MELOXIM TABLET

Composition:
Meloxim 7.5 mg: Each tablet contains meloxicam 7.5 mg
Meloxim 15 mg: Each tablet contains meloxicam 15 mg

Description:
Meloxim 7.5 mg: Yellow coloured round shape tablet with score line on one side
Meloxim 15 mg: Yellow coloured oblong tablet with score line on one side

Pharmacodynamic:
Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties.
The anti-inflammatory activity of meloxicam has been proven in classical models of inflammation. It inhibits the biosynthesis of prostaglandins, known inflammation mediators.

Pharmacokinetic:
Absorption
Meloxicam is well absorbed from the gastrointestinal tract with bioavailability of 89% following oral administration. Mean maximum plasma concentration is achieved within 5-6 hours following single dose administration.
With multiple dosing, steady state conditions were reached within 3 to 5 days. Continuous treatment for periods of more than one year results in similar drug concentrations to those seen once steady state is first achieved. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake.
Distribution
Meloxicam is very strongly bound to plasma proteins, essentially albumin (99%). Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma. Volume of distribution is low, on average 11 L. Inter-individual variation is about 30-40%.
Biotransformation
Meloxicam undergoes extensive hepatic biotransformation. Four different metabolites of meloxicam were identified in urine, which are all pharmacodynamically inactive. The major metabolite, 5'-carboxymeloxicam (60% of dose), is formed by oxidation of an intermediate metabolite 5'-hydroxymethylmeloxicam, which is also excreted to a lesser extent (9% of dose). In vitro studies suggest that CYP 2C9 plays an important role in this metabolic pathway, with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16% and 4% of the administered dose respectively.
Elimination
Meloxicam is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5% of the daily dose is excreted unchanged in faeces, while only traces of the parent compound are excreted in urine.
The mean elimination half-life is about 20 hours. Total plasma clearance amounts on average 8 mL/min.
Linearity/non-linearity
Meloxicam demonstrates linear pharmacokinetics in the therapeutic dose range of 7.5 mg to 15 mg following per oral or intramuscular administration.

Special populations

Hepatic/renal Insufficiency

Neither hepatic, nor mild nor moderate renal insufficiency has a substantial effect on meloxicam pharmacokinetics. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and a daily dose of 7.5 mg must not be exceeded.

Elderly

Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

Indication:

Symptomatic treatment of painful osteoarthritis (arthrosis, degenerative joint disease), rheumatoid arthritis and ankylosing spondylitis.

Recommended dosage:

Osteoarthritis: 7.5mg/day. If necessary, the dose may be increased to 15 mg/day.

Rheumatoid Arthritis: 15 mg/day. According to the therapeutic response, the dose may be reduced to 7.5 mg/day.

Ankylosing Spondylitis: 15 mg/day

In patients with increased risks of adverse reactions, start treatment at the dose of 7.5mg/day.

In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg/day.

Maximum Recommended Daily Dose: 15 mg

The total daily dosage should not exceed 15 mg

The tablets should be swallowed with water or other fluid in conjunction with food.

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

Route of administration:

Oral administration

Contraindication:

This product is contraindicated in the following situations:

- Pregnancy and lactation
- Hypersensitivity to meloxicam or to any of the excipients or hypersensitivity to substances with similar action, e.g. NSAIDS, aspirin. Meloxim should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema or urticaria following the administration of aspirin or other NSAIDS.
- Active gastro-intestinal ulcer or history of recurrent gastro-intestinal ulcer
- Severely impaired liver function
- Non-dialysed severe renal failure
- Gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- Severe uncontrolled heart failure

Warning and precaution:

As with other NSAIDs, caution should be exercised when treating patients with a history of gastrointestinal disease and in patients receiving treatment with anticoagulants. Patients with gastrointestinal symptoms should be monitored. Meloxim should be withdrawn if peptic ulceration or gastrointestinal bleeding occurs.

Any history of oesophagitis, gastritis and/or peptic ulcer must be sought in order to ensure their total cure before starting treatment with meloxicam. Attention should routinely be paid to the possible onset of a recurrence in patients treated with meloxicam and with a past history of this type.

Patients with gastrointestinal symptoms or history of gastrointestinal disease (i.e. ulcerative colitis, Crohn's disease) should be monitored for digestive disturbances, especially for gastrointestinal bleeding.

The possible occurrence of severe skin reactions and serious life threatening hypersensitivity reactions (i.e. anaphylactic reactions) is known to occur with NSAIDs including oxicams. In those cases, meloxicam should be withdrawn immediately and careful observation is necessary.

In rare instances NSAIDs may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.

As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen as well as other laboratory disturbances, have been reported. The majority of these instances involved transitory and slight abnormalities. Should any such abnormality prove significant or persistent, the administration of meloxicam should be stopped and appropriate investigations undertaken.

Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics and consequently possible exacerbations of the condition of patients with cardiac failure or hypertension may occur with NSAIDs.

NSAIDs inhibit the synthesis of renal prostaglandins involved in the maintenance of renal perfusion, in patients with decreased renal blood flow and blood volume. Administration of NSAIDs in such situations may result in the decompensation of latent renal failure. However, renal function returns to its initial status when treatment is withdrawn. This risk concerns all elderly individuals, patients with congestive cardiac failure, cirrhosis, nephrotic syndrome or renal failure as well as patients on diuretics or having undergone major surgery leading to hypovolemia. Careful monitoring of diuresis and renal function during treatment is necessary in such patients

Adverse reactions are often less well tolerated in elderly, fragile or weakened individuals, who therefore require careful monitoring. As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired.

The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven. In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed.

Meloxicam, as any other NSAID, may mask symptoms of an underlying infectious disease.

The use of meloxicam, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair 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 meloxicam should be considered.

WARNING

RISK OF GI ULCERATION, BLEDDING AND PERFORATION WITH NSAID

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

Cardiovascular Thrombotic Events

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, principally myocardial infarction, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk of an adverse cardiovascular event in patient taking NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration.

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening the pre-existing hypertension and patients taking antihypertensive with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart Failure

Fluid retention and oedema have been observed in some patients taking NSAIDs, there caution is advised in patients with fluid retention or heart failure.

Gastrointestinal Events

All NSAIDs can cause gastrointestinal discomfort and rarely serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Caution is advised in patients with risk factors for gastrointestinal events e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about signs and symptoms of serious gastrointestinal toxicity. The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Severe Skin Reactions

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and

symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Drug interaction:

Other NSAIDs Including Salicylates: Concomitant administration of more than one NSAID may increase the risk of gastrointestinal ulceration and bleeding through synergistic action.

Oral Anticoagulants, Ticlopidine, Systemically Administered Heparin, Thrombolytics: Increased risk of bleeding. If such co-prescribing cannot be avoided, close monitoring of the effects of anticoagulants is required.

Lithium: NSAIDs have been reported to increase lithium plasma levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing Meloxim.

Methotrexate: As with other NSAIDs, Meloxim may increase the haematologic toxicity of methotrexate. In this situation, strict monitoring of blood cell count is recommended.

Contraception: NSAIDs have been reported to decrease the efficacy of intrauterine devices.

Diuretics: Treatment with NSAIDs is associated with the potential for acute renal insufficiency in patients who are dehydrated. Patients receiving Meloxim and diuretics should be adequately hydrated and be monitored for renal function prior to initiating treatment.

Antihypertensives (eg, β-blockers, ACE inhibitors, vasodilators, diuretics): A reduced effect of the antihypertensive drug by inhibition of vasodilating prostaglandins has been reported during treatment with NSAIDs. Cholestyramine binds meloxicam in the gastrointestinal tract leading to a faster elimination of meloxicam.

Nephrotoxicity of cyclosporin may be enhanced by NSAIDs via renal prostaglandin-mediated effects. During combined treatment, renal function is to be measured.

Meloxicam is eliminated almost entirely by hepatic metabolism, of which approximately $^{2}/_{3}$ are mediated by cytochrome (CYP) P-450 enzymes (CYP2C9 major pathway and CYP3A4 minor pathway) and $^{1}/_{3}$ by other pathways eg, peroxidase oxidation. The potential for a pharmacokinetic interaction should be taken into account when meloxicam and drugs known to inhibit, or to be metabolised by, CYP2C9 and/or CYP3A4 are administered concurrently. No relevant pharmacokinetic drug-drug interactions were detected with respect to the concomitant administration of antacids, cimetidine, digoxin and furosemide Interactions with oral antidiabetics cannot be excluded.

Pregnancy and lactation:

Pregnancy

− In animals, lethal effects on the embryo have been reported at doses higher than those used clinically.

− It is advisable to avoid the administration of meloxicam during the first two trimesters of pregnancy.

− During the final three months, all prostaglandin synthesis inhibitors may expose the fetus to cardiopulmonary (pulmonary hypertension with premature closure of the ductus arteriosus) and renal toxicity or inhibit the contraction of the uterus. This effect on the uterus has been associated with an increase in the incidence of dystocia and delayed parturition in animals. Thus all NSAIDs are absolutely contra-indicated during the final three months.

Lactation

NSAIDs pass into mother's milk. Administration should therefore be avoided, as a precautionary measure, in women who are breast feeding.

Side effects:
The following adverse events which may be causally related to the administration of Meloxim have been reported. The frequencies given are based on corresponding occurrences in clinical trials, regardless of any causal relationship. The information is based on clinical trials involving 3750 patients who have been treated with daily oral doses of 7.5 or 15 mg Meloxim tablets over a period of up to 18 months (mean duration of treatment 127 days).
Adverse events which may be causally related to the administration of Meloxim that have come to light as a result of reports received in relation to administration of the marketed product are followed by a reference number. The incidence of these rare events is difficult to quantify. All are assumed to occur with a frequency of <0.1%.
Gastrointestinal: More frequent than 1%: Vomiting, abdominal pain, constipation, flatulence, diarrhoea; between 0.1% and 1%: Transitory abnormalities of liver function parameters (eg, raised transaminases or bilirubin), eructation, oesophagitis, gastroduodenal ulcer, occult or macroscopic gastrointestinal bleeding; less frequent than 0.1%: Gastrointestinal perforation, colitis, hepatitis, gastritis.
Haematological: More frequent than 1%: Anaemia; between 0.1% and 1%: Disturbances of blood count, including differential white cell count, leukopenia and thrombocytopenia.
Concomitant administration of a potentially myelotoxic drug, in particular methotrexate, appears to be a predisposing factor to the onset of a cytopenia. Dermatological: More frequent than 1%: Pruritus, skin rash; between 0.1% and 1%: Stomatitis, urticaria; less frequent than 0.1%: Photosensitisation. On rare occasions bullous reactions, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis may develop.
Respiratory: Less frequent than 0.1%: Onset of acute asthma has been reported in certain individuals following the administration of aspirin or other NSAIDs, including Meloxim.
Central Nervous System: More frequent than 1%: Lightheadedness, headache; between 0.1% and 1%: Vertigo, tinnitus, drowsiness; less frequent than 0.1%: Confusion and disorientation, alteration of mood.
Cardiovascular: More frequent than 1%: Oedema; between 0.1% and 1%: Increase of blood pressure, palpitations, flushes.
Genitourinary: Between 0.1% and 1%: Abnormal renal function parameters (increased serum creatinine and/or serum urea); less frequent than 0.1%: Acute renal failure.
Vision Disorders: Less frequent than 0.1%: Conjunctivitis, visual disturbances including blurred vision.
Hypersensitivity Reactions: Less frequent than 0.1%: Angio-oedema and immediate hypersensitivity reactions including anaphylactoid/anaphylactic reactions.

Overdosage:
In case of overdosage, the standard measures of gastric evacuation and in general supportive measures should be used as there is no known antidote. It has been shown in clinical trial that cholestyramine accelerates the elimination of meloxicam.

Storage condition:
Store below 30°C.

Presentation:
Blister of 10 tablets. Box of 1, 10, 50, 100 strips

Manufactured by:
NORIPHARMA SDN. BHD. (792633-A)
Lot 5030, Jalan Teratai,
5 $^{1}/_{2}$ Mile off Jalan Meru,
41050 Klang,
Selangor Darul Ehsan.

Date of revision:
September 2020