MOBIC®
(meloxicam)

NAME OF THE MEDICINE

Active ingredient: meloxicam

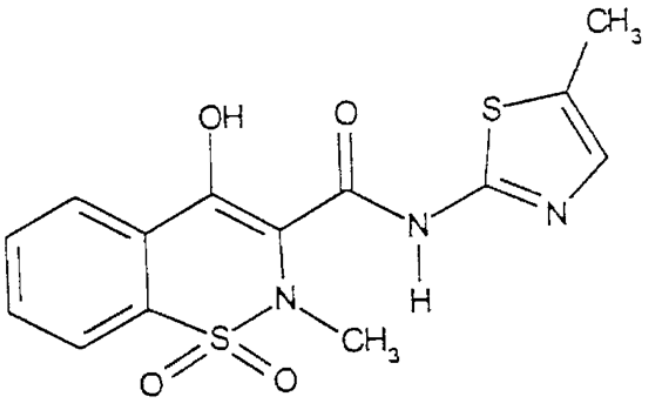
Chemical names: 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide and 2H-1,2-benzothiazine-3-carboxamide,4-hydroxy-2-methy-N-(5-methyl-2-thiazolyl)-,1,1-dioxide

Molecular formula: $C_{14}H_{13}N_3O_4S_2$

CAS number: 71125-38-7

Molecular weight: 351.4

Structural formula:



DESCRIPTION

Meloxicam is a pastel yellow solid with pKa values of 1.09 and 4.18 and a melting point of about 256°C. The substance is practically insoluble in water, soluble in dimethylformamide, slightly soluble in chloroform and acetone, and very slightly soluble in methanol. There are no chiral centres and no polymorphs are formed under normal conditions. MOBIC is available as tablets and capsules. The list of excipients for each dosage form is provided below:

Tablets (7.5 mg and 15 mg): sodium citrate dihydrate, lactose monohydrate, microcrystalline cellulose, povidone, crospovidone, colloidal anhydrous silica, magnesium stearate.

Capsules (7.5 mg and 15 mg): sodium citrate dihydrate, lactose monohydrate, maize starch, magnesium stearate, gelatin, indigo carmine CI73015, iron oxide yellow CI77492, titanium dioxide, purified water.

PHARMACOLOGY

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 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, by inhibition of cyclooxygenase (COX).

Comparison of the ulcerogenic dose and the anti-inflammatory effective dose in rat adjuvant arthritis model confirmed a greater therapeutic margin in animals over other NSAIDs (piroxicam, diclofenac, naproxen, flurbiprofen). In rats, meloxicam showed greater inhibitory effect on prostaglandin biosynthesis at the site of inflammation than in the gastric mucosa or the kidney.

Selective inhibition of the cyclooxygenase-2 (COX-2) isoenzyme, relative to COX-1, by meloxicam has been demonstrated *in vitro* on various cell systems: guinea pig macrophages, bovine aortic endothelial cells (for testing of COX-1 activity), mouse macrophages (for testing for COX-2 activity), and human recombinant enzymes expressed in cos-cells and in human whole blood.

Pharmacokinetics

Absorption

Meloxicam is well absorbed from the gastrointestinal tract following oral administration (absolute bioavailability 89%). MOBIC tablets are bioequivalent to MOBIC capsules. Once daily dosing leads to mean drug plasma concentrations with a relatively narrow C_{maxss} - C_{minss} window in the range of 0.3-1.0 μg/mL for 7.5 mg doses or 0.7-1.9 μg/mL for 15 mg doses. However, values outside of this range have been encountered (C_{min} and C_{max} at steady state, respectively). The absorption is not altered by concomitant food intake. However, food shortens the t_{max} of the capsules by approximately 2.5 hours and marginally increases the C_{max} of the capsules, whereas maximum plasma concentrations were regularly achieved between 5-6 hours following tablet administration, irrespective of concomitant food consumption. Drug concentrations are dose-proportional for oral 7.5 mg and 15 mg doses, respectively. Steady state conditions are achieved in three to five days.

Distribution

Volume of distribution is low (on average, 16L). The volume of distribution following administration of multiple oral doses of meloxicam (7.5 to 15 mg) ranged from 10.1L - 17.0L (%CV 24.6% - 39.9%). In plasma, more than 99% is bound to plasma proteins. Meloxicam penetrates well into synovial fluid to give concentrations approximately half those in plasma.

Metabolism

Meloxicam is eliminated almost entirely by hepatic metabolism: two thirds by cytochrome (CYP) P450 enzymes (CYP 2C9 two thirds and CYP 3A4 one third) and one third by other pathways, such as peroxidase oxidation. Meloxicam is almost completely metabolised to four pharmacologically inactive metabolites. The major metabolite, 5'-carboxymeloxicam (60% of dose), from CYP 2C9 mediated metabolism, 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 excretion is predominantly in the form of metabolites, and occurs to equal extents in the faeces and urine. Only traces of the unchanged parent compound are excreted in the urine (0.2%) and faeces (1.6%). The extent of the urinary excretion was confirmed for unlabeled multiple 7.5 mg doses: 0.5%, 6% and 13% of the dose were found in urine in the form of meloxicam, and the 5'-hydroxymethyl and 5'-carboxy metabolites, respectively.

There is significant biliary and/or enteral secretion of the drug. This was demonstrated when oral administration of colestyramine following a single IV dose of meloxicam decreased the AUC of meloxicam by 50%. Meloxicam is eliminated from the body with a mean elimination half-life of 20 hours. Total plasma clearance ranged from 7-9 mL/min following multiple oral doses of meloxicam.

Hepatic impairment

Following a single 15 mg dose of meloxicam, there was no marked difference in plasma concentrations in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment compared to healthy volunteers. Protein binding of meloxicam was not

affected by hepatic insufficiency. Patients with severe hepatic impairment (Child-Pugh Class III) have not been adequately studied.

Renal impairment

Meloxicam pharmacokinetics has been investigated in subjects with different degrees of renal insufficiency. Mild renal insufficiency does not have any substantial effect on meloxicam pharmacokinetics. Total drug plasma concentrations decreased with the degree of renal impairment, while free AUC values were similar. Total clearance of meloxicam increased in these patients, probably due to the increase in free fraction, leading to an increased metabolic clearance. Subjects with moderate renal impairment had higher total drug clearance. (Total clearance – no impairment: mean 4.80 mL/min (%CV 34.3%), median 4.44 mL/min; moderate impairment: mean 8.02 mL/min (%CV 46.2%), median 6.94 mL/min).

There is no need for dose adjustment in patients with mild to moderate renal failure (creatinine clearance greater than 25 mL/min). Patients with severe renal insufficiency have not been adequately studied. The use of MOBIC in patients with severe renal impairment is not recommended (see CONTRAINDICATIONS and PRECAUTIONS). A reduced protein binding was observed in patients with end stage renal disease on haemodialysis (see DOSAGE AND ADMINISTRATION).

Haemodialysis

Following a single dose of meloxicam, the free C_{max} plasma concentrations were higher in patients with renal failure on chronic haemodialysis (1% free fraction) in comparison to healthy volunteers (0.3% free fraction). Haemodialysis did not lower the total drug concentration in plasma; therefore, additional doses are not necessary after haemodialysis. Meloxicam is not dialysable.

Elderly

Clearance is decreased in the elderly. In clinical studies, steady state pharmacokinetics in the elderly (mean age 67) did not differ significantly from those in a younger population (mean age 50), however elderly females had a higher systemic exposure to meloxicam than did elderly males.

Gender

Young females exhibited slightly lower plasma concentrations relative to young males. After single doses of 7.5 mg MOBIC, the mean elimination half life was 19.5 hours for the female group as compared to 23.4 hours for the male group. At steady state, the data were similar (17.9 hours vs. 21.4 hours). This pharmacokinetic difference due to gender is likely to be of little clinical importance. There was linearity of pharmacokinetics and no appreciable difference in the C_{max} or t_{max} across genders.

CLINICAL TRIALS

The efficacy of meloxicam in treating the symptoms of osteoarthritis and rheumatoid arthritis has been confirmed in several clinical studies.

Osteoarthritis Trials

Two clinical studies of 6 months duration were performed in patients with osteoarthritis of the hip or knee. In the first study, the efficacy of meloxicam 15 mg (n=306) and piroxicam 20 mg (n=149) were found to be comparable, using as efficacy endpoints improvement in overall pain, pain on movement, global efficacy, change in duration of inactivity and change in quality of life score. In the second study, the efficacy of meloxicam 7.5 mg (n=169) was found to be comparable to that of diclofenac 100 mg SR (n=167) using similar endpoints.

Once daily dosing of meloxicam 7.5 mg (n=153) and 15 mg (n=156) showed a consistently more efficacious response than placebo (n=155) in a 12 week trial in patients with

osteoarthritis of the knee or hip. Efficacy was measured by global assessment of disease activity, global assessment of pain and arthritic condition, as measured by the WOMAC (Western Ontario and McMaster University) Osteoarthritis Index. Both doses of meloxicam were also shown to be comparable to diclofenac 50 mg BID (n=152) with regard to efficacy, with a lower incidence of GI adverse events when compared to diclofenac.

Two large scale, randomised, active-controlled clinical studies of 4 weeks duration were conducted in patients with osteoarthritis of the hand, hip, knee or spine. In the first study (MELISSA), the effects of meloxicam 7.5 mg (n=4635) were compared against the effects of diclofenac 100 mg SR (n=4688). In the second study (SELECT), the effects of meloxicam 7.5 mg (n=4320) were compared against the effects of piroxicam 20 mg (n=4336). The results from both studies indicated that meloxicam 7.5 mg was as efficacious as diclofenac 100 mg SR and piroxicam 20 mg, in the treatment of symptomatic osteoarthritis.

Rheumatoid arthritis trials

The use of MOBIC for the symptomatic treatment of rheumatoid arthritis was evaluated in a double-blind controlled trial involving 894 patients treated for 12 weeks. Meloxicam (7.5 mg, 15 mg and 22.5 mg daily) was compared to placebo, with diclofenac (75 mg twice daily) compared to placebo to establish trial sensitivity. The primary endpoints were number of painful or tender joints; number of swollen joints; investigator's global assessment of disease activity; patients global assessment of disease activity and patient's assessment of pain. For all 5 primary endpoints, the meloxicam 7.5 mg group was significantly better than placebo for both mean on trial and last observation. The meloxicam 15 mg group was significantly better for 3 of 5 primary endpoints, excluding painful and swollen joints. In patients who had flared at baseline tender joints, the meloxicam 15 mg group differed almost significantly from the placebo group ($p<0.05$ not met due to the lower number of patients).

A second trial also investigated the use of MOBIC for the symptomatic treatment of rheumatoid arthritis. This double-blind placebo controlled trial used three doses of meloxicam (7.5 mg, 15 mg and 22.5 mg daily), in patients with rheumatoid arthritis over a 12 week period. A total of 898 patients were treated with meloxicam. The primary endpoint in this study was the American College of Rheumatology (20%) response criterion (ACR20) response rate, a composite measure of clinical, laboratory and functional measures of rheumatoid arthritis response. For this parameter, all three doses of meloxicam were more effective than placebo for the duration of the study. For the endpoints that comprised the ACR20 criteria, each of the meloxicam groups was superior to placebo at all visits except for C-Reactive Protein. Efficacy reached a plateau at the meloxicam 15 mg dose (Table 1). The overall incidence and severity of adverse events was similar among all three meloxicam groups.

Table 1: Analysis of ACR20 Response Rate for Evaluable Patients at 12 weeks

				P-value[#]		
Study phase	Treatment	Total	Responder[1]* N (%)	Placebo	Meloxicam 7.5 mg	Meloxicam 15 mg
Week 12	Placebo	292	97 (33.2)			
	Meloxicam 7.5 mg	306	138 (45.1)	0.0008		
	Meloxicam 15 mg	293	158 (53.9)	0.0000	0.0439	

[1]The primary efficacy end-point was the ACR20. A responder was a patient with a response defined as: ≥20% improvement in both tender joint count and swollen joint count, and at least three of the following: ≥20% improvement in: patient pain assessment; patient global (overall) assessment; physician global (overall) assessment; the modified health assessment questionnaire; C-Reactive protein.

*Early terminations were considered as non-responders from the termination date.

[#]Obtained from Cochran-Mantel-Haenszel test stratified by centre.

The data from both studies indicate that meloxicam is effective and safe for the treatment of patients with rheumatoid arthritis.

INDICATIONS

MOBIC tablets and capsules are indicated for the symptomatic treatment of osteoarthritis and rheumatoid arthritis.

CONTRAINDICATIONS

- Peri-operative treatment of pain in patients undergoing coronary artery bypass graft surgery (CABG)
- Known hypersensitivity to meloxicam or any excipients of the product. There is a potential for cross sensitivity to aspirin and other NSAIDs.
- Signs/symptoms of asthma, nasal polyps, angioedema or urticaria, following the administration of aspirin or other NSAIDs.
- Active gastrointestinal ulceration/ perforation
- Active Inflammatory Bowel Disease (Crohn's Disease or Ulcerative Colitis)
- Patients with severe hepatic impairment
- Non-dialysed severe renal insufficiency
- Severe uncontrolled heart failure
- Children and adolescents under 18 years of age
- Breastfeeding
- Concomitant administration of drugs known to inhibit CYP 2C9 (e.g. sulfaphenazole, sulfinpyrazone, sulfamethoxazole and fluconazole)
- The use of MOBIC tablets and capsules is contraindicated in patients with rare hereditary galactose intolerance, due to the lactose content of the formulations.

As with all NSAIDs, MOBIC is contraindicated in patients with recent cerebrovascular bleeding or established systemic bleeding disorders.

PRECAUTIONS

Gastrointestinal effects

As with other NSAIDs gastrointestinal (GI) bleeding, ulceration or perforation, potentially fatal, can occur at any time during treatment, with or without warning symptoms or a previous history of serious GI events. The consequences of such events are generally more serious in the elderly. 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. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. 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, increasing the likelihood of developing a serious adverse GI event at some time during the course of therapy. However, even short term therapy is not without risk.

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 GI bleed than patients with neither of these factors.

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

In clinical trials, meloxicam has been shown to cause fewer GI adverse events (including dyspepsia, abdominal pain, nausea, vomiting, etc) than other NSAIDs with which it has been compared (see Table 2).

Table 2: Incidence of GI adverse events (%) after 4 weeks, 12 weeks and 6 months

4 week treatment			12 week treatment				6 month treatment			
MELISSA/SELECT			placebo-controlled trial				active-controlled trials			
melox. 7.5 mg	diclo. (SR) 100 mg	pirox. 20 mg	melox. 7.5 mg	melox. 15 mg	placebo	diclo. BID (2x50 mg)	melox. 7.5 mg	melox. 15 mg	diclo. 100 mg	pirox. 20 mg
n=8955	n=4688	n=4336	n=154	n=156	n=157	n=153	n=169	n=306	n=167	n=149
12%	19%	15%	20%	17%	17%	28%	27%	24%	28%	30%

KEY: melox. = meloxicam; pirox. = piroxicam; diclo. = diclofenac; SR = slow release; BID = twice daily

Caution should be exercised when treating patients with a history of upper gastrointestinal disease and in patients receiving treatment with anticoagulants. Patients with GI symptoms should be monitored. MOBIC therapy should cease if peptic ulceration or GI ulceration or bleeding occurs.

Co-administration of meloxicam with drugs known to inhibit CYP 3A4 should be undertaken with caution. A combination of meloxicam and substances known to inhibit both CYP 3A4 and CYP 2C9 should be avoided because of the increased risk of toxicity.

Cardiovascular effects

Long term therapy with some COX-2 selective NSAIDs of the coxib class has been shown to increase the risk of serious cardiovascular thrombotic events. MOBIC is a COX-2 selective NSAID. MOBIC has not been demonstrated to increase the risk of cardiovascular adverse events compared to nonselective NSAIDs in clinical trials. However, long term placebo controlled data to adequately assess any cardiovascular risk are not available for MOBIC.

All NSAIDs, both COX-2 selective and nonselective, may cause an increased risk of serious cardiovascular thrombotic events including myocardial infarction and stroke. This may increase with dose and duration of use. Patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking MOBIC especially in those with cardiovascular risk factors the lowest effective dose should be used for the shortest possible duration.

Physicians and patients should remain alert for such cardiovascular events even in the absence of previous cardiovascular symptoms. Patients should be informed about signs and/or symptoms of serious cardiovascular toxicity and the steps to take if they occur.

Skin reactions

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.

Renal effects

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 pretreatment state upon discontinuation of nonsteroidal 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 renal function, including volume of diuresis, should be carefully monitored at the beginning of therapy.

In rare cases, NSAIDs may cause 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).

The extent to which metabolites of meloxicam may accumulate in patients with renal failure has not been studied. As some metabolites are excreted by the kidney, patients with significantly impaired renal function should be more closely monitored.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti inflammatory drugs and thiazide diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine, particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Hepatic effects

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, including MOBIC. These laboratory values may progress, may remain unchanged, or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes, have been reported with NSAIDs.

Physicians and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity. Patients with signs and/or symptoms suggesting liver dysfunction (e.g., nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness in the right upper quadrant and "flu-like" symptoms), or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with MOBIC. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc), MOBIC should be discontinued.

Fluid retention and oedema

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.

Driving and operating machinery

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.

Pre-existing asthma

Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, MOBIC should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Use in patients being treated with corticosteroids

MOBIC cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

Use in patients with fever and infection

The pharmacological activity of MOBIC in reducing inflammation and possibly fever may diminish the utility of these diagnostic signs in detecting complications of presumed non-infectious, painful conditions.

Anaphylactoid reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to meloxicam. MOBIC should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs. Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Lactose monohydrate

MOBIC tablets 7.5 mg contains 47 mg lactose monohydrate and MOBIC tablets 15 mg contains 20 mg lactose monohydrate per maximum recommended daily dose. MOBIC capsules 7.5 mg contains 246 mg lactose monohydrate and MOBIC 15 mg contains 112 mg lactose monohydrate per maximum recommended daily dose. Patients with rare hereditary conditions of galactose intolerance, e.g. galactosaemia should not take this medicine.

Effects on fertility

Oral treatment with meloxicam at doses up to 5 mg/kg/day in female rats (approximately 2.7 times the human dose based on BSA) and up to 9 mg/kg/day (approximately 5 times the human dose based on BSA) in male rats did not affect mating behaviour or fertility.

Oral treatment of female rats with meloxicam at doses of 1 mg/kg/day (approximately half of the human dose based on BSA) reduced the number of embryonic implantations and increased the number of early resorptions. A no-effect dose for these effects was not established. A reduction in the number of corpora lutea was also observed at 5 mg/kg/day, with the no-effect dose being 2.5 mg/kg/day (approximately 1.5 fold greater than the human dose based on BSA).

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.

Use in Pregnancy (Category C)

Meloxicam use is not recommended in pregnancy unless it is considered clinically essential.

Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy.

NSAIDs inhibit prostaglandin synthesis and, when given during the latter part of pregnancy, may cause closure of the fetal ductus arteriosus, fetal renal impairment, inhibition of platelet aggregation and delay of labour and birth. Continuous treatment with NSAIDs during the last trimester of pregnancy should only be given on sound indications. During the last few days before expected birth, agents with inhibitory effects on prostaglandin synthesis should be avoided.

Meloxicam was not teratogenic in rats up to an oral dose of 4 mg/kg/day (approximately 2.2 times the human dose at 15 mg/day for a 50 kg adult based on body-surface-area [BSA]) when given during organogenesis. Meloxicam caused an increased incidence of septal defect of the heart, a rare event, at an oral dose of 60 mg/kg/day (about 60 times the human dose based on BSA) and embryolethality at oral doses $\geq$ 5 mg/kg/day (5 times the human dose based on BSA) when rabbits were treated throughout organogenesis.

Studies in rats with meloxicam, as with other drugs known to inhibit prostaglandin synthesis, showed an increased incidence of still births, increased length of delivery time and delayed parturition at oral doses $\geq$ 1 mg/kg/day (approximately 0.6 times the human dose based on BSA), and decreased pup survival at an oral dose of 4 mg/kg/day (approximately 2.1 times the human dose based on BSA) throughout organogenesis. Similar findings were observed in rats receiving oral doses $\geq$ 0.125 mg/kg/day (less than 0.1 times the human dose based on BSA) during late gestation and the lactation period.

Meloxicam crosses the placental barrier. There are no adequate, well-controlled studies in pregnant women. Meloxicam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

Studies of meloxicam excretion in human milk have not been conducted. However, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. The safety of meloxicam in humans during lactation has not been established and therefore, the drug should not be used during lactation.

Paediatric Use

MOBIC is not recommended for use in children and adolescents under 18 years of age (see CONTRAINDICATIONS).

Use in the Elderly

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.

Genotoxicity

Meloxicam did not demonstrate genotoxic potential in assays for gene mutation *in vitro* and chromosomal damage *in vitro* and *in vivo*.

Carcinogenicity

Two year dietary studies showed no evidence for carcinogenic activity at meloxicam doses up to 0.8 mg/kg/day (approximately half of the highest human dose at 15 mg/day for a 50 kg person based on body-surface-area [BSA]) in rats and up to 8 mg/kg/day (2.2 times the highest human dose based on BSA) in mice. In rats, the highest dose used was nephrotoxic, while the highest dose used in mice was subtoxic.

INTERACTIONS WITH OTHER MEDICINES

General

In vitro drug interaction studies revealed that the metabolism of meloxicam is predominantly mediated via the CYP 2C9 isoenzyme, with a minor contribution of the CYP 3A4 isoenzyme in the liver. Co-administration of meloxicam with drugs known to inhibit CYP 2C9 is contraindicated. Co-administration of meloxicam with drugs known to inhibit CYP 3A4 (ketoconazole, itraconazole, erythromycin) or drugs known to be metabolised by CYP 3A4 (terfenadine, astemizole, ciclosporin, class III antiarrhythmic drugs such as amiodarone and quinidine) should be undertaken with caution (see PRECAUTIONS - Gastrointestinal effects).

Antacids

No pharmacokinetic interaction was detected with concomitant administration of antacids.

Cimetidine

Concomitant administration of 200 mg cimetidine QID did not alter the single dose pharmacokinetics of 30 mg meloxicam.

Digoxin

Meloxicam 15 mg once daily for 7 days did not alter the plasma concentration profile of digoxin after beta-acetyldigoxin administration for 7 days at clinical doses. *In vitro* testing found no protein binding drug interaction between digoxin and meloxicam.

Furosemide (Frusemide)

Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide (frusemide) and thiazide diuretics in some patients. This effect has been attributed to inhibition of renal prostaglandin synthesis. Studies with furosemide (frusemide) agents and meloxicam have not demonstrated a reduction in natriuretic effect. Furosemide (frusemide) single and multiple dose pharmacodynamics and pharmacokinetics are not affected by multiple doses of meloxicam. Nevertheless, during concomitant therapy with furosemide (frusemide) and meloxicam, patients should be observed closely for signs of declining renal function (see INTERACTIONS WITH OTHER MEDICINES, Diuretics), as well as to assure diuretic efficacy.

Cytochrome P450 inhibitors

Co-administration of meloxicam with drugs known to inhibit CYP 2C9 is contraindicated. Co-administration of meloxicam with drugs known to inhibit CYP 3A4 should be undertaken with caution (see PRECAUTIONS - Gastrointestinal effects).

Other Prostaglandin Synthetase Inhibitors (PSIs) including 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 meloxicam with other NSAIDs is not recommended.

Oral anticoagulants, antiplatelet drugs, systemically administered heparin, thrombolytics and Selective Serotonin Reuptake Inhibitors (SSRIs)

There is an increased risk of bleeding via inhibition of platelet function, when NSAIDs are co-administered. If such co-prescribing cannot be avoided, close monitoring of their effects on coagulation is required.

Lithium

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

Methotrexate

Meloxicam did not have a significant effect on the pharmacokinetics of single doses of methotrexate. In vitro, methotrexate did not displace meloxicam from human serum binding sites. However, as with other NSAIDs, MOBIC may increase the haematologic toxicity of methotrexate. In this situation, strict monitoring of blood cell count is recommended.

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 NSAIDs 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 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 affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAIDs.

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.

Contraception

NSAIDs have been reported to decrease the efficacy of intrauterine devices.

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.

Ciclosporin

Nephrotoxicity of ciclosporin may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment, renal function is to be measured.

Antihypertensives (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.

Angiotensin-II receptor antagonists

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.

Colestyramine

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

Oral hypoglycaemics

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

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.

A 12-week, multicentre, double-blind, randomised trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of MOBIC with placebo and with an active control. Table 3 presents the adverse events that occurred in $\geq$ 1% of the MOBIC treatment groups.

Table 3: Adverse events (%) occurring in ≥ 1% of MOBIC patients in a 12-week osteoarthritis placebo- and active-controlled trial

	Placebo	MOBIC 7.5 mg daily	MOBIC 15 mg daily	Diclofenac 100 mg daily
No. of patients	157	154	156	153
Ear and labyrinth disorders				
Ear disorder	0	0	1.3	0.7
Vertigo	0	0.6	1.3	0.7
Eye disorders				
Cataract	0	0	1.3	1.3
Gastrointestinal				
Abdominal pain	2.5	1.9	2.6	1.3
Constipation	1.9	1.9	0.6	3.9
Diarrhoea	3.8	7.8	3.2	9.2
Dyspepsia	4.5	4.5	4.5	6.5
Eructation	0	0	1.3	0
Flatulence	4.5	3.2	3.2	3.9
Gastro-oesophageal reflux disease	0	0.6	1.9	1.3
Nausea	3.2	3.9	3.8	7.2
Vomiting	1.9	1.3	1.3	2.6
General disorders and administration site conditions				
Fatigue	1.9	1.9	1.3	1.3
Gravitational oedema	0.6	1.3	1.9	3.3
Influenza like illness	5.1	4.5	5.8	2.6
Oedema peripheral	1.3	0.6	3.2	0
Immune system disorders				
Hypersensitivity	1.9	1.9	0.6	1.3
Infections and infestations				
Pharyngitis	1.3	0.6	3.2	1.3
Sinusitis	5.1	1.3	1.9	5.9
Upper respiratory tract infection	1.9	3.2	1.9	5.9
Injury, poisoning and procedural complications				
Accident at home	1.9	4.5	3.2	2.6
Fall	0.6	2.6	0	1.3
Metabolism and nutrition disorders				
Dehydration	0	1.3	0	0
Increased appetite	0.6	0	1.3	0

	Placebo	MOBIC 7.5 mg daily	MOBIC 15 mg daily	Diclofenac 100 mg daily
Musculoskeletal and connective tissue disorders				
Arthralgia	1.9	1.9	1.3	1.3
Arthritis	0	0	1.9	0
Back pain	3.2	1.3	1.9	2.0
Bursitis	0.6	1.9	1.3	0
Muscle spasms	1.3	1.3	1.9	1.3
Myalgia	0	1.3	1.3	0
Pain in extremity	0	1.3	0.6	0.7
Nervous system disorders				
Carpal tunnel syndrome	0	1.3	0.6	1.3
Dizziness	3.2	2.6	3.8	2.0
Headache	10.2	7.8	8.3	5.9
Psychiatric disorders				
Insomnia	0.6	0	1.9	2.0
Renal and urinary disorders				
Haematuria	0.6	0	1.3	0.7
Respiratory, thoracic and mediastinal disorders				
Cough	0.6	1.3	0.6	1.3
Dyspnoea	0	0	1.3	0.7
Pleuritic pain	0	0	1.3	0
Skin and subcutaneous tissue disorders				
Hyperhidrosis	0	0	1.3	0
Pruritus	0.6	1.3	0.6	0
Purpura	1.3	1.9	0	0.7
Rash	1.9	1.9	0	0.7
Vascular disorders				
Hypertension	2.5	0.6	1.9	0

Adverse events that occurred in ≥ 1% of the MOBIC treatment groups in two 12-week placebo controlled rheumatoid arthritis trials are presented in Table 4.

Table 4: Adverse Events (%) occurring in ≥ 1% of MOBIC patients in two 12-week rheumatoid arthritis placebo- and active controlled trials.

	Placebo	MOBIC 7.5 mg daily	MOBIC 15 mg daily	Diclofenac 150mg daily
No. of Patients	**470**	**482**	**478**	**182**
Gastrointestinal disorders				
Abdominal pain	0.6	3.1	2.3	4.4
Abdominal pain upper	0.9	1.9	1.0	0
Constipation	0.9	1.5	1.7	3.8
Diarrhoea	5.3	5.2	3.3	6.0
Dyspepsia	3.6	5.6	3.6	7.1
Flatulence	1.1	1.2	1.5	5.5
Nausea	2.6	3.3	3.8	7.7
Vomiting	2.3	0.8	1.3	1.1
General disorders and administration site conditions				
Influenza like illness	2.1	2.3	2.3	5.5
Immune system disorders				
Hypersensitivity	0.4	1.2	0.2	0
Infection and infestations				
Bronchitis	0.2	0.6	1.3	0.5
Nasopharyngitis	0.6	1.7	1.9	0
Pharyngitis	0.6	0.8	1.0	1.1
Rhinitis	0.4	0.6	1.0	1.1
Sinusitis	1.3	1.7	1.5	1.6
Upper respiratory tract infection	2.1	4.1	4.0	2.7
Urinary tract infection	1.3	1.2	1.3	1.6
Injury, poisoning and procedural complications				
Fall	0.2	0.6	1.0	0.5
Musculoskeletal and connective tissue disorders				
Arthralgia	1.9	1.0	1.7	2.2
Back pain	2.3	1.5	1.9	2.2
Myalgia	0.2	1.0	0.6	0.5
Rheumatoid arthritis	2.3	1.9	1.5	1.6
Nervous system disorders				
Dizziness	3.0	2.3	0.6	3.3
Headache	6.6	6.6	5.4	9.3
Psychiatric disorders				
Insomnia	0.6	1.0	0.6	1.1

	Placebo	MOBIC 7.5 mg daily	MOBIC 15 mg daily	Diclofenac 150mg daily
Respiratory, thoracic and mediastinal disorders				
Cough	1.5	0.8	1.5	2.2
Skin and subcutaneous tissue disorders				
Pruritus	1.3	0.6	1.0	1.1
Purpura	0.2	0.2	1.0	0
Rash	1.7	1.0	2.3	3.8
Vascular disorders				
Hypertension	0.9	1.5	1.0	2.2

Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events, therefore the daily dose of MOBIC should not exceed 15 mg.

The following is a list of adverse events occurring in <1% of patients, which may be causally related to the administration of MOBIC. The information is based on clinical trials involving patients who have been treated with daily oral doses of 7.5 or 15 mg MOBIC tablets or capsules over a period of up to 18 months (mean duration of treatment 127 days).

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.

Cardiac disorders: palpitations

Ear and labyrinth disorders: tinnitus

Gastrointestinal disorders: gastrointestinal perforation, occult or macroscopic gastrointestinal haemorrhage, gastroduodenal ulcer, colitis, oesophagitis, stomatitis

Gastro-intestinal haemorrhage, ulceration or perforation may potentially be fatal.

Hepatobiliary disorders: transitory abnormalities of liver function parameters (e.g. raised transaminases or bilirubin)

Nervous system disorders: somnolence

Renal and urinary disorders: renal function test abnormal (increased serum creatinine and/or serum urea)

Respiratory, thoracic and mediastinal disorders: onset of asthma attacks in individuals allergic to aspirin or other NSAIDs

Skin and subcutaneous tissue disorders: urticaria, photosensitivity reaction

Vascular disorders: flushing

Post-Market Adverse Drug Reactions

Additional reports of adverse events which may be causally associated to the administration of MOBIC during worldwide post-marketing experience are included below.

General disorders and administration site conditions: In rare cases, other drugs of this class are reported to cause meningitis

Eye disorders: visual disturbance including blurred vision, conjunctivitis

Gastrointestinal disorders: gastritis

Hepatobiliary disorders: hepatitis

Immune system disorders: anaphylactic reaction, anaphylactoid reaction and other immediate hypersensitivity

Psychiatric disorders: confusional state, disorientation, mood altered

Renal and urinary disorders: acute renal failure. The use of NSAIDs may be related to micturition disorders, including acute urinary retention.

Reproductive system and breast disorders: infertility female, ovulation delayed.

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, dermatitis bullous, erythema multiforme.

Other adverse events

Additional adverse events, reported from clinical trials or from spontaneous reports, where evidence for a causal association with meloxicam use is unclear, are the following: cardiac failure, angina, myocardial infarction, arrhythmia, vasculitis, agranulocytosis, interstitial nephritis, convulsion, liver failure.

DOSAGE AND ADMINISTRATION

MOBIC should be used at the lowest dose and for the shortest duration consistent with effective treatment.

The maximum recommended daily dose of MOBIC is 15 mg. A dose of 15 mg/day should not be exceeded. As a dose for children has not been established, use should be restricted to adults (see PRECAUTIONS - Paediatric Use).

The dose of MOBIC in patients with end-stage renal failure on haemodialysis should not exceed 7.5 mg/day (see PHARMACOLOGY – Renal Impairment and PHARMACOLOGY Pharmacokinetics - Haemodialysis). 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) nor in patients with mild to moderate hepatic impairment. In non-dialysed patients with severe renal impairment MOBIC is contraindicated (see CONTRAINDICATIONS).

In patients with increased risks 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 and increased to 15 mg/day only if clinically justified.

Patients on long term treatment should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

Osteoarthritis

The recommended dose of MOBIC is 7.5 mg once daily, to be swallowed with fluid, in conjunction with food. Depending on the adequacy of response, the severity of the arthritic condition and the patient’s concomitant diseases, the dose may be increased to 15 mg/day. Patients should generally be maintained on the lowest dose consistent with achieving a satisfactory therapeutic response.

Rheumatoid Arthritis

The recommended dose of MOBIC is 15 mg once daily, to be swallowed with fluid, in conjunction with food. Depending on the adequacy of response and the severity of the condition, the dose may be reduced to 7.5 mg/day. Patients should generally be maintained on the lowest dose consistent with achieving a satisfactory therapeutic response.

OVERDOSAGE

In case of poisoning or overdose, advice should be sought from a Poisons Information Centre (telephone 13 11 26).

Patients should be managed with symptomatic and supportive care following an NSAID overdose. In cases of acute overdose, activated charcoal is recommended. Administration of activated charcoal is recommended for patients who present 1-2 hours after overdose. For substantial overdose or severely symptomatic patients, activated charcoal may be administered repeatedly.

It has been shown in a clinical trial that colestyramine accelerates the elimination of meloxicam.

The typical signs and symptoms of NSAID overdose include nausea, vomiting, headache, drowsiness, blurred vision and dizziness. Rare cases of seizures, hypotension, apnoea, coma and renal failure have been reported with severe NSAID overdose.

PRESENTATION AND STORAGE CONDITIONS

Tablets 7.5 mg:	Pastel-yellow, round tablets, marked 59D on one side with break bar, and company logo on the other. Each tablet contains meloxicam 7.5 mg. Blister packs: 10*, 20*, 30, 60*, 100* tablets.
Tablets 15 mg:	Pastel-yellow, round tablets, marked 77C on one side with break bar, and company logo on the other. Each tablet contains meloxicam 15 mg. Blister packs: 10*, 20*, 30, 60*, 100* tablets.
Capsules 7.5 mg:	Oblong, hard gelatin capsule with pale green opaque cap and body, containing a fine yellow granulate. Each capsule contains meloxicam 7.5 mg. Blister packs: 10*, 20*, 30, 100* capsules.
Capsules 15 mg:	Oblong, hard gelatin capsule with pale green opaque cap and yellow opaque body, containing a fine yellow granulate. Each capsule contains meloxicam 15 mg. Blister packs: 10*, 20*, 30, 100* capsules.

*not currently distributed in Australia

TABLETS and CAPSULES: Store below 25°C. Protect from direct sunlight.

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 23 February 2001

DATE OF MOST RECENT AMENDMENT: 23 May 2017