New Zealand Datasheet

1 PRODUCT NAME
Melorex

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Meloxicam tablets 7.5 mg, 15 mg.

Excipient(s) with known effect:

Each 7.5 mg tablet contains 43 mg of lactose monohydrate.
Each 15 mg tablet contains 86 mg of lactose monohydrate.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Melorex 7.5 mg tablets are pale yellow coloured, circular flat beveled uncoated tablets.

Melorex 15 mg tablets are pale yellow coloured, circular flat beveled uncoated tablets with central breakline on one side and plain on the other.

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use may be required, treatment efficacy should be reviewed within the first month of treatment and Melorex tablets withdrawn if there is a lack of therapeutic benefit.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
Melorex tablets may be administered in a dose of 7.5mg daily. As the potential for adverse reactions increases with dose and duration of exposure, all patients taking

Melorex tablets should commence therapy at the lowest recommended dose, and be titrated to the lowest dose compatible with effective control of symptoms for the shortest possible period.

Osteoarthritis:
7.5 mg per 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.

In dialysis patients with severe renal failure:
The dose should not exceed 7.5mg per day.

In patients with mild to moderate renal impairment (creatinine clearance of greater than 25mL/min):
The dose should not exceed 7.5mg per day.

Adolescents:
The maximum recommended dose for adolescents is 0.25mg/kg.
In general usage should be restricted to adolescents and adults, see contraindications.
Tablets should be swallowed with water and other fluid in conjunction with food.

4.3 Contraindications

- Patients with known hypersensitivity to meloxicam or its excipients. There is a potential for cross sensitivity to aspirin and other NSAIDs.
- Rare hereditary conditions that may be incompatible with an excipient of the product (see section 4.4)
- Melorex tablets should not be given to patients who have developed signs of asthma, nasal polyps, angioedema or urticaria following the administration of aspirin or other NSAIDs.
- Active or recent gastro-intestinal ulceration/perforation.
- Active Inflammatory Bowel Disease (Crohn's Disease or Ulcerative Colitis)
- Severe hepatic insufficiency.
- Non-dialysed severe renal insufficiency.
- Overt gastro-intestinal bleeding, recent cerebrovascular bleeding or established systemic bleeding disorders.
- Severe uncontrolled heart failure.
- Patients who have previously had a myocardial infarction or stroke.
- Melorex tablets should not be given in the peri-operative period in patients undergoing cardiac surgery, including coronary artery bypass graft (CABG), or major vascular surgery
- Children and adolescents aged less than 12 years.
- Pregnancy or lactation.

4.4 Special warnings and precautions for use

Gastrointestinal effects
As with other NSAIDs caution should be exercised when treating patients with a history of upper gastrointestinal disease and in patients receiving treatment with anticoagulants. Patients with gastrointestinal symptoms should be monitored. Melorex tablets should be withdrawn if peptic ulceration or gastrointestinal bleeding occurs.

Serious gastrointestinal (GI) toxicity such as bleeding, ulceration and perforation of the stomach, small intestine or large intestine, which may be potentially fatal, can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. The consequences of such events are generally more serious in the elderly.

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. Adverse cardiovascular events can occur with both short term and long-term use.

Prescribers should inform the individual patient of the (possible or potential) increased risks when prescribing Melorex tablets 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.

Melorex tablets are 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 Melorex tablets.

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

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 NSAIDs. 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. Melorex tablets should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Renal function
As with other NSAIDs, meloxicam 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, 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 volume of diuresis and the renal function 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 Melorex tablets in patients with end-stage renal failure on haemodialysis should not be higher than 7.5mg. Patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25mL/min) may take 7.5mg daily.

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, Melorex tablets 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 meloxicam 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, as any other NSAID may mask symptoms of an underlying infectious disease.

The use of Melorex tablets, 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 Melorex tablets should be considered.

Meloxicam tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

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

Associations to be taken into account:

- 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, antiplatelet drugs, systemically administered heparin, thrombolytics and Selective Seratonin Reuptake Inhibitors (SSRIs): increased risk of bleeding via inhibition of platelet function. If such co-prescribing cannot be avoided, close monitoring is required.
- Lithium: NSAIDs have been reported to increase lithium plasma levels.
- Methotrexate: NSAIDs can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of NSAIDs is not recommended. The risk of an interaction between NSAID preparations and methotrexate, should be considered also in patients on low dosage of methotrexate, especially in patients with impaired renal function. In case combination treatment is necessary blood cell count and the renal function should be monitored. Caution should be taken in case both NSAID and methotrexate are given within 3 days, in which case the plasma level of methotrexate may increase and cause increased toxicity. Although the pharmacokinetics of methotrexate (15 mg/week) were not relevantly affected by concomitant meloxicam treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with NSAID drugs.

- Contraception: A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported but needs further confirmation.
- Diuretics: Treatment with NSAIDs is associated with the potential for acute renal insufficiency in patients who are dehydrated. Patients receiving meloxicam and diuretics should be adequately hydrated and be monitored for renal function prior to initiating treatment.
- Antihypertensives (e.g. beta-blockers, ACE-inhibitors, vasodilators, diuretics): A reduced effect of the antihypertensive drug by inhibition of vasodilating prostaglandins has been reported during treatment with NSAIDs.
- NSAIDs and angiotensin-II receptor antagonists as well as ACE inhibitors exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment this may lead to acute renal failure.
- Cholestyramine binds meloxicam in the gastrointestinal tract leading to a faster elimination of meloxicam.
- Nephrotoxicity of cyclosporin may be enhanced by NSAID's via renal prostaglandin mediated effects. During combined treatment renal function is to be measured.
- Interactions with oral antidiabetics cannot be excluded.
- 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.
- Antiplatelet drugs and Selective Serotonin Reuptake Inhibitors (SSRIs): Increased risk of bleeding via inhibition of platelet function.

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

Pregnancy

Meloxicam is contraindicated during pregnancy.

Inhibition of prostaglandin-synthesis may adversely affect pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation and gastrochisis was increased from less than 1

%, up to approximately 1.5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increase pre- and post implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

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

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension)
- renal dysfunction, which may progress to renal failure with oligo-hydroamniosis;

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

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour

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

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

4.7 Effects on ability to drive and use machines

There are no specific studies about the 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.

4.8 Undesirable effects

The meloxicam phase II/III safety database includes 10,122 osteoarthritis patients and 1012 rheumatoid arthritis patients treated with meloxicam 7.5 mg/day and 3,505 osteoarthritis patients and 1351 rheumatoid arthritis patients treated with meloxicam 15 mg/day. Meloxicam 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 meloxicam trials.

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

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

The adverse events that occurred in <2% of patients, treated with daily oral doses of 7.5 or 15 mg meloxicam 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 meloxicam, 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		

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 continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose
In case of overdose the standard measures of gastric evacuation and general supportive measures should be used, as there is no known antidote. It has been shown in a clinical trial that cholestyramine accelerates the elimination of meloxicam.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory and Anti-rheumatic products, Non-steroids, Oxicams. ATC code: M01AC06

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.

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 (7.5mg and 15mg) 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.

In clinical trials, gastro-intestinal adverse events overall were reported less frequently with meloxicam 7.5mg and 15mg 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 gastro-intestinal perforation, obstruction, or bleeds between meloxicam and other NSAIDs. A pooled analysis has been conducted involving patients treated with meloxicam in 35 clinical trials in the indications osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. Exposure to meloxicam in these trials ranged from 3 weeks to one year (most patients were enrolled in one-month studies). Almost all patients participated in trials that permitted enrolment of patients with a prior history of gastro-intestinal perforation, ulcer or bleed. The incidence of clinically significant upper gastro-intestinal perforation, obstruction, or bleed (POB) was assessed retrospectively following independent blinded review of cases. Results are shown in the following table.

Cumulative risk of POBs for meloxicam 7.5mg and 15mg from 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 7.5mg	1 - <30	9636	2	0.02	0.00 - 0.05
	30 - <91	551	1	0.05	0.00 - 0.13
Meloxicam 15mg	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 100mg	1 - <30	5110	7	0.14	0.04 - 0.24
	30 - <91	493	2	0.55	0.00 - 1.13
Piroxicam 20mg	1 - <30	5071	10	0.20	0.07 - 0.32
	30 - <91	532	6	1.11	0.35 - 1.86

5.2 Pharmacokinetic properties

Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 89% following oral administration.

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

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

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

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, on average 11 L. Interindividual variation is 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. 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 extent 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 about 20 hours. Total plasma clearance amounts on average to 8mL/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:
Neither hepatic insufficiency, nor mild to moderate renal insufficiency have a substantial effect on meloxicam pharmacokinetics. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and a daily dose of 7.5 mg must not be exceeded.

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

Children:
In a study of 36 children, kinetic measurements were made in 18 children at doses of 0.25mg/kg BW. 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 (13h) were similar for both groups and tended to be shorter than in adults (15-20h).

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

Colloidal anhydrous silica, Pregelatinised starch 1500, Lactose monohydrate, Magnesium stearate, Maize starch, Microcrystalline cellulose, Sodium citrate dihydrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Shelf life is 36 months (3 years) from manufacture.

6.4 Special precautions for storage

Store below 25°C in a safe place out of the reach of children

6.5 Nature and contents of container

Al/PVC/PVdC blister packs:
7.5mg = 30 tablets

15mg = 30 tablets

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

REX Medical Ltd
PO Box 18-119
Glen Innes 1743
AUCKLAND.

Ph (09) 574 6060
Fax (09) 574 6070

Distributor
Douglas Pharmaceuticals Ltd
P.O. Box 45027
Auckland 0651
Telephone (09) 835 0660

9 DATE OF FIRST APPROVAL

15 November 2007

10 DATE OF REVISION OF THE TEXT

7 August 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	“Adverse cardiovascular events can occur with both short term and long term use” added.