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This information is intended for use by health professionals

1. Name of the medicinal product

Ketoprofen-50 film coated Tablet

2. Qualitative and quantitative composition

Each Tablet contains Ketoprofen 50 mg

3. Pharmaceutical form

Film coated Tablet

4. Clinical particulars

4.1 Therapeutic indications

Ketoprofen-50 is recommended in the management of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute articular and peri-articular disorders, (bursitis, capsulitis, synovitis, tendinitis), cervical spondylitis, low back pain (strain, lumbago, sciatica, fibrositis), painful musculo-skeletal conditions, acute gout, dysmenorrhoea and control of pain and inflammation following orthopaedic surgery.

Ketoprofen-50 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

Adults: 100 – 200 mg once daily, depending on patient weight and on severity of symptoms.

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

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.

Paediatric dosage not established.

Ketoprofen-50 Tablets are for oral administration. To be taken preferably with or after food.

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

4.3 Contraindications

Ketoprofen is contraindicated in patients who have a history of hypersensitivity reactions such as bronchospasm, asthmatic attacks, rhinitis, angioedema, urticaria or other allergic-type reactions to ketoprofen, any other ingredients in this medicine, ASA or other NSAIDs. Severe, rarely fatal, anaphylactic reactions have been reported in such patients (see section 4.8 Undesirable effects).

Ketoprofen is contraindicated in patients with hypersensitivity to any of the excipients of the drug.

Ketoprofen is also contraindicated in the third trimester of pregnancy.

Ketoprofen is contraindicated in the following cases:

- Severe heart failure

- active peptic ulcer, or any history of gastrointestinal bleeding, ulceration or perforation

- haemorrhagic diathesis

- severe hepatic insufficiency

- severe renal insufficiency

4.4 Special warnings and precautions for use

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

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

Elderly:

The elderly have an increased risk of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal (see Section 4.2 Posology and method of administration).

Cardiovascular, Renal and Hepatic impairment:

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 (see Section 4.3 Contra-indications).

NSAIDs have also been reported to cause nephrotoxicity in various forms and this can lead to interstitial nephritis, nephrotic syndrome and renal failure.

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

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.

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. Similar consideration should be made before initiating long-term treatment in patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

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).

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, and in the elderly. Elderly 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). 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 Undesirable effects).

Patients with a history of gastrointestinal toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding), particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, 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 ketoprofen, the treatment should be withdrawn.

SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosis (SLE) and mixed connective tissue disorders, there may be an increased risk of aseptic meningitis (see Section 4.8 Undesirable effects).

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.

Skin reactions:

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. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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.

Visual disturbances:

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

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants:

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)

If coadministration is unavoidable, patient should be closely monitored.

Lithium:

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

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 Special warnings and precautions for use).

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 15mg/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.

Mifepristone:

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

Pentoxifylline:

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

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

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

Diuretics:

Risk of reduced diuretic effect. 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 Special warnings and precautions for use).

Cardiac glycosides:

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

Ciclosporin:

Increased risk of nephrotoxicity, particularly in elderly subjects.

Corticosteroids:

Increased risk of gastrointestinal ulceration or bleeding. (see Section 4.4 Special warnings and precautions for use).

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.

Tacrolimus:

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

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 (Section 4.4 Special warnings and precautions for use).

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 cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure.

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 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. 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.

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; 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.

Lactation

No data are available 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, drowsiness, fatigue and visual disturbances and be advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

The following CIOMS frequency rating is used, when applicable:

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:

<u>Blood and lymphatic system disorders</u>

- *rare:* haemorrhagic anaemia, anaemia due to bleeding

- *not known:* agranulocytosis, thrombocytopenia, bone marrow failure, neutropenia

<u>Immune system disorders</u>

- *rare:* anaphylactic reactions (including shock)

Psychiatric disorders

- *not known:* mood altered

Nervous system disorders

- *uncommon:* headache, dizziness, somnolence

- *rare:* paraesthesia

- *not known:* convulsions, dysgeusia, depression, confusion, hallucinations, vertigo, malaise, drowsiness, reports of aseptic meningitis (especially in patients with existing auto-immune disorders such as systemic lupus erythematosis, mixed connective tissue disease) with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4 Special warnings and precautions for use).

Eye disorders

- *rare:* visual disturbances such as blurred vision (see section 4.4 Special warnings and precautions for use)

- *not known:* optic neuritis

Ear and labyrinth disorders

- *rare:* tinnitus

Cardiac disorders

- *not known:* heart failure, oedema

Vascular disorders

- *not known:* hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders

- *rare:* asthma, asthmatic attack

- *not known:* 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:* 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, gastralgia, melaena, haematemesis

Gastrointestinal bleeding may sometimes be fatal, particularly in the elderly (see section 4.4 Special warnings and precautions for use).

Hepatobiliary disorders

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

- *not known:* abnormal liver function, jaundice

Skin and subcutaneous disorders

- *uncommon:* rash, pruritis

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

General disorders and administration site conditions

- *uncommon:* oedema, fatigue

- *not known:* headache, taste perversion

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 Special warnings and precautions for use).

In all cases of major adverse effects Ketoprofen-50 should be withdrawn at once.

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

4.9 Overdose

Symptoms

Cases of overdose have been reported with doses up to 2.5 g 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.

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.

Therapeutic measures:

There are no specific antidotes to ketoprofen overdosages. 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-50, 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.

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.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Ketoprofen overall has the properties of a potent non-steroidal anti-inflammatory agent. It has the following pharmacological effects:

Anti-inflammatory

It inhibits the development of carageenan-induced abscesses in rats at 1mg/kg, UV radiation induced erythema in guinea pigs at 6mg/kg. It is also a potent inhibitor of PGE_2 and $PFG_2\propto$ 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 6 mg/kg.

Antipyretic

Ketoprofen (2 and 6 mg/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 10 mg/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 Ketoprofen-50 Tablets. 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 protein

5.3 Preclinical safety data

No additional data of relevance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet contains: Lactose; Sugar powder; Colloidal anhydrous silica; Shellac ;Ethylcellulose; Talc

The tablet film-coat consists of: hypromellose, lactose monohydrate, macrogol 4000.

6.2 Incompatibilities

None stated

6.3 Shelf life

36 months

6.4 Special precautions for storage

Securitainer / HDPE bottle: Store below 30°C in a dry place.

Blister pack: Store below 25°C in a dry place and protect from light.

6.5 Nature and contents of container

Securitainer or HDPE bottle containing 100 Tablet

UPVC/Aluminium foil blister or UPVC coated with PVDC aluminium foil blister containing either 10, 20, or 10x10Tablets

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Ningbo Voice Biochemic Co., Ltd.

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