MOBIC®

Boehringer Ingelheim

1. NAME OF THE MEDICINAL PRODUCT

MOBIC® Tablet 7.5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

3.1 Product description

Round, pastel yellow, snap-tab tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MOBIC® is a non-steroidal anti-inflammatory drug indicated for
- symptomatic treatment of painful osteoarthritis (arthrosis, degenerative joint disease)
- symptomatic treatment of rheumatoid arthritis
- symptomatic treatment of ankylosing spondylitis

4.2 Posology and method of administration

Posology

Painful 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.

Special population
In patients with increased risks of adverse reactions, e.g. a history of gastro-intestinal disease or risk factors for cardiovascular disease, the treatment should be started at the dose of 7.5 mg/day (see Special warnings and precautions for use).

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). In non-dialysed patients with severe renal impairment MOBIC® is contraindicated (see Contraindications). In patients with end-stage renal failure on haemodialysis the maximum daily dose should not exceed 7.5 mg/day.

Paediatric population
As a dosage for use in children and adolescents has not yet been established, usage should be restricted to adults. There are no data for children and adolescents available in the indications painful osteoarthritis, rheumatoid arthritis or ankylosing spondylitis.

General recommendation:
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.

The total daily dosage of MOBIC® should be administered as a single dose. The maximum recommended daily dose regardless of formulation is 15 mg.

Method of administration

MOBIC® tablets are swallowed with water or other fluid in conjunction with food.
There is insufficient information on the effect of mixing crushed tablets with food or fluids.
Tablet break mark does not allow subdividing the 7.5 mg tablet into fractions of a full dose.
Tablets 7.5 mg can only be subdivided for ease of swallowing.

4.3 Contraindications

- Known hypersensitivity to meloxicam or any excipient of the product.
- Use in patients who have developed signs of asthma, nasal polyps, angio-oedema or urticaria following the administration of acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs), because of a potential for cross sensitivity.
- Peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- 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
- Pregnancy or breastfeeding
- Rare hereditary conditions that may be incompatible with an excipient of the product (see "Special warnings and precautions for use")

4.4 Special warnings and precautions for use

Gastrointestinal disorders
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.
Caution should be exercised when treating patients with a history of gastro-intestinal disease. Patients with gastro-intestinal symptoms should be monitored. MOBIC® should be withdrawn if gastro-intestinal ulceration or bleeding occurs.

As with other NSAIDs caution should be exercised in patients receiving treatment with anticoagulants.

Serious skin reactions
Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported rarely in association with the use of MOBIC®. 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.

Cardiovascular disorders
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.

Renal disorders
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 renal function including the volume of diuresis 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 exceed 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).

Liver disorders
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.

Risks in specific population
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.

Sodium, potassium and water retention
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.

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

Effects on 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. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.

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

MOBIC® contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

- 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 if

such co-prescribing cannot be avoided, close monitoring of their effects on coagulation is required. (for solution for injection: see section Contraindications)

- 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 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.
- Pemetrexed: For the concomitant use of meloxicam with pemetrexed in patients with creatinine clearance from 45 to 79 ml/min, the administration of meloxicam should be paused for 5 days before, on the day of, and 2 days following pemetrexed administration. If a combination of meloxicam with pemetrexed is necessary, patients should be closely monitored, especially for myelosuppression and gastro-intestinal adverse reactions. In patients with creatinine clearance below 45 ml/min the concomitant administration of meloxicam with pemetrexed is not recommended.

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. Interactions via CYP 2C9 can be expected in combination with medicinal products such as oral antidiabetics (sulphonylureas, nateglinide), which may lead to increased plasma levels of these drugs and meloxicam. Patients concomitantly using meloxicam with sulfonylureas or nateglinide should be carefully monitored for hypoglycaemia.

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.

4.6 Fertility, pregnancy and lactation

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 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. In preclinical studies, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in 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

Lactation

While no specific experience exists for MOBIC® in human, 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.

4.7 Effects 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 patient experience any of these events, they should avoid potentially hazardous tasks such as driving or operating machinery.

4.8 Undesirable effects

The following adverse events, which may be causally related to the administration of MOBIC®, have been reported in clinical trials and during the use of meloxicam in the post-marketing experience.

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.

Very common ≥ 1/10
Common ≥ 1/100 to < 1/10
Uncommon ≥ 1/1,000 to < 1/100
Rare ≥ 1/10,000 to < 1/1,000
Very rare < 1/10,000
Not known (cannot be estimated from the available data)

Body System	**Side Effect**	**Frequencies**
Blood and Lymphatic system disorders	Blood count abnormal *(including differential white cell count)*	Rare

	Leukopenia	Rare
	Thrombocytopenia	Rare
	Anaemia	Uncommon
Immune system disorders	Anaphylactic reaction	Not Known
	Anaphylactoid reaction	Not Known
	Other immediate hypersensitivity	Uncommon
Psychiatric disorders	Confusional state	Not Known
	Disorientation	Not Known
	Mood altered	Rare
Nervous system disorders	Dizziness	Uncommon
	Somnolence	Uncommon
	Headache	Common
Eye disorders	Visual disturbance *including* vision blurred	Rare
	Conjunctivitis	Rare
Ear and labyrinth disorders	Vertigo	Uncommon
	Tinnitus	Rare
Cardiac disorders	Palpitations	Rare
Vascular disorders	Blood pressure increased	Uncommon
	Flushing	Uncommon
Respiratory, thoracic and mediastinal disorders	Asthma in individuals allergic to aspirin or other NSAIDs	Rare
Gastrointestinal disorders	Gastrointestinal perforation	Very Rare
	Occult or macroscopic gastrointestinal haemorrhage	Uncommon
	Gastroduodenal ulcer	Rare
	Colitis	Rare
	Gastritis	Uncommon
	Oesophagitis	Rare
	Stomatitis	Uncommon
	Abdominal pain	Common
	Dyspepsia	Common
	Diarrhoea	Common
	Nausea, Vomiting	Common
	Constipation	Uncommon
	Flatulence	Uncommon
	Eructation	Uncommon
Hepatobiliary disorders	Hepatitis	Very Rare
	Liver function test abnormal (e.g. raised transaminases or bilirubin) [4]	Uncommon
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis, Stevens-Johnson syndrome	Rare
	Angioedema	Uncommon
	Dermatitis bullous, Erythema multiforme	Very Rare
	Rash	Uncommon
	Urticaria	Rare
	Photosensitivity reaction	Not Known
	Pruritus	Uncommon
Renal and urinary disorders	Renal failure acute	Very Rare
	Renal function test abnormal (increased serum creatinine and/or serum urea)[4]	Uncommon
	Micturition disorders, including acute	Uncommon

	urinary retention	
General disorders and administration site conditions	Oedema	Uncommon
Endocrine disorders	Ovulation delayed	Uncommon
Reproduction and breast disorders	Infertility Female	Not known

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS, Oxicams

ATC code: M01AC06

Mode of action and Pharmacodynamics

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 PGE_2 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.

Clinical Trials
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	1 - <30	5110	7	0.14	0.04 – 0.24
100 mg	30 - <91	493	2	0.55	0.00 – 1.13
Piroxicam	1 - <30	5071	10	0.20	0.07 – 0.32
20 mg	30 - <91	532	6	1.11	0.35 – 1.86

5.2 Pharmacokinetics properties

Absorption
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 2 hours for the suspension and within 5-6 hours with solid oral dosage forms (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 - 1.0µg/mL for 7.5 mg doses and 0.8 - 2.0 µg/mL for 15 mg doses, respectively (C_{min} and C_{max} at steady state, correspondingly).

Mean maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours for the tablet. 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, i.e. approx. 11 L after i.m. or i.v. administration, and shows interindividual variation in the order of 7 - 20%.
The volume of distribution following administration of multiple oral doses of meloxicam (7.5 to 15 mg) is about 16L with coefficients of variation ranging from 11 to 32%.

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. adminstration.
Total plasma clearance amounts about 7-12mL/min following single doses orally, intravenously or rectally administered.

Linearity/non-linearity
Meloxicam demonstrates linear pharmacokinetics in the therapeutic dose range of 7.5 mg to 15 mg following per oral administration.

PK in specific 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.

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.

5.3 Preclinical safety data

General 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.

Repeat 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.

Reproductive and Developmental Toxicology
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. Nonclinical studies indicate that meloxicam can be found in the milk of nursing rats.

Genotoxicity
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
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.

Special toxicology
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate
Lactose monohydrate
Microcrystalline cellulose
Povidone K25
Colloidal anhydrous silica
Crospovidone
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to packaging for information on shelf-life.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Packed in blister cards consisting of a printed aluminum lidding foil (PVC/PVAC Copolymers) and a molded aluminum based forming foil (Polyamide-film/Aluminum-foil/Polyvinyl Chloride film; transparent).

Box of 10 x 10’s; Box of 3 x 10’s; Box of 1 x 10’s

10 tablets per aluminium blister strip

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. MANUFACTURER

Manufactured by
Rottendorf Pharma GmbH
Ostenfelder Straße 51 - 61

59320 Ennigerloh
Germany
for
Boehringer Ingelheim International GmbH
Binger Strasse 173
Ingelheim am Rhein
Germany

8. PRODUCT REGISTRATION NUMBER

MAL11060027ACZ

9. DATE OF REVISION OF THE TEXT

11 July 2025

WARNINGS

RISK OF GI ULCERATION, BLEEDING 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. In patients observed in clinical trials of several months to 2 years duration, symptomatic upper GI ulcers, gross bleeding or perforation occurred in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for 1 year. Higher percentages have been reported by other independent studies.
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, 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.
Measures such as the use of physical therapy and mild analgesics like paracetamol (when inflammation is not a major factor) should be instituted prior to initiation of therapy with NSAID. NSAIDs should only be used after proper appraisal of potential risks to patients. It should be used with the lowest effective dose for only as long as needed. This drug should not be co-administered with other NSAIDs. Prescribers should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should offset the potential increased risk of GI toxicity.