NEW ZEALAND DATA SHEET

1. PRODUCT NAME

MOBIC 7.5 mg tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One MOBIC 7.5 mg tablet contains 7.5 mg of meloxicam.

Excipient(s) with known effect:
Each tablet contains 23.5 mg of lactose monohydrate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Symptomatic treatment of rheumatoid arthritis.

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longer-term use may be required, treatment efficacy should be reviewed within the first month of treatment and MOBIC withdrawn if there is a lack of therapeutic benefit.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

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

4.2 Dose and method of administration

Dose

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 in all patients.

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

Painful Osteoarthritis: 7.5 mg/day. If necessary, the dose may be increased to 15 mg/day.

Rheumatoid arthritis: 15 mg/day. According to the therapeutic response, the dose may be reduced to 7.5 mg/day.

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 section 4.4).

Renal impairment
No dose reduction is required in patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 mL/min). In non-dialysed patients with severe renal impairment MOBIC is contraindicated (see section 4.3) . In patients with end-stage renal failure on haemodialysis the maximum daily dose should not exceed 7.5 mg per day.

Paediatric population
The maximum recommended daily dose for adolescents aged 12 to 18 years is 0.25 mg/kg and should not exceed 15 mg.

MOBIC tablets are contraindicated in children below 12 years of age because the strengths of these dosage forms do not allow appropriate dosing in this age group (see section 4.3).

Method of administration
MOBIC tablets are swallowed with water or other fluid in conjunction with food.
There is insufficient information on the effect of mixing crushed tablets with food or fluids. The MOBIC 7.5 mg tablet break mark should not be used to subdivide the tablet into fractions of a full dose e.g. 3.75 mg. MOBIC 7.5 mg tablets can only be subdivided for ease of swallowing.

4.3 Contraindications

- Patients with known hypersensitivity to meloxicam or any excipient of the product (see section 6.1)
- Rare hereditary conditions that may be incompatible with an excipient of the product (see section 4.4)
- Use in patients who have developed signs of asthma, nasal polyps, angioedema or urticaria following the administration of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) because of a potential for cross sensitivity
- 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
- Severe uncontrolled heart failure
- Patients who have previously had a myocardial infarction or stroke
- Peri-operative pain in the setting of cardiac surgery, including coronary artery bypass graft (CABG), or major vascular surgery
- Use in children below 12 years of age
- Pregnancy or lactation

4.4 Special warnings and precautions for use

Gastrointestinal effects
As with other NSAIDs, 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.

Caution should be exercised when treating patients with a history of upper gastrointestinal disease. Patients with gastrointestinal symptoms should be monitored. MOBIC should be withdrawn if gastrointestinal ulceration or bleeding occurs.

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

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

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

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

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

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

Cardiovascular and cerebrovascular effects

NSAIDs may increase the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

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

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

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

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

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

Skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported rarely in association with the use of MOBIC. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. MOBIC should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Renal function

NSAIDs inhibit the synthesis of renal prostaglandins which play a supportive role in the maintenance of renal perfusion. In patients whose renal blood flow and blood volume are decreased, administration of an NSAID may precipitate overt renal decompensation which is typically followed by recovery to pre-treatment state upon discontinuation of non-steroidal anti- inflammatory therapy.

Patients at greatest risk of such a reaction are elderly individuals, dehydrated patients, those with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease, those receiving concomitant treatment with a diuretic, ACE inhibitor or angiotensin II receptor antagonist or those having undergone major surgical procedures, which led to hypovolaemia. In such patients, the renal function, including the volume of diuresis, should be carefully monitored at the beginning of therapy.

In rare instances, NSAIDs may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.

The dose of MOBIC in patients with end-stage renal failure on haemodialysis should not exceed 7.5 mg. No dose reduction is required in patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 mL/min).

Liver function

As with most other NSAIDs, occasional elevations of serum transaminases or other parameters of liver function have been reported. In most cases, these have been small and transient increases above the normal range. If the abnormality is significant or persistent, MOBIC should be stopped and follow up tests carried out.

No dose reduction is required in patients with clinically stable liver cirrhosis.

Sodium, potassium and water retention

Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with NSAIDs. Use of COX-2 inhibitors (of which MOBIC is one) or other NSAIDs may precipitate or exacerbate pre-existing hypertension, cardiac failure or oedema in susceptible patients, and the treatment of these conditions may be compromised. For patients at risk, clinical monitoring is recommended.

Other warnings and precautions

Frail or debilitated patients may be less tolerant to side effects and such patients should be carefully supervised. As with other NSAIDs, caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function.

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

The use of MOBIC, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of MOBIC should be considered.

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

4.5 Interactions with other medicines and other forms of interaction

Interaction studies have only been performed in adults.

Other Prostaglandin Synthetase Inhibitors (PSI) 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. Concomitant administration of aspirin (1000 mg tid) to healthy volunteers tended to increase the AUC (10%) and C_{max} (24%) of meloxicam. The clinical significance of this interaction is not known.

Oral anticoagulants, systemically administered heparin, thrombolytics
Increased risk of bleeding. If such co-prescribing cannot be avoided, close monitoring of their effects on coagulation is required.

Antiplatelet drugs and Selective Serotonin Reuptake Inhibitors (SSRIs)
Increased risk of bleeding via inhibition of platelet function.

Diuretics
Treatment with NSAIDs is associated with the potential for acute renal insufficiency in patients who are dehydrated. Patients receiving MOBIC and diuretics should be adequately hydrated and be monitored for renal function prior to initiating treatment.

Antihypertensives (e.g. beta-blockers, ACE-inhibitors, vasodilators, diuretics)
A reduced effect of the antihypertensive drug by inhibition of vasodilating prostaglandins has been reported during treatment with NSAIDs.

NSAIDs and angiotensin-II receptor antagonists as well as ACE inhibitors exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment this may lead to acute renal failure.

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

Contraception
A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported but needs further confirmation.

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

Methotrexate
NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of NSAIDs is not recommended.

The risk of an interaction between NSAID preparations and methotrexate, should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In case combination treatment is necessary, blood cell count and the renal function should be monitored. Caution should be taken in case both NSAID and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity.

Although the pharmacokinetics of methotrexate (15 mg/week) were not relevantly affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAID drugs.

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 two days following pemetrexed administration. If a combination of meloxicam 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 meloxicam with pemetrexed is not recommended.

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

Meloxicam is eliminated almost entirely by hepatic metabolism, of which approximately two thirds are mediated by cytochrome (CYP) P450 enzymes (CYP 2C9 major pathway and CYP 3A4 minor pathway) and one-third by other pathways, such as peroxidase oxidation. The potential for a pharmacokinetic interaction should be taken into account when meloxicam and drugs known to inhibit, or to be metabolised by, CYP 2C9 and/or CYP 3A4 are administered concurrently.

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

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

4.6 Fertility, pregnancy and lactation

Fertility
The use of meloxicam, as with any drug known to inhibit cyclooxygenase/prostaglandin synthesis, may impair fertility and is not recommended in women attempting to conceive. Meloxicam may delay ovulation. Therefore, in women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.

Pregnancy
MOBIC is contraindicated during pregnancy (see section 4.3 Contraindications).

Inhibition of prostaglandin-synthesis may adversely affect pregnancy and/or the embryo-fetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation and gastroschisis was increased from less than 1 %, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In preclinical studies, administration of a prostaglandin synthesis inhibitor has been shown to result in

increased pre- and post- implantation loss and embryo-fetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in preclinical studies given a prostaglandin synthesis inhibitor during the organogenetic period.

During the third trimester of pregnancy all prostaglandin-synthesis inhibitors may expose

- the foetus to:
  - cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
  - renal dysfunction, which may progress to renal failure with oligohydramnios;
- the mother and the neonate, at the end of pregnancy, to:
  - possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses
  - inhibition of uterine contractions resulting in delayed or prolonged labour.

Oligohydramnios and Fetal Renal Impairment:
Use of NSAIDs in the second or third trimester may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Oligohydramnios is generally seen after days to weeks of treatment, although it has been reported as soon as 48 hours after NSAID initiation. Oligohydramnios is usually, but not always, reversible after treatment discontinuation.

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

4.7 Effects on ability to drive and use machines

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

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

4.8 Undesirable effects

a. Summary of the safety profile
The MOBIC phase II/III safety database includes 10,122 osteoarthritis patients and 1,012 rheumatoid arthritis patients treated with MOBIC 7.5 mg/day and 3,505 osteoarthritis patients and 1,351 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 2,362 of these patients were treated in ten placebo and or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across MOBIC trials.

Gastrointestinal disorders
Adverse events occurring in ≥ 2% of MOBIC patients in a 12 week osteoarthritis placebo and active controlled trial: abdominal pain, diarrhoea, dyspepsia, flatulence, nausea.

The adverse events that occurred with MOBIC in ≥ 2% of patients treated short-term (4-6 weeks) and long-term (6 months) in active controlled osteoarthritis trials: abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, nausea, vomiting.

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

occult or macroscopic gastrointestinal haemorrhage, gastrointestinal perforation, colitis, gastritis.

b. Tabulated list of adverse reactions

The following adverse drug reactions, which may be causally related to the administration of MOBIC, have been reported.

Adverse drug reactions that have come to light as a result of reports received in relation to administration of the marketed product are included.

The following terms are used to rank the adverse drug reactions by frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Table 1: Summary of adverse drug reactions per frequency category.

System Organ class	Common	Uncommon	Rare	Very Rare	Not Known
Blood and lymphatic system disorders		anaemia	blood count abnormal (*including differential white cell count*), leukopenia, thrombocytopenia[1]		
Immune system disorders		other immediate hypersensitivity			anaphylactic reaction[2], anaphylactoid reaction[2]
Psychiatric disorders			mood altered		confusional state[2], disorientation[2]
Nervous system disorders	headache	dizziness, somnolence			
Eye disorders			visual disturbance including vision blurred, conjunctivitis		
Ear and labyrinth disorders		vertigo	tinnitus		
Cardiac disorders			palpitations		
Vascular disorders		blood pressure increased, flushing			
Respiratory, thoracic and mediastinal disorders			asthma in individuals allergic to aspirin or other NSAIDs		

System Organ class	Common	Uncommon	Rare	Very Rare	Not Known
Gastro-intestinal disorders[3]	abdominal pain, dyspepsia, diarrhoea, nausea, vomiting	occult or macroscopic gastrointestinal haemorrhage, gastritis, stomatitis, constipation, flatulence, eructation	gastroduodenal ulcer, colitis, oesophagitis	gastro-intestinal perforation	
Hepatobiliary disorders		liver function test abnormal (e.g. raised transaminases or bilirubin)		hepatitis	
Skin and sub-cutaneous tissue disorders		angioedema, rash, pruritus	toxic epidermal necrolysis, Stevens-Johnson syndrome, urticaria	dermatitis bullous, erythema multiforme	photosensitivity reaction[2]
Renal and urinary disorders		renal function test abnormal (increased serum creatinine and/or serum urea), micturition disorders, including acute urinary retention		renal failure acute	
Reproductive system and breast disorders					infertility female[4]
Endocrine disorders		ovulation delayed			
General disorders		oedema			

[1] Concomitant administration of a potentially myelotoxic drug, in particular methotrexate, appears to be a predisposing factor to the onset of cytopenia.
[2] Frequency not known, no adverse drug reactions observed in 15,197 patients in clinical trials.
[3] Gastrointestinal haemorrhage, ulceration or perforation may potentially be fatal.
[4] Frequency not known, no adverse drug reactions observed in 286 female patients with an age ≤ 50 years in clinical trials which are a subpopulation of the 15,197 patients in clinical trials with an observation period of at least 90 days.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continue monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions http://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

In case of overdose, the standard measures of gastric evacuation and general supportive measures

should be used, as there is no known antidote. It has been shown in a clinical trial that cholestyramine accelerates the elimination of meloxicam.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and Anti-rheumatic products, Non-steroids, Oxicams

ATC code: M01AC06

Mechanism of action

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the enolic acid class, which has shown anti-inflammatory, analgesic and antipyretic properties in animals. Meloxicam showed potent anti-inflammatory activity in all standard models of inflammation. A common mechanism for the above effects may exist in the ability of meloxicam to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.

Pharmacodynamic effects

Comparison of the ulcerogenic dose and the anti-inflammatory effective dose in the rat adjuvant arthritis model confirmed a superior therapeutic margin in animals over standard NSAIDs. In vivo, meloxicam inhibited prostaglandin biosynthesis more potently at the site of inflammation than in the gastric mucosa or the kidney.

These differences are thought to be related to a selective inhibition of COX-2 relative to COX-1 and it is believed that COX-2 inhibition provides the therapeutic effects of NSAIDs whereas inhibition of constitutive COX-1 may be responsible for gastric and renal side effects.

The COX-2 selectivity of meloxicam has been confirmed both in vitro and ex vivo in a number of test systems. In the human whole blood assay, meloxicam has been shown in vitro to inhibit COX-2 selectively. Meloxicam (7.5 and 15 mg) demonstrated a greater inhibition of COX-2 ex vivo, as demonstrated by a greater inhibition of lipopolysaccharide-stimulated PGE_2 production (COX-2) as compared with thromboxane production in clotting blood (COX-1). These effects were dose-dependent. Meloxicam has been demonstrated to have no effect on either platelet aggregation or bleeding time at recommended doses ex vivo, while indomethacin, diclofenac, ibuprofen and naproxen significantly inhibited platelet aggregation and prolonged bleeding.

Clinical efficacy and safety

In clinical trials, gastrointestinal adverse events overall were reported less frequently with meloxicam 7.5 mg and 15 mg than with the NSAIDs with which it has been compared, due predominantly to a lower reporting incidence of events such as dyspepsia, vomiting, nausea and abdominal pain.

There is no single study powered adequately to detect statistically differences in the incidence of clinically significant upper gastrointestinal perforation, obstruction, or bleeds between meloxicam and other NSAIDs. A pooled analysis has been conducted involving patients treated with meloxicam in 35 clinical trials in the indications osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Exposure to meloxicam in these trials ranged from 3 weeks to one year (most patients were enrolled in one-month studies). Almost all patients participated in trials that permitted enrolment of patients with a prior history of gastrointestinal perforation, ulcer or bleed.

The incidence of clinically significant upper gastrointestinal perforation, obstruction, or bleed (POB) was assessed retrospectively following independent blinded review of cases. Results are shown in the following table.

Cumulative risk of POBs for meloxicam 7.5 mg and 15 mg from BI clinical trials compared to diclofenac and piroxicam (Kaplan-Meier estimates)

TREATMENT Daily dose	Interval (days)	Patients at interval midpoint	POBs within interval	Risk (%)	95% confidence interval
Meloxicam					
7.5 mg	1 - <30	9636	2	0.02	0.00 – 0.05
	30 - <91	551	1	0.05	0.00 – 0.13
15 mg	1 - <30	2785	3	0.12	0.00 – 0.25
	30 - <91	1683	5	0.40	0.12 – 0.69
	91 - <182	1090	1	0.50	0.16 – 0.83
	182 - <365	642	0	0.50	
Diclofenac	1 - <30	5110	7	0.14	0.04 – 0.24
100 mg	30 - <91	493	2	0.55	0.00 – 1.13
Piroxicam	1 - <30	5071	10	0.20	0.07 – 0.32
20 mg	30 - <91	532	6	1.11	0.35 – 1.86

5.2 Pharmacokinetic properties

Absorption

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

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

Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake or the use of inorganic antacids.

With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to mean drug plasma concentrations with a relatively small peak-trough fluctuation in the range of 0.4 - 1.0 µg/mL for 7.5 mg doses and 0.8 - 2.0 µg/mL for 15 mg doses, respectively (C_{min} and C_{max} at steady state, correspondingly). Mean maximum plasma concentrations of meloxicam at steady state, are achieved within five hours for the tablet.

Distribution

Meloxicam is very strongly bound to plasma proteins, essentially albumin (99%). Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma. Volume of distribution is low, i.e. approx. 11 L. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake or the use of inorganic antacids.

Biotransformation

Meloxicam undergoes extensive hepatic biotransformation. Four different metabolites of meloxicam were identified in urine, which are all pharmacodynamically inactive. The major metabolite, 5'-carboxymeloxicam (60% of dose), is formed by oxidation of an intermediate metabolite 5'-hydroxymethylmeloxicam, which is also excreted to a lesser extent (9% of dose). In vitro studies suggest that CYP 2C9 plays an important role in this metabolic pathway, with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16% and 4% of the administered dose respectively.

Elimination
Meloxicam is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5% of the daily dose is excreted unchanged in faeces, while only traces of the parent compound are excreted in urine. The mean elimination half-life varies between 13 and 25 hours after oral i.m. and i.v. administration. Total plasma clearance amounts to about 7 - 12 mL/min following single doses orally, intravenously or rectally administered.

Linearity/non-linearity
Dose linearity was demonstrated after oral administration in the therapeutic dose range of 7.5 to 15 mg.

Special populations
Patients with hepatic/renal insufficiency
Neither hepatic insufficiency, nor mild renal insufficiency has a substantial effect on meloxicam pharmacokinetics. Subjects with moderate renal impairment had significantly higher total drug clearance. A reduced protein binding is observed in patients with terminal renal failure. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and a daily dose of 7.5 mg must not be exceeded.

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

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

5.3 Preclinical safety data

An extensive toxicological program confirmed that meloxicam has an acceptable safety profile.

Oral LD50 values ranged from about 98 mg/kg in female rats up to >800 mg/kg in minipigs. Intravenous values ranged from about 52 mg/kg in rats to 100 - 200 mg/kg in minipigs. Main signs of toxicity included reduced motor activity, anaemia, and cyanosis. Most deaths occurred as a consequence of gastric ulcers and subsequent perforation leading to peritonitis.

Repeated dose toxicity studies in rats and minipigs showed characteristic changes reported with other NSAIDs e.g. gastrointestinal ulceration and erosions, and in the long term studies, renal papillary necrosis. Gastrointestinal side effects were observed at oral doses of 1mg/kg and higher in rats, and of 3 mg/kg and above in minipigs. After intravenous administration doses of 0.4 mg/kg in rats and 9 mg/kg in minipigs caused gastrointestinal lesions. Renal papillary necrosis occurred only in rats at doses of 0.6 mg/kg or higher after lifetime exposure to meloxicam.

Studies of toxicity on reproduction in rats and rabbits did not reveal teratogenicity up to oral doses of 4 mg/kg in rats and 80 mg/kg in rabbits. Oral reproductive studies in the rat have shown a decrease of ovulations and inhibition of implantations and embryotoxic effects (increase of resorptions) at maternotoxic dose levels at 1 mg/kg and higher.

The affected dose levels exceeded the clinical dose (7.5 - 15 mg) by a factor of 10 to 5-fold on an mg/kg dose basis (75 kg person). Fetotoxic effects at the end of gestation, shared by all prostaglandin synthesis inhibitors, have been described. Nonclinical studies indicate that meloxicam can be found in the milk of nursing rats.

Meloxicam was not mutagenic in the Ames test, the host-mediated assay, and a mammalian gene mutation assay (V79/HPRT), nor is it clastogenic in the chromosomal aberration assay in human lymphocytes and the mouse bone marrow micronucleus test.

Carcinogenicity studies in rats and mice did not show a carcinogenic potential up to dose levels of 0.8 mg/kg in rats and 8 mg/kg in mice. In these studies meloxicam was chondro-neutral, i.e. it did not damage the articular cartilage following long-term exposure.

Meloxicam did not induce immunogenic reactions in tests on mice and guinea pigs. In several tests, meloxicam proved to be less phototoxic than older NSAIDs but similar in this respect to both piroxicam and tenoxicam.

In local tolerance studies; meloxicam was well tolerated by all tested routes of administration; intravenous, intramuscular, rectal, dermal, and ocular administration.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium citrate dihydrate
lactose monohydrate
microcrystalline cellulose
povidone
colloidal silicon dioxide
crospovidone
magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25ºC (blister pack).

6.5 Nature and contents of container

PVC/PVDC/Aluminium blister. Pack sizes of 10 and 30 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Boehringer Ingelheim (N.Z.) Limited
P.O. Box 76-216
Manukau City
Auckland
NEW ZEALAND

Telephone: 0800 802 461

9. DATE OF FIRST APPROVAL

23 July 1998

10. DATE OF REVISION OF THE TEXT

31 August 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.6	Addition of warning on the use of NSAIDs in pregnancy and the risk of oligohydramnios and fetal renal impairment Minor editorial changes
4.8	Minor editorial change