

# New Zealand Datasheet

## Name of Medicine

MOBIC<sup>®</sup>

Meloxicam

## Presentation

Tablets 7.5mg: Pale yellow, round uncoated tablets marked 59D on one side with break-bar, and company logo on the other.

## Uses

### Actions

Meloxicam 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 PGE<sub>2</sub> 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.

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	Interval (days)	Patients at interval midpoint	POBs within interval	Risk (%)	95% confidence interval
Daily dose					
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

### Absorption

Oral administration: Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of about 90% following oral administration.

Following single dose administration of meloxicam, median maximum plasma concentrations are achieved within 5-6 hours for the tablets.

Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake or the use of inorganic antacids. Dose linearity was demonstrated after oral administration in the therapeutic dose range of 7.5 to 15 mg.

With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to mean 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 (C<sub>min</sub> and C<sub>max</sub> at steady state, correspondingly). Mean maximum plasma concentrations of meloxicam at steady state, are achieved within five hours for the tablet.

### 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, i.e. approx. 11 L. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake or the use of inorganic antacids.

### 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 varies between 13 and 25 hours after oral i.m. and i.v. administration. Total plasma clearance amounts to about 7 - 12 mL/min following single doses orally, intravenously or rectally administered. .

## Special populations

### *Patients with hepatic/renal insufficiency:*

Neither hepatic insufficiency, nor mild renal insufficiency has a substantial effect on meloxicam pharmacokinetics. Subjects with moderate renal impairment had significantly higher total drug clearance. A reduced protein binding is observed in patients with terminal renal failure. 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:*

Elderly male subjects exhibited similar mean pharmacokinetic parameters compared to those of young male subjects. Elderly female patients showed higher AUC-values and longer elimination half-lives compared to those of young subjects of both genders. Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

### *Children:*

In a study of 36 children, kinetic measurements were made in 18 children at doses of 0.25 mg/kg BW administered in the form of an oral suspension. Maximum plasma concentration  $C_{max}$  (-34%) as well as  $AUC_{0-\infty}$  (-28%) tended to be lower in the younger age group (aged 2 to 6 years, n = 7) as compared to the older age group (7 to 14 years, n = 11) while weight normalised clearance appeared to be higher in the younger age group. A historical comparison with adults revealed that plasma concentrations were at least similar for older children and adults. Plasma elimination half-lives (13 h) were similar for both groups and tended to be shorter than in adults (15-20 h).

## Indications

Symptomatic treatment of painful osteoarthritis (arthrosis, degenerative joint disease).

Symptomatic treatment of rheumatoid arthritis.

In patients for whom longer-term use may be required, treatment efficacy should be reviewed within the first month of treatment and MOBIC withdrawn if there is a lack of therapeutic benefit. Patients on long-term treatment should be reviewed regularly, such as every three months with regards to efficacy, risk factors and the ongoing need for treatment.

The decision to prescribe a selective COX-2 inhibitor should only be made after assessment of the individual patient's overall risk for developing severe adverse events e.g. history of cardiovascular, renal, or gastrointestinal disease, and after use of alternative therapies such as non-pharmacological interventions and simple analgesic therapy where these have been found to lack analgesic efficacy or to have unacceptable adverse effects.

## Dosage and Administration

MOBIC may be administered in a dose of 7.5mg daily. As the potential for adverse reactions increases with dose and duration of exposure, all patients taking MOBIC should commence therapy at the lowest recommended dose, and be titrated to the lowest dose compatible with effective control of symptoms for the shortest possible period.

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.

In dialysis patients with severe renal failure:

The dose should not exceed 7.5mg per day.

In patients with mild to moderate renal impairment (creatinine clearance of greater than 25 mL/min):

The dose should not exceed 7.5 mg per day.

Adolescents:

The maximum recommended dose for adolescents is 0.25 mg/kg.

In general usage should be restricted to adolescents and adults, see contraindications.

The total daily dose of tablets should be taken as a single dose and should be swallowed with water and other fluid in conjunction with food.

## **Contraindications**

- Patients with known hypersensitivity to MOBIC or its excipients. There is a potential for cross sensitivity to aspirin and other NSAIDs.
- In case of rare hereditary conditions that may be incompatible with an excipient of the product (please refer to Warnings and Precautions) the use of the product is contraindicated. MOBIC should not be given to patients who have developed signs of asthma, nasal polyps, angioedema or urticaria following the administration of aspirin 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 established systemic bleeding disorders.
- Severe uncontrolled heart failure.
- Patients who have previously had a myocardial infarction or stroke.
- MOBIC should not be given in the peri-operative period in patients undergoing cardiac surgery, including coronary artery bypass graft (CABG), or major vascular surgery
- Children and adolescents aged less than 12 years.
- Pregnancy or lactation.

## **Warnings and Precautions**

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

Serious gastrointestinal (GI) toxicity such as bleeding, ulceration and perforation of the stomach, small intestine or large intestine, which may be potentially fatal, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. The consequences of such events are generally more serious in the elderly.

Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

Studies have shown that patients with a prior history of ulcer disease and/or gastrointestinal bleeding and who use NSAIDs have a greater than 10-fold higher risk of developing a gastrointestinal bleed than patients with neither of these factors.

Caution is advised in patients most at risk of developing a gastrointestinal complication with NSAIDs: the elderly, patients using any other NSAID or aspirin concomitantly or patients with a prior history of or recent gastrointestinal disease such as ulceration and gastrointestinal bleeding.

NSAIDs should be prescribed with caution in patients with a prior history of or recent ulcer disease or gastrointestinal bleeding. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Minor upper GI problems, such as dyspepsia, are common and may occur at any time during NSAID therapy. Therefore physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur.

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.

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.

As with other NSAIDs, MOBIC inhibits 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 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 7.5mg. Patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25mL/min) may take 7.5mg daily.

As with most 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.

Use of COX-2 inhibitors (of which meloxicam is one) has been associated with an increased risk of cardiovascular adverse events (myocardial infarction and stroke). This association has been demonstrated with agents of the Coxib class.

Prescribers should inform the individual patient of the (possible or potential) increased risks when prescribing meloxicam for patients at high risk of cardiovascular adverse events (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension or smokers).

Two large, controlled clinical trials of a different COX-2 selective inhibitor for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. In the absence of comparable data with meloxicam, it may be assumed that patients at high risk of cardiovascular disease (including patients with diabetes, ischaemic heart disease, cardiac failure, hyperlipidaemia, hypertension, or smokers) who are undergoing any major surgery may face an increased risk of developing a cardiovascular event. Such patients with significant risk factors for cardiovascular events should only be treated with meloxicam after careful consideration of the patient's overall risk and the potential risks and benefits of alternative analgesic therapies.

MOBIC is not a substitute for cardiovascular prophylaxis and concurrent anti-platelet therapies should not be discontinued. There is no evidence that concurrent use of aspirin decreases the risk of cardiovascular adverse events associated with COX-2 inhibitors, including MOBIC.

Concurrent use of aspirin negates most of the gastrointestinal benefit associated with COX-2 inhibitors, including meloxicam.

Frail or debilitated patients may be less tolerant to side effects 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. Use of COX-2 inhibitors (of which MOBIC is one) or other NSAIDs may precipitate or exacerbate pre-existing hypertension, cardiac failure or oedema in susceptible patients, and the treatment of these conditions may be compromised. For patients at risk, clinical monitoring is recommended.

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

The use of MOBIC, 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 MOBIC should be considered.

For relevant drug interactions that require particular attention, see Interactions

There are no specific studies about the 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.

MOBIC tablets 7.5 mg contains 47 mg lactose per maximum recommended daily dose. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia should not take this medicine.

### **Use in Pregnancy**

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 after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation and gastrochisis was increased from less than 1 %, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In preclinical studies, 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 preclinical studies 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-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

### **Use in Lactation**

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

### **Fertility**

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. Meloxicam may delay ovulation. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.

### **Effect on Ability to Drive and Use Machines**

No studies on the effect on the ability to drive and use machines have been performed. However, patients should be advised that they may experience undesirable effects like visual disturbance including blurred vision, dizziness, somnolence, vertigo and other central nervous system disturbances.

Therefore, caution should be recommended when driving a car or operating a machinery.

If patients experience any of these events, they should avoid potentially hazardous tasks such as driving or operating machinery.

### **Adverse Effects**

The MOBIC phase II/III safety database includes 10,122 osteoarthritis patients and 1012 rheumatoid arthritis patients treated with MOBIC 7.5 mg/day and 3,505 osteoarthritis patients and 1351 rheumatoid arthritis patients treated with MOBIC 15 mg/day. MOBIC at these doses was administered to 661 patients for at least six months and to 312 patients for at least one year. Approximately 10,500 of these patients were treated in ten placebo and or active-controlled osteoarthritis trials and 2362 of these patients were treated in ten placebo and or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across MOBIC trials.

#### Gastrointestinal disorders

Adverse events occurring in  $\geq 2\%$  of MOBIC patients in a 12-week osteoarthritis placebo- and active-controlled trial:

abdominal pain, diarrhoea, dyspepsia, flatulence, nausea

The adverse events that occurred with MOBIC in  $\geq 2\%$  of patients treated short-term (4-6 weeks) and long-term (6 months) in active controlled osteoarthritis trials:

abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, vomiting

The adverse events that occurred in  $<2\%$  of patients, treated with daily oral doses of 7.5 or 15 mg MOBIC tablets or capsules over a period of up to 18 months:

oesophagitis, gastroduodenal ulcer, occult or macroscopic gastrointestinal bleeding, gastrointestinal perforation, colitis, gastritis.

#### Gastrointestinal disorders not mentioned above

stomatitis, eructation.

Gastrointestinal haemorrhage, ulceration or perforation may potentially be fatal.

#### Blood and lymphatic system disorders

blood count abnormal (including differential white cell count), leukopenia, thrombocytopenia, anaemia

Concomitant administration of a potentially myelotoxic drug, in particular methotrexate, appears to be a predisposing factor to the onset of a cytopenia.

#### Immune system disorders

anaphylactic reaction, anaphylactoid reaction, and other immediate hypersensitivity

#### Psychiatric disorders

confusional state, disorientation, mood altered

#### Nervous system disorders

dizziness, somnolence, headache

#### Eye disorders

visual disturbance including vision blurred, conjunctivitis

#### Ear and labyrinth disorders

vertigo, tinnitus

#### Cardiac disorders

palpitations

#### Vascular disorders

blood pressure increased, flushing

#### Respiratory, thoracic and mediastinal disorders

asthma, in individuals allergic to aspirin or other NSAIDs

#### Hepatobiliary disorders

Hepatitis, liver function test abnormal (e.g. raised transaminases or bilirubin)

#### Skin and subcutaneous tissue disorders

toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, dermatitis bullous, erythema multiforme, rash, urticaria, photosensitivity reaction, pruritus

#### Renal and urinary disorders

renal failure acute, renal function test abnormal (increased serum creatinine and/or serum urea)

The use of NSAIDs may be related to micturition disorders, including acute urinary retention.

#### General disorders and administration site conditions

oedema

## **Interactions**

No relevant pharmacokinetic drug-drug interactions were detected with respect to the concomitant administration of antacid, cimetidine, digoxin and frusemide.

Associations to be taken into account:

- Other Prostaglandin Synthetase 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, systemically administered heparin, thrombolytics increased risk of bleeding via inhibition of platelet function. If such co-prescribing cannot be avoided, close monitoring of their effects on coagulation is required.
- Antiplatelet drugs and Selective Serotonin Reuptake Inhibitors (SSRIs): increased risk of bleeding via inhibition of platelet function.
- 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 gastrointestinal tract leading to a faster elimination of Meloxicam.
- Nephrotoxicity of cyclosporin may be enhanced by NSAID's 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.

## Overdosage

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.

## Pharmaceutical Precautions

Store below 25°C (blister pack)

Store below 30°C (glass / polypropylene tube)

Store in a safe place out of the reach of children

## Medicine Classification

Prescription Medicine

## Package Quantities

Tablets 7.5mg :10 and 30.

## Further Information

MOBIC<sup>®</sup> is a registered Trademark

## Excipients

*Tablets:* sodium citrate, lactose monhydrate, microcrystalline cellulose, povidone K25, colloidal anhydrous silica, crospovidone, magnesium stearate

## 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 1mg/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.

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