PROFESSIONAL INFORMATION

SCHEDULING STATUS: **S3**

PROPRIETARY NAME (and dosage form):

Mobic® 15 mg/1,5 mL **abcd**

injection

COMPOSITION:
Each ampoule of 1,5 mL contains 15 mg meloxicam.
Excipients: glycine, glycofurol, meglumine, poloxamer 188, sodium chloride, sodium hydroxide, water for injection.
Sugar free.

PHARMACOLOGICAL CLASSIFICATION:
A3.1 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**:*
Absorption: Meloxicam is completely absorbed after intramuscular administration.
Dose-adjustment switching from intramuscular to oral treatment is not necessary.
Following a 15 mg intramuscular injection, peak plasma concentrations of about 1,62 µg/mL are reached in about 1 – 6 hours.

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 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.

Elderly: Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

INDICATIONS:
MOBIC injection is indicated for the short-term symptomatic treatment of acute exacerbation of:
- rheumatoid arthritis
- painful osteoarthritis
- ankylosing spondylitis
- sciatica

CONTRA-INDICATIONS:
- Known hypersensitivity to meloxicam or any excipient of MOBIC
- Use in patients who have developed signs of asthma, nasal polyps, angioedema or urticaria following the administration of acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory drugs (NSAIDs), because of a potential cross-sensitivity
- Use in patients treated with anticoagulants as intramuscular haematomas may occur
- Peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery
- Active or history of recurrent gastrointestinal ulceration/perforation/haemorrhage
- 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
- Heart failure
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including MOBIC
- Pregnancy or lactation. Refer to PREGNANCY AND LACTATION
- Use in children and adolescents aged below 18 years of age

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

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.

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of MOBIC, in patients with a history of ulcers, and the elderly.

MOBIC should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastroesophageal reflux disease, angiodysplasia), as the condition may be exacerbated. (See CONTRA-INDICATIONS).

Patients with gastrointestinal symptoms should be monitored.
When gastrointestinal bleeding or ulceration occurs in patients receiving MOBIC, treatment with MOBIC should be stopped.

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

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as MOBIC. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue MOBIC and evaluate the patient immediately.

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. Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and they should only be treated with MOBIC after careful consideration.

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. In view of MOBIC's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

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 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).

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.

Regular use of NSAIDs such as MOBIC during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus *in utero*, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased (see PREGNANCY AND LACTATION).

For relevant medicine interactions that require particular attention, see **INTERACTION**S.

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.

Effects on ability to drive and use machines:
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 machinery.

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

INTERACTIONS:
Other prostaglandin synthetase inhibitors (PSIs) including NSAIDs and salicylates (acetylsalicylic acid (aspirin)): Use of two or more NSAIDs concomitantly could result in an increase in side effects. The concomitant use of MOBIC with other NSAIDs is not recommended.
Concomitant administration of aspirin (1 000 mg t.i.d.) to healthy volunteers led to increases in the AUC (10 %) and C_{max} (24 %) of MOBIC. The clinical significance of this interaction is not known.

Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

Oral anticoagulants, systemically administered heparin, thrombolytics: MOBIC may enhance the effects of anticoagulants such as warfarin, with an increased risk of bleeding. The concomitant use of anticoagulants with MOBIC injection is contra-indicated. (See CONTRA-INDICATIONS).

Antiplatelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding, via inhibition of platelet function.

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 also be considered 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. beta-blockers, ACE-inhibitors, vasodilators, diuretics): A reduced effect of the antihypertensive medicine 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.

Nephrotoxicity of ciclosporin 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.

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

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. 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 medicines and MOBIC. Patients concomitantly using MOBIC with sulphonylureas or nateglinide should be carefully monitored for hypoglycaemia.

No relevant pharmacokinetic medicine interactions were detected with respect to the concomitant administration of antacids, cimetidine, digoxin and furosemide.

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 oligohydramnios;

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

Fertility:
The use of MOBIC may impair fertility and is not recommended in women attempting to conceive. MOBIC may delay ovulation. 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 in humans, NSAIDs are known to pass into mother's milk. Administration therefore is contra-indicated in women who are breastfeeding.

DOSAGE AND DIRECTIONS FOR USE:
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 dose of MOBIC should be administered as a single dose. The maximum recommended daily dose regardless of formulation is 15 mg.

Rheumatoid arthritis, ankylosing spondylitis, painful osteoarthritis:
The recommended dosage of MOBIC injection is 7,5 mg or 15 mg once daily, depending on the pain intensity and severity of inflammation.

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

Special populations:
In patients with an increased risk of adverse reactions, e.g. a history of gastrointestinal disease or risk factors for cardiovascular disease, the treatment should be started at a dose of 7,5 mg/day (see WARNINGS AND SPECIAL PRECAUTIONS).

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 contra-indicated (see CONTRA-INDICATIONS). In patients with end-stage renal failure on haemodialysis the maximum daily dose should not exceed 7,5 mg/day.

As safety in children has not yet been established, MOBIC injection should not be used in children and adolescents aged below 18 years of age (see CONTRA-INDICATIONS).

Method of administration:

THE LIQUID IN THE AMPOULE MUST BE ASPIRATED VERY SLOWLY TO AVOID FOAMING OF THE SOLUTION.

MOBIC injection should be administered by ***deep intramuscular*** injection.

***MOBIC injection should not be administered intravenously*.**

Because there is no information about possible incompatibilities, MOBIC injection must not be mixed with other medicines in the same syringe.

Intramuscular administration should only be used for up to 3 days.
For continuation of treatment, the oral formulations (MOBIC 15 mg tablets or MOBIC 7,5 mg tablets) should be used.

SIDE EFFECTS:
The following possibly causally related side effects and corresponding frequencies are from the clinical trials involving MOBIC. Frequencies are indicated as follows:
Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥1/1 000, <1/100); rare (≥ 1/10 000, < 1/1 000); very rare (<1/10 000), including isolated reports. Not known: cannot be estimated from the available data.

Blood and lymphatic system disorders:
Uncommon: anaemia
Rare: disturbances of blood count, including differential white cell count, leukopenia, thrombocytopenia.

Concomitant administration of a potentially myelotoxic medicine, 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.

Immune system disorders:
Uncommon: other immediate hypersensitivity

Psychiatric disorders:
Rare: altered mood

Nervous system disorders:
Common: headache
Uncommon: dizziness, somnolence

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

Eye disorders:
Rare: visual disturbance including blurred vision, conjunctivitis

Ear and labyrinth disorders:
Uncommon: vertigo
Rare: tinnitus

Cardiac disorders:
Rare: palpitations
Uncommon: oedema, increased blood pressure (hypertension)

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

Vascular disorders:
Uncommon: flushing

Respiratory, thoracic and mediastinal disorders:
Rare: asthma in individuals allergic to aspirin or other NSAIDS

Gastrointestinal disorders:
The most commonly observed adverse events are gastrointestinal in nature.
Common: dyspepsia, nausea, vomiting, abdominal pain, diarrhoea
Uncommon: gastritis, constipation, flatulence, ulcerative stomatitis, gastrointestinal bleeding (melaena, haematemesis **–** sometimes fatal), eructation
Rare: colitis (exacerbation of colitis and Crohn's disease), peptic ulcer, oesophagitis
Very rare: gastrointestinal perforation (sometimes fatal)

Hepatobiliary disorders:
Uncommon: abnormal liver function test (e.g. raised transaminases or bilirubin)
Very rare: hepatitis

Skin and subcutaneous tissue disorders:
Uncommon: rash, angioedema, pruritus
Rare: bullous reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome, urticaria
Very rare: bullous dermatitis, erythema multiforme

Renal and urinary disorders:
Uncommon: abnormal renal function test (increased serum creatinine and/or serum urea), micturition disorders including acute urinary retention
Very rare: acute renal failure

Reproductive system and breast disorders:
Uncommon: delayed ovulation

General disorders and administration site conditions:
Common: injection site mass and injection site pain

***Post-Marketing Experience*:**
The following possibly causally related side effects are from post-marketing data for which the frequency is not known.

***Immune system disorders*:** anaphylactoid reaction and anaphylactic reaction, including anaphylactic shock, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see WARNINGS AND SPECIAL PRECAUTIONS)

***Psychiatric disorders*:** confusional state, disorientation

***Skin and subcutaneous tissue disorders*:** photosensitivity reaction

Reproductive system and breast disorders: female infertility

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
In case of overdose general symptomatic and supportive treatment should be used as there is no known antidote.

IDENTIFICATION:
MOBIC 15 mg/1,5 mL injection is a clear, yellow solution with a green tinge contained in colourless glass ampoules.

PRESENTATION:
Packs of 5 ampoules.

STORAGE INSTRUCTIONS:
Store at or below 30 °C. Keep out of reach of children.

REGISTRATION NUMBER:
29/3.1/0420

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
Ingelheim Pharmaceuticals (Pty) Ltd
407 Pine Avenue
Randburg
South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
Date of registration: 20 August 1999
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