MOBIC 7,5 mg & MOBIC 15 mg TABLETS: APPROVED PACKAGE INSERT

SCHEDULING STATUS : S3

PROPRIETARY NAME (and dosage form):

Mobic® 7,5 mg
Mobic® 15 mg
tablets

abcd

COMPOSITION:
Each MOBIC 7,5 mg tablet contains 7,5 mg meloxicam.
Each MOBIC 15 mg tablet contains 15 mg meloxicam.
Sugar free.

PHARMACOLOGICAL CLASSIFICATION:
A 3.1 Antirheumatics (anti-inflammatory agents).

PHARMACOLOGICAL ACTION:
Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class, which has shown anti-inflammatory, analgesic and antipyretic properties.
A common mechanism for the above effects may exist in the ability of meloxicam to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.
A selective inhibition of cyclo-oxygenase-2 (COX-2) relative to cyclo-oxygenase-1 (COX-1) by meloxicam has been demonstrated.
COX-2 inhibition relates to the anti-inflammatory effects of NSAIDs whereas inhibition of constitutive COX-1 is thought to be responsible for gastric and renal side-effects.

***Pharmacokinetic properties**:*
Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 89 % following oral administration.
Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 5 to 6 hours.
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 (C_{min} and C_{max} at steady state, respectively).
Maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours.

Continuous treatment for longer periods (e.g. six months) did not point to any changes in pharmacokinetics compared to steady state pharmacokinetics after two weeks of oral treatment with 15 mg meloxicam/day.

Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake.

Distribution: Meloxicam is 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 in 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.

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 20 hours.
Total plasma clearance amounts on average to 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: Mild or moderate hepatic insufficiency and mild or moderate renal insufficiency do not 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:
MOBIC is indicated for:
- symptomatic treatment of rheumatoid arthritis.
- symptomatic treatment of painful osteoarthritis.
- symptomatic treatment of ankylosing spondylitis.
- symptomatic treatment of episodes of acute sciatica.

CONTRA-INDICATIONS:
Known hypersensitivity to meloxicam (MOBIC) or any excipient of the medicine.
There is a potential for cross sensitivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs).

MOBIC should not be given to patients who have developed signs of asthma, nasal polyps, angio-oedema or urticaria following the administration of acetylsalicylic acid or other NSAIDs.

Further contra-indications for the use of MOBIC are:
- active or recent gastrointestinal ulceration/perforation
- active inflammatory bowel disease (Crohn's disease or ulcerative colitis)
- severe hepatic insufficiency
- non-dialysed severe renal insufficiency
- overt gastrointestinal bleeding, recent cerebrovascular bleeding or established systemic bleeding disorders
- uncontrolled heart failure
- history of gastrointestinal bleeding or perforation (PUBs) related to previous NSAIDs
- children under 12 years.

Refer to **PREGNANCY AND LACTATION.**

MOBIC is contra-indicated 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 PRECAUTIONS**) the use of the product is contra-indicated.

WARNINGS:
Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with MOBIC therapy.

Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs including MOBIC, especially gastrointestinal bleeding and perforation (PUBs), which may be fatal.

The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of MOBIC, in patients with a history of ulcers, and the elderly.
When gastrointestinal bleeding or ulceration occurs in patients receiving MOBIC, treatment with MOBIC should be stopped.
MOBIC should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia), as the condition may be exacerbated. (See **CONTRA-INDICATIONS.)**

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 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.

INTERACTIONS:
Other prostaglandin synthetase inhibitors (PSIs) including NSAIDs, glucocorticoids and salicylates (acetylsalicylic acid): Co-administration of PSIs may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect and is not recommended. The concomitant use of MOBIC with other NSAIDs is not recommended.
Concomitant administration of aspirin (1000 mg t.i.d.) to healthy volunteers led to increase in the AUC (10 %) and C_{max} (24 %) of MOBIC. The clinical significance of this interaction is not known.

Oral anticoagulants, antiplatelet drugs, systemically administered heparin, thrombolytics and selective serotonin reuptake inhibitors (SSRIs): An increased risk of bleeding via inhibition of platelet function. If such a co-prescription cannot be avoided, close monitoring is required.

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

Methotrexate: MOBIC 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 MOBIC is not recommended. The risk of an interaction between MOBIC and methotrexate should be considered, also in patients on low dosage of methotrexate, especially in patients with impaired renal function. When combination treatment is necessary, blood cell count and the renal function should be monitored. When MOBIC and methotrexate are given within 3 days of each other, 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 MOBIC treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with MOBIC.

Contraception: MOBIC has been reported to decrease the efficacy of intrauterine devices.

Diuretics: Treatment with MOBIC 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. β-blockers, ACE-inhibitors, vasodilators, diuretics): A reduced effect of antihypertensive medicines by inhibition of vasodilating prostaglandins has been reported during treatment with MOBIC.

MOBIC 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.

Concomitant treatment with probenecid leads to reduced excretion and thereby increased effects of MOBIC.

Cholestyramine binds meloxicam in the gastrointestinal tract leading to a faster elimination of MOBIC.

Nephrotoxicity of cyclosporin may be enhanced by MOBIC via renal prostaglandin mediated effects. During combined treatment renal function should be assessed regularly.

Tacrolimus should not be combined with MOBIC.

MOBIC 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 MOBIC and medicines 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 anti-diabetics cannot be excluded.

Simultaneous administration of alcohol and MOBIC increases the risk of bleeding.

PREGNANCY AND LACTATION:
MOBIC is contra-indicated 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.

During the third trimester of pregnancy prostaglandin synthesis inhibition 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-hydramnios;

the mother and the neonate, at the end of pregnancy, to:

- 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.

The use of MOBIC 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.

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

DOSAGE AND DIRECTIONS FOR USE:

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.

Osteoarthritis:

7,5 mg/day. If necessary, the dose may be increased to 15 mg/day.

Episodes of acute sciatica:

7,5 mg/day. If necessary, in the absence of improvement, the dose may be increased to 15 mg/day.

In patients with increased risks of adverse reactions (e.g. the elderly), 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.

The maximum recommended daily dose of MOBIC is 15 mg.

Combined administration: The total daily dosage of MOBIC administered as tablets, suppositories and injections should not exceed 15 mg.

As a dosage for use in children has yet to be established, MOBIC should not be used in children aged less than 12 years.

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

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Precautions:

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.

Gastrointestinal bleeding, ulceration or perforation, potentially fatal, can occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. The consequences of such events are generally more serious in the elderly.

MOBIC 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.

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. In these patients administration of MOBIC may precipitate overt renal decompensation which is typically followed by recovery to pre-treatment state upon discontinuation of 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.

MOBIC may cause interstitial nephritis, glomerulonephritis, papillary necrosis and the 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).

Occasional elevations of serum transaminases or other indicators 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. 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 natriuretic effects of diuretics may occur with MOBIC. Cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. For patients at risk, clinical monitoring is recommended.

MOBIC may mask symptoms of an underlying infectious disease.

For relevant drug interactions that require particular attention, see **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.

MOBIC 7,5 mg tablets contain 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 15 mg tablets contain 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.

Side-effects:
The following adverse events, which may be causally related to the administration of MOBIC, have been reported.

Gastrointestinal disorders:

Frequency between 1 and 10 %:	dyspepsia, nausea, abdominal pain, vomiting and diarrhoea.
Frequency between 0,1 and 1 %:	constipation, flatulence, gastritis, eructation, occult or macroscopic gastrointestinal haemorrhage and stomatitis.
Frequency between 0,01 and 0,1 %:	gastroduodenal ulcer, colitis and oesophagitis.

Less frequent than 0,01 %: gastrointestinal perforation.
The following side-effects have been reported and the frequencies are unknown: peptic ulcers, melaena, haematemesis, Crohn's disease.
Gastrointestinal haemorrhage, ulceration or perforation may potentially be fatal.

Hepatobiliary disorders:
Frequency between 0,1 and 1 %: liver function test abnormal (eg. raised transaminases or bilirubin)
Less frequent than 0,01 %: hepatitis

Blood and lymphatic system disorders:
Frequency between 0,1 and 1 %: anaemia.
Frequency between 0,01 and 0,1 %: blood count abnormal (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.
The following side-effect has been reported and the frequency is unknown: agranulocytosis.

Skin and subcutaneous tissue disorders:
Frequency between 0,1 and 1 %: pruritus, rash and angioedema.
Frequency between 0,01 and 0,1 %: toxic epidermal necrolysis, Stevens-Johnson syndrome and urticaria.
Less frequent than 0,01 %: dermatitis bullous and erythema multiforme.
Frequency not known: photosensitivity reaction.

Respiratory, thoracic and mediastinal disorders:
Frequency between 0,01 and 0,1 %: asthma in individuals allergic to aspirin or other NSAIDs.

Psychiatric disorders:
Frequency between 0,01 and 0,1 %: mood altered.
Frequency not known: confusional state, disorientation.

Nervous system disorders:

Frequency between 1 and 10 %: headache.

Frequency between 0,1 and 1 %: dizziness, somnolence.

The following side-effects have been reported and the frequencies are unknown: insomnia, nightmares.

Ear and labyrinth disorders:
Frequency between 0,1 and 1 %: vertigo.
Frequency between 0,01 and 0,1%: tinnitus.

Cardiac disorders:
Frequency between 0,01 and 0,1 %: palpitations.

Vascular disorders:
Frequency between 0,1 and 1 %: blood pressure increased, flushing.

The following side-effect has been reported and the frequency is unknown: cardiac failure.

Renal and urinary disorders:
Frequency between 0,1 and 1 %: renal function test abnormal (increased serum creatinine and/or serum urea) and micturition disorders, including acute urinary retention.
Less frequent than 0,01 %: acute renal failure.

Eye disorders:
Frequency 0,01 to 0,1 %: conjunctivitis, visual disturbance including blurred vision.

Immune system disorders:
Frequency not known: anaphylactic reaction, anaphylactoid reaction and other immediate hypersensitivity.

General disorders and administration site conditions:
Frequency between 0,1 and 1 %: oedema.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
In case of overdose, the standard measures of gastric evacuation and general symptomatic and supportive treatment should be used as there is no known antidote. It has been shown in a clinical trial that cholestyramine accelerates the elimination of MOBIC.

IDENTIFICATION:
MOBIC 7,5 mg tablets are round, pastel yellow to lemon yellow tablets. One face is convex, has a bevelled edge and is impressed with the Company's symbol; the other face is impressed with the tablet code 59D and is scored across its entire diameter. The surface of the tablets may be slightly rough.

MOBIC 15 mg tablets are round, pastel yellow to lemon yellow tablets. One face is convex, has a bevelled edge and is impressed with the Company's symbol; the other face is impressed with the tablet code 77C and is scored across its entire diameter. The surface of the tablets may be slightly rough.

PRESENTATION:

Cartons of 30 MOBIC 7,5 mg tablets packed in blister strips (either aluminium foil on one side /white blister film on the other, or aluminium foil on both sides).
Cartons of 10 or 30 MOBIC 15 mg tablets packed in blister strips (either aluminium foil on one side /white blister film on the other, or aluminium foil on both sides).

STORAGE INSTRUCTIONS:
Aluminium foil/white blister film pack: Store below 25 °C.
Aluminium foil/aluminium foil pack: Store below 30 °C.

Keep out of reach of children.

REGISTRATION NUMBER:
MOBIC 7,5 mg tablets: 29/3.1/0421
MOBIC 15 mg tablets: 29/3.1/0422

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
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