vasodilatation, vasculitis (including leukocytoclastic vasculitis)

Respiratory, thoracic and mediastinal disorders

Rare: respiratory tract reactivity compromising of asthma, asthma attack

Not known: aggravated asthma or dyspnoea, bronchospasm (particularly in patients with known hypersensitivity to ASA and other NSAIDs), rhinitis, non-specific allergic reactions, dyspnoea

Gastrointestinal disorders:

Common: dyspepsia, nausea, abdominal pain, vomiting

Uncommon: diarrhoea, constipation, flatulence, gastritis

Rare: stomatitis, peptic ulcer,

Very rare: pancreatitis (very rare reports of pancreatitis have been noted with NSAIDs)

Not known: exacerbation of colitis and Crohn's disease, gastrointestinal haemorrhage and perforation, gastralgia, melaena, haematemesis

Gastrointestinal bleeding may sometimes be fatal, particularly in the elderly (see section 4.4).

Hepatobiliary disorders:

Rare: hepatitis, transaminase increased, elevated serum bilirubin due to hepatitis disorders

Not known: abnormal liver function, hepatic damage, jaundice

Skin and subcutaneous tissue disorders:

Uncommon: rash, pruritus,

Not known: photosensitivity reactions, alopecia, urticaria, angioedema, bullous eruption including Stevens-Johnson syndrome, toxic epidermal necrolysis acute generalised exanthematous pustulosis, exfoliative and bullous dermatoses (including epidermal necrolysis, erythema multiforme), purpura

Renal and urinary disorders:

Not known: renal failure acute, tubulointerstitial nephritis, nephritic syndrome, renal function tests abnormal, nephrotoxicity in various forms, including interstitial nephritis.

General disorders and administration site conditions:

Uncommon: oedema, fatigue

Not known: headache, taste perversion

Metabolism and nutritional disorders:

Not known: hyponatraemia, hyperkalaemia (see sections 4.4 and 4.5)

Investigations

Rare: weight increased

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Should any severe adverse event occur, treatment should be stopped immediately.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the

Google Play or Apple App Store.

4.9 Overdose

Symptoms

Cases of overdose have been reported with doses up to 2.5g of ketoprofen. Symptoms observed have been benign and limited to lethargy, drowsiness, nausea, vomiting and epigastric pain. Headache, rarely diarrhoea, disorientation, excitation, coma, dizziness, tinnitus, fainting, occasionally convulsions may also occur. Adverse effects seen after overdose with propionic acid derivatives such as hypotension, bronchospasm and gastro-intestinal haemorrhage should be anticipated.

In cases of significant poisoning, acute renal failure and liver damage are possible.

If renal failure is present, haemodialysis may be useful to remove circulating medicinal product.

Management:

There are no specific antidotes to ketoprofen overdoses.

In cases of suspected massive overdosages, a gastric lavage is recommended and symptomatic and supportive treatment should be instituted to compensate for dehydration, to monitor urinary excretion and to correct acidosis, if present.

Owing to the slow release characteristics of Ketoprofen, it should be expected that ketoprofen will continue to be absorbed for up to 16 hours after ingestion.

Within one hour of ingestion, consideration should be given to administering activated charcoal in an attempt to reduce absorption of slowly-released ketoprofen.

Alternatively, in adults, gastric lavage, aimed at recovering pellets that may still be in the stomach, should be considered if the patient presents within 1 hour of ingesting a potentially toxic amount.

It should be possible to identify the pellets in the gastric contents. Correction of severe electrolyte abnormalities may need to be considered.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

If renal failure is present, haemodialysis may be useful to remove circulating medicinal product.

Patients should be observed for at least four hours after ingestion of

potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

The benefit of gastric decontamination is uncertain.

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

The correction of severe electrolyte abnormalities may need to be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Propionic acid derivatives, ATC Code: M01AE03.

Larafen CR is a potent non-steroidal anti-inflammatory analgesic agent and a strong inhibitor of prostaglandin synthetase. It has an inhibitory effect on platelet aggregation. Larafen CR reduces joint pain and inflammation and facilitates increase in mobility and functional independence. As with other non-steroidal anti-inflammatory agents, it does not cure the underlying disease.

Anti-inflammatory It inhibits the development of carageenan-induced abscesses in rats at 1 mg/kg and UV-radiation induced erythema in guinea pigs at 6mg/kg. It is also a potent inhibitor of PGE_2 and PGF_{2oc} synthesis in guinea pig and human chopped lung preparations.

Analgesic Ketoprofen effectively reduced visceral pain in mice caused by phenyl benzoquinone or by bradykinin following p.o. administration at about 6mg/kg.

Antipyretic Ketoprofen (2 and 6mg/kg) inhibited hyperthermia caused by s.c injection of brewer's yeast in rats and, at 1 mg/kg hyperthermia caused by i.v. administration of anticoagulant vaccine to rabbits.

Ketoprofen at 10mg/kg i.v. did not affect the cardiovascular, respiratory, central nervous system or autonomic nervous systems.

5.2 Pharmacokinetic properties

Ketoprofen is slowly but completely absorbed from Larafen CR. Maximum plasma concentration occurs after 6-8 hours. It declines thereafter with a half-life of about 8 hours.

There is no accumulation on continued daily dosing.

Ketoprofen is very highly bound to plasma proteins.

Excretion is essentially via urine: glycoconjugates represent between approximately 65 and 75 % of the administered dose of ketoprofen.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polyethylene glycol, ethylcellulose, purified stearic acid, talc, polymers of methacrylic acid, acrylic esters and methacrylic acid esters, sucrose, corn starch, gelatin, erythrosine (E127) and titanium dioxide (E171).

6.2 Incompatibilities

Not reported.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store in a dry place below 25 °C. Protect from light.

6.5 Nature and contents of container

Blister strips composed of PVC/aluminium. Pack size[1]: 28, 30, 56, 60 and 100 tablets.

6.6 Special precautions for disposal

[1] Only marketed pack size will be shown.

7 MARKETING AUTHORISATION HOLDER

Ennogen Pharma Limited
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8 MARKETING AUTHORISATION NUMBER(S)

PL 40147/0053

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 September 1993.

10 DATE OF REVISION OF THE TEXT

03/09/2025