For the Use Only of a Registered Medical Practitioner

MELARTIN TABLETS

(Meloxicam Tablets 7.5/15 mg)

COMPOSITION

MELARTIN 7.5
Each Tablet contains
Meloxicam BP……..7.5 mg

MELARTIN 15
Each Tablet contains
Meloxicam BP……..15 mg

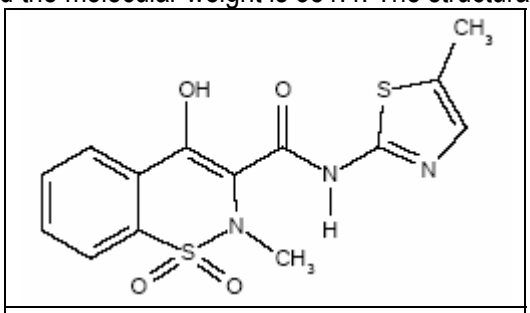
PRODUCT DESCRIPTION

MELARTIN 7.5 Pastel yellow colored, slightly mottled round biconvex uncoated tablet

MELARTIN 15 Pastel yellow colored, slightly mottled round uncoated tablet with a snap break-line on one side and plain on other side

DESCRIPTION[1]

MELARTIN tablet contains meloxicam, which is an oxicam derivative, is a member of enolic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Meloxicam is chemically designated as 4- hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide.The empirical formula of meloxicam is $C_{14}H_{13}N_3O_4S_2$ and the molecular weight is 351.4. The structural formula is as follows:



MELOXICAM

PHARMACOLOGY[1, 2]

- Mechanism of Action

Meloxicam is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits antiinflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of meloxicam, like that of other NSAIDs, may be related to prostaglandin synthetase (cyclo-oxygenase) inhibition.

- Pharmacokinetics

Absorption

Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 89% following oral administration (capsule).

Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 5-6 hours with solid oral dosage forms (capsules and tablets).

With multiple dosing, steady state conditions were reached within 3 to 5 days. Maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively. Continous 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. Interindividual variation is the order of 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).

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 15 mg following per oral or intramuscular administration.

Special populations

Hepatic/renal Insufficiency
Neither hepatic, mild nor moderate renal insufficiency have 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.

INDICATIONS[3]

MELARTIN (Meloxicam) tablets are indicated in the following conditions:

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

DOSAGE AND ADMINISTRATION[3]

For oral use

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

Maximum Recommended Daily Dose of MELARTIN tablet is 15 mg/day. 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.

Special Populations

Elderly patients and patients with increased risks for adverse reaction:
The recommended dose for long term treatment of rheumatoid arthritis and ankylosing spondylitis in elderly patients is 7.5 mg per day. Patients with increased risks for adverse reactions should start treatment with 7.5 mg per day.

Renal impairment:
In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg per day. No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min). (For patients with non-dialysed severe renal failure, see Contraindication.)

Hepatic impairment:
No dose reduction is required in patients with mild to moderate hepatic impairment.

Children:
Meloxicam should not be used in children aged under 15 year.

CONTRAINDICATIONS[1, 2]

MELARTIN tablets are contraindicated in:

- Patients with known hypersensitivity to meloxicam or to any of the excipients or hypersensitivity to substances with a similar action.
- Patients who have experienced asthma, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see Warnings, Anaphylactoid Reactions, and PRECAUTIONS, Pre-existing Asthma).
- For the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see Warnings).
- 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.
- Pregnancy and lactation.
- Children and adolescents <15 years.

Pregnancy

Meloxicam is contraindicated during pregnancy. Inhibition of prostaglandin-synthesis may adversely affect pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastrochisis 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.

During the third trimester of pregnancy all prostaglandin-synthesis inhibitors may expose :
i) 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;

ii) 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

Lactation

NSAIDs are known to pass into mother's milk. Administration therefore is contraindicated in women who are breastfeeding.

Pediatrics
Meloxicam should not be used in children aged under 15 years.

Geriatrics
As with any NSAID, caution should be exercised in treating the elderly (65 years and older).

DRUG INTERACTIONS[2]

Other NSAIDs, including salicylates
Administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect. The concomitant use of meloxicam with other NSAIDs is not recommended.

Corticosteroids
Increased risk of gastrointestinal ulceration or bleeding.

Oral anticoagulants
Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. NSAIDs may enhance the effects of anti-coagulants, such as warfarin. The concomitant use of NSAIDs and oral anticoagulants is not recommended. Careful monitoring of the INR is required if it proves impossible to avoid such combination.

Thrombolytics and antiplatelet drugs
Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa.

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

Diuretics, ACE inhibitors and Angiotensin-II Antagonists
NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin-II antagonists and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Other antihypertensive drugs (e.g. Beta-blockers)
As for the latter, a decrease of the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.

Cyclosporin
Nephrotoxicity of cyclosporin may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function is to be measured. A careful monitoring of the renal function is recommended, especially in the elderly.

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

Lithium
NSAIDs have been reported to increase blood lithium levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and NSAIDs is not recommended. If this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of meloxicam treatment.

Methotrexate
NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of NSAIDs is not recommended.

The risk of an interaction between NSAID preparations and methotrexate, should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In case combination treatment is necessary blood cell count and the renal function should be monitored. Caution should be taken in case both NSAID and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity.

Cholestyramine
Cholestyramine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that clearance for meloxicam increases by 50% and the half-life decreases to 13+3 hrs.

PRECAUTIONS/WARNINGS[1, 2]

RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAIDs
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 theraphy, 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.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms.

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. The use of meloxicam with concomitant NSAIDs including

cyclooxygenase-2 selective inhibitors should be avoided.

In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed.

Any history of esophagitis, 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.

Cardiovascular Effects

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.

Congestive Heart Failure and Edema

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

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation

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 patient about signs and symptoms of serious gastrointestinal toxicity. The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Anaphylactoid Reactions

As with other NSAIDS, anaphylactoid reactions have occurred in patients without known prior exposure to meloxicam. Meloxicam should not be given to patients with the aspirin triad. This symptom complex

typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see Contraindications and PRECAUTIONS, Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

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.

Functional renal failure

NSAIDs, by inhibiting the vasodilating effect of renal prostaglandins, may induce a functional renal failure by reduction of glomerular filtration. This adverse event is dose-dependant. At the beginning of the treatment, or after dose increase, careful monitoring of diuresis and renal function is recommended in patients with the following risk factors

- Elderly
- Concomitant treatments such as ACE inhibitors, angiotensin-II antagonists, sartans, diuretics
- Hypovolemia (whatever the cause)
- Congestive heart failure
- Renal failure
- Nephrotic syndrome
- Lupus nephropathy
- Severe hepatic dysfunction (serum albumin < 25 g/l or Child-Pugh score ≥ 10)

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

Hyperkalaemia

Hyperkalaemia can be favoured by diabetes or concomitant treatment known to increase kalaemia. Regular monitoring of potassium values should be performed in such cases.

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 elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

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.

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

ADVERSE REACTIONS [2]

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been reported following administration. Less frequently, gastritis has been observed.

Blood and the lymphatic system disorders
Common : Anemia
Uncommon : Disturbances of blood count: leucocytopenia ; thrombocytopenia ; agranulocytosis

Immune system disorders
Rare : Anaphylactic / anaphylactoid reactions

Psychiatric disorders
Rare : Mood disorders, insomnia and nightmares

Nervous system disorders
Common : Light-headedness, headache
Uncommon : Vertigo, tinnitus, drowsiness
Rare : Confusion

Eye disorders
Rare : Visual disturbances including blurred vision

Cardiac disorders
Uncommon : Palpitations

Vascular disorders
Uncommon : Increase in blood pressure, flushes

Respiratory, thoracic and mediastinal disorders :
Rare : Onset of asthma attacks in certain individuals allergic to aspirin or other NSAIDs

Gastrointestinal disorders
Common : Dyspepsia, nausea and vomiting symptoms, abdominal pain, constipation, flatulence, diarrhea
Uncommon : Gastrointestinal bleeding, gastroduodenal ulcers, esophagitis, stomatitis
Rare : Gastrointestinal perforation, gastritis, colitis
The peptic ulcers, perforation or gastrointestinal bleeding, that may occur can be sometimes severe, especially in elderly.

Hepato-biliary disorders
Rare : Hepatitis

Skin and subcutaneous tissue disorders
Common : Pruritus, rash
Uncommon : Urticaria
Rare : Stevens-Johnson Syndrome and toxic epidermal necrolysis, angioedema, bullous reactions such as erythema multiforme, photosensitivity reactions

Renal and urinary disorders
Uncommon: Sodium and water retention, hyperkalaemia,
Rare: Acute functional renal failure in patients with risk factors

General disorders and administration site conditions
Common : Edema including edema of the lower limbs.

Investigations
Uncommon : Transitory disturbance of liver function test (e.g. raised transaminases or bilirubin) Disturbance of laboratory tests investigating renal function (e.g. raised creatinine or urea)

OVERDOSAGE[1]

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an overdose.

Patients should be managed with symptomatic and supportive care following an NSAID overdose. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.

STORAGE
Store below 30°C, protected from moisture

KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN

SUPPLY
Blister of 10 X 10's; Blister Strips of 10 X 10's (cold form)

REFERENCES

1. US Prescribing Information for *MOBIC* ®, Boehringer Ingelheim Pharmaceuticals Inc. USA. July 2006.

2. ABPI Compendium of Data Sheets. Summary of Product Characteristics for *MOBIC* Boehringer Ingelheim Ltd. April 2007.
3. Prescribing Information for *MOBIC* Tablet, Boehringer Ingelheim Pharmaceuticals. Malaysia

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