SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tiloket CR 100 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains ketoprofen 100 mg

Excipient with known effect: Each capsule contains 16.850mg of neutral micrograins (sugar-starch)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Controlled release capsules.

White cap, colourless body, size 3 capsules, containing homogeneous creamy white microgranules, printed TILOKET 100mg CR

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tiloket CR Capsules are indicated for:

- Rheumatoid arthritis
- Osteoarthritis
- Ankylosing spondylitis
- Acute articular and periarticular disorders (bursitis, capsulitis, synovitis, tendonitis)
- Cervical spondylitis
- Low back pain (strain, lumbago, sciatica, fibrositis)
- Painful musculoskeletal conditions
- Dysmenorrhoea.

4.2 Posology and method of administration

Posology

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

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)

Adults:
100 - 200 mg daily depending on patient weight and on severity of symptoms, to be taken preferably with food.

Older people*:*
As for adult dosage as there is no evidence that the pharmacokinetics of ketoprofen are altered in the elderly.

The elderly are at risk of 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 gastrointestinal bleeding during NSAID therapy.

Paediatric population*:*
The safety and efficacy of Tiloket Capsules in children has not yet been established.
No data are available.

Method of Administration
For oral administration

4.3 Contraindications

Tiloket CR Capsules 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, asthmatic attacks, rhinitis, angioedema, urticaria or other allergic-type reactions in response to ketoprofen, ibuprofen, aspirin or 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 last trimester of pregnancy (see section 4.6).
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

4.4 Special warnings and precautions for use

Warnings

Masking of symptoms of underlying infections
Tiloket 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 Tiloket is 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 Tiloket 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).

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).

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 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.

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 can be fatal (see section 4.2).

When GI bleeding or ulceration occurs in patients receiving Tiloket, 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 (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.

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, liver dysfunction, cirrhosis, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

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

Cardiovascular and cerebrovascular effects
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:
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 have 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).

At the start of treatment, renal function must be carefully monitored in patients with heart failure, 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 decompensation.

If visual disturbances, such a 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.

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).

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 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 rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Patients with rare hypersensitivity for sulphur dioxide should not take this medicine; which may cause hypersensitivity reactions and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Not recommended medicinal product associations

Other 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 (in particular gastrointestinal ulceration and bleeding) (see section 4.4).

Anticoagulants, Sulphonamides and Hydantoins
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).
Increased risk of bleeding (see section 4.4)
If coadministration 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 at doses greater than 15mg/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.

<u>Medicinal product associations requiring precaution for use</u>

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 coadministration therapy and renal function monitored when the treatment is started (see section 4.4).

ACE inhibitor and Angiotensin II antagonist
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.

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.

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.

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

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 to 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.

<u>Medicinal product associations to be taken into account</u>

Anti-hypertensives 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.

Selective serotonin reuptake inhibitors (SSRIs)
Increased risk of gastrointestinal bleeding (see section 4.4).

Probenecid
Reduction in metabolism and elimination of NSAID/ketoprofen and metabolites may occurs with probenecid.
Ciclosporin
Increased risk of nephrotoxicity particularly in elderly subjects.

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

4.6 Pregnancy and lactation

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

- Cardiopulmonary toxicity (risk of premature closure of the ductus arteriosus and pulmonary hypertension) of NSAIDs on the foetal cardiovascular system. Use in the last trimester or pregnancy is contraindicated.
- Renal dysfunction, which may progress to renal failure with oligo-hydroamniosis; the mother and the neonate, at the end of 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.
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 excretion of ketoprofen in human milk. Ketoprofen is not recommended in nursing mothers.

Fertility
See section 4.4 Special warnings and precautions for use, 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 be advised not to 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 lymphatic system disorders
Rare: haemorrhagic anaemia
Not known: agranulocytosis, thrombocytopenia, bone marrow failure, aplastic anaemia and haemolytic anaemia, neutropenia

Immune system disorders
Not known: non-specific allergic reactions , anaphylactic reactions / anaphylaxis (including shock)

Psychiatric disorders
Not known: mood altered

Nervous system disorders
Uncommon: headache, dizziness, somnolence
Rare: paraesthesia
Not known: convulsions, dysgeusia

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: cardiac failure have been reported in association with NSAID treatment.

Vascular disorders
Not known: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders
Rare: respiratory tract reactivity comprising of asthma
Not known: aggravated asthma, or dyspnoea, bronchospasm (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
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
Abnormal liver function and jaundice

Skin and subcutaneous disorders
Uncommon: rash, pruritis
Not known: rashes of various types photosensitivity reaction, alopecia, urticaria, purpura, angioedema
less commonly bullous dermatoses (including toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome and exfoliative dermatitis)
Should any severe adverse event occur, treatment should be stopped immediately.

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
Not known: fatigue

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).

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

4.9 Overdose

Symptoms
Cases of overdose have been reported with doses up to 2.5 g of ketoprofen. Symptoms observed have been benign and limited to lethargy, nausea, vomiting, and epigastric pain. Gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions, hypotension and bronchospasm have also been reported. In cases of significant poisoning acute renal failure and liver damage are possible.

Management
There are no specific antidotes to ketoprofen overdosages.

Patients should be treated symptomatically as required and supportive treatment should be instituted to compensate for dehydration, to monitor urinary excretion and to correct acidosis, if present.

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.
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.

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: Tiloket 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. Tiloket 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.

ATC Code: M01AE

5.2 Pharmacokinetic properties

Ketoprofen is slowly but completely absorbed from Tiloket 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: glucoronoconjugates 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

Povidone
Ethylcellulose
Talc
Neutral microgranules

Capsule Shell.
Gelatin
Sulfur dioxide
Titanium Dioxide
95 % Denatured Ethanol
Black ink code 1007

6.2. Incompatibilities

None known.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Blister packs in cardboard box.
56 capsules in PVC/foil blister strips.

6.6 Special precautions for disposal and other handling

No special requirements for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Tillomed Laboratories Limited
220 Butterfield
Great Marlings
Luton
LU2 8DL
UK

8. Marketing Authorisation Number

PL 11311/0103

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/03/2009

10 DATE OF REVISION OF THE TEXT

26/11/2020