Mobic® Tablets

(Meloxicam)

7.5 mg/15 mg

Boehringer Ingelheim

Composition
1 tablet contains 7.5 mg or 15 mg
4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide (= Meloxicam)

Pharmacological properties
MOBIC is a non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class, which has shown anti-inflammatory, analgesic and antipyretic properties in animals. Meloxicam showed potent anti-inflammatory activity in all standard models of inflammation. A common mechanism for the above effects may exist in the ability of meloxicam to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.
Comparison of the ulcerogenic dose and the anti-inflammatory effective dose in the rat adjuvant arthritis model confirmed a superior therapeutic margin in animals over standard NSAIDs. In vivo, meloxicam inhibited prostaglandin biosynthesis more potently at the site of inflammation than in the gastric mucosa or the kidney.
These differences are thought to be related to a selective inhibition of COX-2 relative to COX-1 and it is believed that COX-2 inhibition provides the therapeutic effects of NSAIDs whereas inhibition of constitutive COX-1 may be responsible for gastric and renal side effects.
The COX-2 selectivity of meloxicam has been confirmed both in vitro and ex vivo in a number of test systems. In the human whole blood assay, meloxicam has been shown in vitro to inhibit COX-2 selectively. Meloxicam (7.5 and 15 mg) demonstrated a greater inhibition of COX-2 ex vivo, as demonstrated by a greater inhibition of lipopolysaccharide-stimulated PGE2 production (COX-2) as compared with thromboxane production in clotting blood (COX-1). These effects were dose-dependent. Meloxicam has been demonstrated to have no effect on either platelet aggregation or bleeding time at recommended doses ex vivo, while indomethacin, diclofenac, ibuprofen and naproxen significantly inhibited platelet aggregation and prolonged bleeding.
In clinical trials, gastro-intestinal adverse events overall were reported less frequently with meloxicam 7.5 mg and 15 mg than with the NSAIDs with which it has been compared, due predominantly to a lower reporting incidence of events such as dyspepsia, vomiting, nausea and abdominal pain. The incidence of upper gastro-intestinal perforation, ulcers, and bleeds reported in association with meloxicam is low and dose dependent. There is no single study powered adequately to detect statistically differences in the incidence of clinically significant upper gastro-intestinal perforation, obstruction, or bleeds between meloxicam and other NSAIDs. A pooled analysis has been conducted involving patients treated with meloxicam in 35 clinical trials in the indications osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Exposure to meloxicam in these trials ranged from 3 weeks to one year (most patients were enrolled in one-month studies). Almost all patients participated in trials that permitted enrolment of patients with a prior history of gastro-intestinal perforation, ulcer or bleed.
The incidence of clinically significant upper gastro-intestinal perforation, obstruction, or bleed (POB) was assessed retrospectively following independent blinded review of cases. Results are shown in the following table. Cumulative risk of POBs for meloxicam 7.5 mg and 15 mg from BI clinical trials compared to diclofenac and piroxicam (Kaplan-Meier estimates)

TREATMENT Daily dose	Interval (days)	Patients at interval midpoint	POBs within interval	Risk (%)	95% confidence interval
Meloxicam					
7.5 mg	1 - < 30	9636	2	0.02	0.00-0.05
	30 - < 91	551	1	0.05	0.00-0.13
15 mg	1 - < 30	2785	3	0.12	0.00-0.25
	30 - < 91	1683	5	0.40	0.12-0.69
	91 - <182	1090	1	0.50	0.16-0.83
	182 - <365	642	0	0.50	
Diclofenac					
100 mg	1 - < 30	5110	7	0.14	0.04-0.24
	30 - < 91	493	2	0.55	0.00-1.13
Piroxicam					
20 mg	1 - < 30	5071	10	0.20	0.07-0.32
	30 - < 91	532	6	1.11	0.35-1.86

Pharmacokinetics
Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 89% following oral administration.
Tablets, oral suspension and capsules were shown to be bioequivalent.
Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 2 hours for the suspension and 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. Once daily dosing leads to drug plasma concentrations with a relatively small peak-trough fluctuation in the range of 0.4 - 1.0 µg/mL for 7.5 mg doses and 0.8 - 2.0 µg/mL for 15 mg doses, respectively (Cmin and Cmax at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours for the tablet, capsule and the oral suspension, respectively.
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). 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 insufficiency, nor mild to 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
Symptomatic treatment of painful osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Dosage and Administration
The product should be used by physician prescription.
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. According to the therapeutic response, the dose may be reduced to 7.5 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.
As the potential for adverse reactions increases with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used.
Adolescents:
The maximum recommended dose for adolescents is 0.25 mg/kg.
As a dosage for use in children has not yet been established, usage should be restricted to adolescents and adults.
The maximum recommended daily dose of MOBIC is 15 mg.
Tablets should be swallowed with water or other fluid in conjunction with food.
Combined administration: The total daily dosage of MOBIC administered as capsules, tablets, suppositories, oral suspension and injections should not exceed 15 mg.

Contraindications
Known hypersensitivity to meloxicam or any excipient of the product. There is a potential for cross sensitivity to acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (NSAIDs).
MOBIC should not be given to patients who have developed signs of asthma, nasal polyps, anglo-oedema or urticaria following the administration of acetylsalicylic acid or other NSAIDs.
- Active or recent gastro-intestinal ulceration / perforation
- Active Inflammatory Bowel Disease (Crohn's Disease or Ulcerative Colitis)
- Severe hepatic insufficiency
- Non-dialysed severe renal insufficiency
- overt gastro-intestinal bleeding, recent cerebrovascular bleeding or other bleeding disorders - severe uncontrolled heart failure
- Children under 12 years
- Pregnancy or breastfeeding.

MOBIC is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to "Special warnings and precautions") the use of the product is contraindicated.

Special warnings and precautions
As with other NSAIDs caution should be exercised when treating patients with a history of gastro-intestinal disease and in patients receiving treatment with anticoagulants. Patients with gastro-intestinal symptoms should be monitored. MOBIC should be withdrawn if peptic ulceration or gastro-intestinal bleeding occurs. As with other NSAIDs gastro-intestinal bleeding, ulceration or perforation, potentially fatal, can occur at any time during treatment, with or without warning symptoms or a previous history of serious gastro-intestinal events. The consequences of such events are generally more serious in the elderly.
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. MOBIC should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity. NSAIDs may increase the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. NSAIDs inhibit the synthesis of renal prostaglandins, which play a supportive role in the maintenance of renal perfusion. In patients whose renal blood flow and blood volume are decreased, administration of an NSAID may precipitate overt renal decompensation which is typically followed by recovery to pre-treatment state upon discontinuation of non-steroidal anti-inflammatory therapy. Patients at greatest risk of such a reaction are elderly individuals, dehydrated patients, those with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease, those receiving a concomitant treatment with a diuretic, ACE inhibitor or angiotensin II receptor antagonist or those having undergone major surgical procedures, which led to hypovolaemia. In such patients the volume of diuresis and the renal function should be carefully monitored at the beginning of therapy.
In rare instances NSAIDs may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.
The dose of MOBIC in patients with end-stage renal failure on haemodialysis should not be higher than 7.5 mg. No dose reduction is required in patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 ml/min).
As with other NSAIDs, occasional elevations of serum transaminases or other parameters of liver function have been reported. In most cases these have been small and transient increases above the normal range. If the abnormality is significant or persistent, MOBIC should be stopped and follow up tests carried out.
No dose reduction is required in patients with clinically stable liver cirrhosis.
Frail or debilitated patients may tolerate side effects less well and such patients should be carefully supervised. As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function. Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with NSAIDs. Cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. For patients at risk, clinical monitoring is recommended. 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. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.
For relevant drug interactions that require particular attention, see section "Interactions".
There are no specific studies about effects on the ability to drive vehicles and to use machinery. Patients who experience visual disturbances, drowsiness or other central nervous system disturbances should refrain from these activities.
Meloxicam should be used with caution in patients with cardiovascular diseases, since cardiovascular events have been observed with other selective cyclooxygenase (COX)-2 inhibitors as well as the safety profile of long term use not yet established for selective COX-2 inhibitors for Taiwanese.
MOBIC tablets 7.5 mg contains 47 mg lactose per maximum recommended daily dose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.
MOBIC tablets 15 mg contains 20 mg lactose per maximum recommended daily dose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interactions
- Other Prostaglandin Syntethase Inhibitors (PSI) including glucocorticoids and salicylates (acetylsalicylic acid): Co-administration of PSIs may increase the risk of gastro-intestinal ulcers and bleeding, via a synergistic effect, and is not recommended. The concomitant use of meloxicam with other NSAIDs is not recommended.
  Concomitant administration of aspirin (1000 mg tid) to healthy volunteers tended to increase the AUC (10%) and Cmax (24%) of meloxicam. The clinical significance of this interaction is not known.
- Oral anticoagulants, antiplatelet drugs, systemically administered heparin, thrombolytics and Selective Serotonin Reuptake Inhibitors (SSRIs): increased risk of bleeding, via inhibition of platelet function. If such co-prescribing cannot be avoided, close monitoring is required.
- Lithium: NSAIDs have been reported to increase lithium plasma 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. Although the pharmacokinetics of methotrexate (15 mg/week) were not relevantly affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAID drugs.
- Contraception: A decrease of the efficacy of Intrauterine devices by NSAIDs has been previously reported but needs further confirmation.
- Diuretics: Treatment with NSAIDs is associated with the potential for acute renal insufficiency in patients who are dehydrated. Patients receiving MOBIC and diuretics should be adequately hydrated and be monitored for renal function prior to initiating treatment.
- Antihypertensives (e.g. beta-blockers, ACE-inhibitors, vasodilators, diuretics): A reduced effect of the Antihypertensive drug by inhibition of vasodilating Prostaglandins has been reported during treatment with NSAIDs.
- NSAIDs and angiotensin-II receptor antagonists as well as ACE inhibitors exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment this may lead to acute renal failure.
- Cholestyramine binds meloxicam in the gastro-intestinal tract leading to a faster elimination of meloxicam.
- Nephrotoxicity of cyclosporine 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 two thirds are mediated by cytochrome (CYP) P450 enzymes (CYP 2C9 major pathway and CYP 3A4 minor pathway) and one-third by other pathways, such as 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, CYP 2C9 and/or CYP 3A4 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
MOBIC 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 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 increase 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 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-hydroamnionisis;

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

While no specific experience exists for MOBIC, NSAIDs are known to pass into mother's milk. Administration should therefore be avoided in women who are breastfeeding.

Side effects
The following adverse events, which may be causally related to the administration of MOBIC, have been reported. The frequencies given below 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 MOBIC tablets or capsules 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 MOBIC 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 less than 0.1%.
Gastro-intestinal:
more frequent than 1%: dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea
between 0.1 and 1%: transitory abnormalities of liver function (involving 3750 patients who have been treated with daily oral doses of 7.5 or 15 mg MOBIC tablets or capsules over a period of up to 18 months (mean duration of treatment 127 days).
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Gastro-intestinal:
more frequent than 1%: dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea
between 0.1 and 1%: transitory abnormalities of liver function parameters (e.g. raised transaminases or bilirubin), eructation, oesophagitis, gastroduodenal ulcer, occult or macroscopic gastro-intestinal bleeding
less frequent than 0.1%: gastro-intestinal perforation, colitis, hepatitis, gastritis.
Gastro-intestinal bleeding, ulceration or perforation may potentially be fatal.
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 asthma attacks in individuals allergic to aspirin or other NSAIDs
Central nervous system:
more frequent than 1%: light-headedness, 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
The use of NSAIDs may be related to micturition disorders, including acute urinary retention.
Vision disorders:
less frequent than 0.1%: conjunctivitis, visual disturbances including blurred vision.
Hypersensitivity reactions:
less frequent than 0.1%: anglo-oedema and immediate hypersensitivity reactions, including anaphylactoid / anaphylactic reactions

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

Toxicology
An extensive toxicological program confirmed that meloxicam has an acceptable safety profile.
Oral LD50 values ranged from about 98 mg/kg in female rats up to >800 mg/kg in minipigs. Intravenous values ranged from about 52 mg/kg in rats to 100 - 200 mg/kg in minipigs. Main signs of toxicity included reduced motor activity, anaemia, and cyanosis. Most deaths occurred as a consequence of gastric ulcers and subsequent perforation leading to peritonitis.
Repeated dose toxicity studies in rats and minipigs showed characteristic changes reported with other NSAIDs e.g. gastro-intestinal ulceration and erosions, and in the long term studies, renal papillary necrosis. Gastro-intestinal side effects were observed at oral doses of 1 mg/kg and higher in rats, and of 3 mg/kg and above in minipigs. After intravenous administration doses of 0.4 mg/kg in rats and 9 mg/kg in minipigs caused gastro-intestinal lesions. Renal papillary necrosis occurred only in rats at doses of 0.6 mg/kg or higher after lifetime exposure to meloxicam.
Studies of toxicity on reproduction in rats and rabbits did not reveal teratogenicity up to oral doses of 4 mg/kg in rats and 80 mg/kg in rabbits. Oral reproductive studies in the rat have shown a decrease of ovulations and inhibition of implantations and embryotoxic effects (increase of resorptions) at maternotoxic dose levels at 1 mg/kg and higher.
The affected dose levels exceeded the clinical dose (7.5-15 mg) by a factor of 10 to 5-fold on an mg/kg dose basis (75 kg person).
Fetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described.
Meloxicam was not mutagenic in the Ames test, the host-mediated assay, and a mammalian gene mutation assay (V79/HPRT), nor is it clastogenic in the chromosomal aberration assay in human lymphocytes and the mouse bone marrow micronucleus test.
Carcinogenicity studies in rats and mice did not show a carcinogenic potential up to dose levels of 0.8 mg/kg in rats and 8 mg/kg in mice. In these studies meloxicam was chondro-neutral, i.e. it did not damage the articular cartilage following long-term exposure.
Meloxicam did not induce immunogenic reactions in tests on mice and guinea pigs. In several tests meloxicam proved to be less phototoxic than older NSAIDs but similar in this respect to both piroxicam and tenoxicam.
In local tolerance studies meloxicam was well tolerated by all tested routes of administration; intravenous, intramuscular, rectal, dermal, and ocular administration.

Availability
Tablets 7.5 mg: 4-1000's pack in plastic bottle or in aluminium foil of box
Tablets 15 mg: 2-1000's pack in plastic bottle or in aluminium foil of box

Store in a safe place out of the reach of children!
Store below 30°C

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