SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ketoprofen Capsules BP 50mg.

2

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains ketoprofen BP 50mg.

Excipient(s) with known effect
Lactose

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ketoprofen capsules are recommended for the management of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute articular and periarticular disorders, fibrositis, cervical spondylitis, low back pain, painful musculoskeletal conditions and dysmenorrhoea. Ketoprofen 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.

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).

Ketoprofen capsules should always be taken with food to reduce the occurrence of gastrointestinal disturbance.

Adults:

50-100mg twice daily. The dosage can be altered depending on the patient weight and on the severity of symptoms.

Dysmenorrhoea:

50mg up to 3 times a day. Three to 4 days treatment is normally required from the onset of menstruation or symptoms of dysmenorrhoea.

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 for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Children:

Dosage has not been established.

4.3 Contraindications

Ketoprofen is contraindicated in the following cases:

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

Known allergy to aspirin and to other substances with similar effect (non-steroidal anti-inflammatory agents): who have a history of hypersensitivity reactions such as bronchospasm, asthmatic attacks, rhinitis, urticaria or other allergic-type reactions to ketoprofen. Severe, rarely fatal, anaphylactic reactions have been reported in such patients (see section 4.8).

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

Severe hepatocellular insufficiency.

Severe renal insufficiency.

Children aged less than 15 years.

Severe heart failure.

Haemorrhagic diathesis.

Ketoprofen is also contraindicated in the third trimester of pregnancy.

4.4 Special warnings and precautions for use

Warnings

Masking of symptoms of underlying infections

Ketoprofen 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 Ketoprofen 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.

The use of Ketoprofen 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).

Ketoprofen should be used with caution:

At the start of treatment, close supervision is necessary of the volume of urine passed and of renal function in patients with cardiac insufficiency, cirrhosis and nephrosis, in patients on diuretics, in patients with chronic renal insufficiency and in particular, in elderly patients intrauterine device: a possible reduction of the device's effectiveness.

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 section 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 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 ulceration or bleeding, such as corticosteroids, or anti-coagulants 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 ketoprofen, the treatment should be withdrawn.

Elderly:

The elderly have an increased risk of adverse reactions to NSAIDs, especially gastro-intestinal bleeding and perforation which may be fatal (see section 4.2).

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 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.

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.

Precautions

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).

At the start of treatment, renal function must be carefully monitored in patients with heart impairment, heart failure, liver dysfunction, cirrhosis and 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.

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.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Ketoprofen after careful consideration as fluid retention and oedema has been reported in association with NSAID therapy. 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).

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

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.

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.

The use of NSAIDs 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 the NSAID should be considered.

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).

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

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended medicinal product associations

Ketoprofen may alter the action of certain other medicaments by exerting a potentiating or inhibiting effect on them.

Co-administration of ketoprofen with the following drug product necessitates stringent supervision of the clinical and biochemical state of the patient:

Other NSAIDS (including cyclooxygenase-2 selective inhibitors) and high dose of salicylates

Increased risk of gastrointestinal ulcer and haemorrhages.

Anticoagulants (heparin and warfarin) and platelet aggregation inhibitors (i.e.ticlopidine, clopidogrel):

Ketoprofen may heighten the effects of oral anticoagulants (heparin and warfarin) and platelet aggregation inhibitors (i.e. ticlopidine, clopidogrel): increased risk of haemorrhage through inhibition of platelet function and irritation of digestive system mucosa. (see section 4.4)

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

Where concomitance with K antivitamins is necessary, supervise the prothrombin time on account of the possible risk of potentiation.

Ketoprofen may result in an increase in the hypoglycaemic effect of sulphonamides (displacement of their bonds to plasma proteins).

Lithium: Ketoprofen is a lithaemia-elevating factor, possibly up to the threshold of toxicity due to decreased lithium renal excretion. Where necessary, plasma lithium levels should be closely monitored and adjust lithium dosage during co-administration and after it has been discontinued.

Methotrexate at doses greater than 15mg/week:

Ketoprofen increases the risk of haematological toxicity of methotrexate (potentiation), particularly if administered at high doses (> 15 mg/week), possibly related to displacement of protein-bound methotrexate and to its decreased renal clearance.

Medicinal product associations requiring precautions for use

Methotrexate 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.

Antihypertensive agents: (beta-blockers, angiotensin converting enzyme inhibitors, diuretics, 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.

Ketoprofen may decrease the action of antihypertensive potency antihypertensive effects (inhibition of vasodilator prostaglandins by NSAIDs).

Diuretics: 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).

Potential NSAID drug interactions: cyclosporin, corticosteroids, mifepristone, cardiac glycosides, quinolone antibiotics

Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4).

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

Medicinal product associations to be taken into account

Antihypertensive agents (beta-blockers, angiotensin converting enzyme inhibitors, diuretics):

Risk of decreased antihypertensive potency (inhibition of vasodilator prostaglandins by NSAIDs).

Thrombolytics: Increased risk of bleeding.

Selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (section 4.4).

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

Combinations to be taken into consideration:

Cyclosporin, tacrolimus: Risk of additive nephrotoxic effects, particularly in elderly subjects.

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.

4.6 Fertility, pregnancy and lactation

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 Capsules 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 Capsules for several days from gestational week 20 onward. Ketoprofen Capsules should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

Ketoprofen is not recommended:

During the first 3 months of pregnancy on account of a possible teratogenic effect. In rodents ketoprofen was neither embryotoxic nor teratogenic. In rabbits there remains a doubt: in one study there was a marked dose-dependence in the percentage of resorption, a fall in the number of live foetuses and a higher number of abnormal foetuses. In the monkey ketoprofen was not embryotoxic nor teratogenic. These facts can be explained as mainly due to the ketoprofen mechanism of action, and are standard for the NSAID class.

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 sections 4.3 and 5.3).

Breast-feeding

In the absence of a pharmacological data on excretion of ketoprofen in human milk, ketoprofen is not recommended in nursing mothers.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for somnolence, dizziness or convulsions, and be advised not to drive or operate machinery if these symptoms occur.

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 lymphatic system disorders

- rare: haemorrhagic anaemia

- not known: agranulocytosis, thrombocytopenia, bone marrow failure, neutropenia, a moderate fall in red blood cells have been reported

Immune system disorders

- not known: anaphylactic reactions (including shock)

Psychiatric disorders

- not known: mood altered, insomnia

Nervous system disorders

- uncommon: headache, dizziness, somnolence

- rare: paraesthesia

- not known: convulsions, dysgeusia, 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, vertigo, malaise, drowsiness

Eye disorders

- rare: vision blurred (see section 4.4)

- not known: visual disturbances, optic neuritis

Ear and labyrinth disorders

- rare: tinnitus

Cardiac disorders

- not known: heart failure

Vascular disorders

- not known: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders

- rare: asthma

- not known: bronchospasm (possibility of asthma attacks, particularly in patients with known hypersensitivity to ASA and other NSAIDs), rhinitis

Gastrointestinal disorders

- common: dyspepsia, nausea, abdominal pain, vomiting

- uncommon: constipation, diarrhoea, 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

Hepatobiliary disorders

- rare: hepatitis, transaminases increased, elevated serum bilirubin due to hepatitis disorders

Skin and subcutaneous disorders

- uncommon: rash, pruritis

- not known: photosensitivity reaction, alopecia, urticaria, angioedema, bullous eruption including Stevens-Johnson syndrome and toxic epidermal necrolysis

Renal and urinary disorders

- not known: renal failure acute, tubulointerstitial nephritis, nephritic syndrome, renal function tests abnormal, possible aggravation of an existing renal condition (see section 4.4)

General disorders and administration site conditions

- uncommon: oedema

- not known: fatigue

Investigations

- rare: weight increase

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).

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 the 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
Cases of overdose have been reported with doses up to 2.5g of ketoprofen. In most instances, the 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. There are no specific antidotes to ketoprofen overdoses. In cases of suspected massive overdoses, 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.
If renal failure is present, haemodialysis may be useful to remove circulating medicinal product.

3 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Ketoprofen is a non-steroidal anti-inflammatory of the propionic groups, a derivative of aryl carboxylic acid. It has anti-inflammatory, analgesic and antipyretic effects; it inhibits prostaglandin synthesis and has an inhibitory effect on platelet aggregation.

5.2 Pharmacokinetic properties

Absorption
Successive measurements of serum concentrations following administration of a therapeutic dose show that ketoprofen is very rapidly absorbed. Time-to-peak serum concentration is 60-90 minutes after oral dose.

Distribution
Mean plasma half-life for the oral route is 1.5 to 2 hours. 99% of ketoprofen binds to plasma proteins. Ketoprofen passes into synovial fluid where it persists at concentrations higher than those found in serum after Hour 4 following an oral dose. It crosses the placental barrier.

Metabolism
Biotransformation of ketoprofen is performed via 2 processes: one very minor (hydroxylation) and the other largely predominant (conjugation with glucuronic acid). Less than 1% of the administered dose of ketoprofen is recovered from urine as parent drug, while glucuronoconjugates represent between approximately 65 and 75%.

Excretion
In the 5 days following oral dosing, 75-90% of the dose is excreted through the
kidneys and 1-8% in faeces. Excretion, which is essentially via urine, is very rapid: 50% of the administered dose is eliminated in the 6 hours following dosing.

Elderly Patients
Ketoprofen absorption is not affected: the lengthening of the elimination half-life and the reduction in total clearance would seem to reflect a slowing of metabolic transformation.

Renal Insufficiency
Plasma clearance is reduced and elimination half-life lengthened.

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate and lactose. The capsule shells contain gelatin, erythrosine (E127), indigotine (E132), titanium dioxide (E171) and quinoline yellow (E104).

6.2 Incompatibilities

Not recorded.

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store in a dry place not above 25 °C.

6.5 Nature and contents of container

Amber glass bottles. Pack sizes: 28 30 56 60 84 90 100 112 and 500.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Ennogen Pharma Limited
Unit G4,
Riverside Industrial Estate,

Riverside Way,
Dartford
DA1 5BS
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 40147/0051

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26/02/2009

10 DATE OF REVISION OF THE TEXT

30/10/2024