MELOX® 7,5mg and 15mg tablets
Meloxicam

PRODUCT INFORMATION LEAFLET

Composition
Melox 7.5 mg tablets each containing 7.5 mg meloxicam
Melox 15 mg tablets each containing 15 mg meloxicam

Meloxicam: 4 - hydroxy - 2 - methyl - N - (5 - methyl - 2 - thiazolyl) - 2H - 1, 2 - benzothiazine - 3 - carboxamide 1, 1 dioxide

Pharmaceutical Form
Tablets for oral administration.

Melox 7.5 mg: light yellow, round, flat, scored on one side, 7 mm diameter tablets.
Melox 15 mg: light yellow, round, flat, scored on one side, 10.5 mm diameter tablets.

PHARMACODE

Therapeutic Indications
Meloxicam is indicated for the short term symptomatic therapy of acute exacerbations of osteoarthritis, long term symptomatic therapy of rheumatoid arthritis (chronic polyarthritis), and the symptomatic therapy of ankylosing spondylitis.

Dosage and Method of Administration
Melox tablets are for oral administration only. The total daily dose should be taken as a single dose, with water or another liquid, during a meal.
The maximum daily dose is 15 mg. Do not exceed this dose.

Adults:
Acute exacerbations of osteoarthritis: The recommended dose is 7.5 mg (one **Melox** 7.5 mg tablet, half a **Melox** 15 mg tablet). If necessary, and depending upon the severity of symptoms, dosage may be increased to 15 mg daily (two **Melox** 7.5 mg tablets, one **Melox** 15 mg tablet).
Rheumatoid arthritis: The recommended dose is 15 mg (two **Melox** 7.5 mg tablets, one **Melox** 15 mg tablet) a day. Patients at increased risk for adverse reactions should initiate therapy at 7.5 mg (one **Melox** 7.5 mg tablet, half a **Melox** 15 mg tablet) a day.
Ankylosing spondylitis: The recommended dose is 15 mg (two **Melox** 7.5 mg tablets, one **Melox** 15 mg tablet) a day. Patients at increased risk for adverse reactions should initiate therapy at 7.5 mg (one **Melox** 7.5 mg tablet, half a **Melox** 15 mg tablet) a day.

Elderly:
In elderly patients being treated for rheumatoid arthritis the recommended dose for long term treatment is 7.5 mg (one **Melox** 7.5 mg tablet, half a **Melox** 15 mg tablet) a day.

Children:
The safety and efficacy of meloxicam have not been established in children under the age of fifteen years.

Hepatic impairment: Meloxicam is contraindicated in severe hepatic impairment (see Contraindications). Caution should be exercised in patients with lesser degrees of hepatic impairment, and they should be closely monitored. Diuresis and renal function should be carefully monitored during meloxicam therapy (see also Special Warnings and Precautions for Use).

Renal impairment: Meloxicam is contraindicated in none dialysed severe renal failure. Patients with severe renal failure undergoing dialysis should not exceed a dose of 7.5 mg (one **Melox** 7.5 mg tablet, half a **Melox** 15 mg tablet) a day. Diuresis and renal function should be carefully monitored during meloxicam therapy (see also Special Warnings and Precautions for Use).

Contra-indications
Meloxicam is contraindicated in the following situations:
- Hypersensitivity to meloxicam, or to any other components of the tablet (see 6.1). The possibility of cross sensitivity of meloxicam with other non steroidal anti inflammatory drugs (NSAIDS) or aspirin exists. Therefore, in patients who have developed asthma, nasal polyps, angioneurotic oedema, urticaria, or any other hypersensitivity reaction following administration of any NSAIDS or aspirin, meloxicam is also contraindicated.
- Active peptic ulcer, or a history of recurrent peptic ulcer disease.
- Severe hepatic impairment.
- Severe renal impairment without dialysis.
- Cerebrovascular bleeding, gastrointestinal bleeding, or any other bleeding disorder.

Special Warnings and Precautions for Use
Before initiating therapy with meloxicam in patients with a history of oesophagitis, gastritis, or peptic ulcer, freedom from these conditions must be established. Routine attention should be given to the possibility of recurrence of these conditions in meloxicam treated patients with a history of these conditions.
Monitoring for digestive disturbances, particularly gastrointestinal bleeding, should be done in patients with gastrointestinal symptoms, or a history of gastrointestinal disease.
In common with other NSAIDS, gastrointestinal bleeding, or ulceration and / or perforation, has been reported with meloxicam at any stage of treatment, in rare instances resulting in fatalities. These events can occur with or without any warning symptoms, and in patients with or without a previous history of serious gastrointestinal events. The elderly generally experience more serious consequences of gastrointestinal bleeding or gastrointestinal ulceration and / or perforation.
In the rare instances where gastrointestinal bleeding or ulceration occurs in patients on meloxicam therapy, the drug should promptly be withdrawn.
In the event of severe cutaneous or mucosal adverse effects occurring, meloxicam withdrawal must be considered. The possible occurrence of severe skin reactions and hypersensitivity reaction that are severe and life threatening is known to occur with NSAIDS, including oxicams.
NSAIDS may cause glomerulonephritis, interstitial nephritis, nephritic syndrome, or renal medullary necrosis in rare cases.
In common with the majority of NSAIDS, there are occasional reports of serum transaminase level increases, serum bilirubin increases, and increases in other liver function parameters, increases in serum creatinine and blood urea nitrogen, and other laboratory test disturbances. In most cases these have been transitory and minor abnormalities. However, if such an abnormality be significant or persist, meloxicam should be withdrawn and appropriate clinical investigation performed.
NSAIDS may cause the retention of sodium, potassium, and water, and may interfere with the natriuretic effects of diuretics. This may result in consequential exacerbation of the condition of patients with cardiac insufficiency or hypertension.
In patients with decreased renal blood flow and blood volume, synthesis of renal prostaglandins responsible for maintenance of renal perfusion may be inhibited by NSAIDS. Administration of NSAIDS in such patients may cause the decompensation of latent renal failure, although renal function reverts to original status following therapy withdrawal. This risk affects all elderly patients, patients with congestive heart failure, cirrhosis, nephritic syndrome, or renal failure. Patients who have undergone major surgery resulting in hypovolaemia, or on diuretic therapy are similarly affected. Diuresis and renal function should be carefully monitored during meloxicam therapy (see also Posology and Method of Administration).
Elderly, fragile, or weakened patients are often less tolerant of adverse effects and therefore require careful monitoring during therapy. In common with other NSAIDS, particular caution should be exercised with the elderly, who frequently have impairment of cardiac, hepatic, and renal functions.
Daily dosage recommendations should not be exceeded if there is inadequate therapeutic efficacy. Additional NSAIDS should not be added to the dosage regimen as toxicity may be increased, and therapeutic efficacy has not been demonstrated.
The safety and efficacy of meloxicam has not been demonstrated in children aged less than fifteen years.

Interactions with other Medicaments and other forms of Interaction
Simultaneous administration of meloxicam with the drugs itemised in this section mandates careful supervision and monitoring of the clinical and laboratory status of the patient.

It is inadvisable to use the following combinations:
Other NSAIDS, high dosages of salicylates: The risk of gastrointestinal ulceration and / or gastrointestinal bleeding is increased when administering several NSAIDS together due to synergistic effects.
Lithium: Blood lithium levels are increased by NSAIDS due to decreased renal excretion of lithium. Consequently lithium levels may reach toxic levels, therefore blood lithium levels should be monitored during initiation, dose titration, and withdrawal of meloxicam.
Oral anticoagulants, ticlopidine, parenteral heparin: Due to inhibition of platelet function and gastroduodenal mucosa damage there is an increased risk of bleeding. In the event that use of such combinations is unavoidable, the effect of the anticoagulants must be closely monitored.
High dosage methotrexate, 15 mg / week or more: NSAIDS decrease the renal clearance of methotrexate resulting in increased haematological toxicity of methotrexate. Although causality has not been confirmed, there is a report of agranulocytosis in a patient treated with methotrexate and meloxicam. Prescription of such combination requires caution, and close monitoring of the blood cell count is recommended in such an instance (see also following section).

Simultaneous administration of meloxicam with the drugs itemised in this section requires precautions:
Cyclosporin: NSAIDS may enhance the nephrotoxicity of cyclosporin due to renal prostaglandin mediated effects. Renal function must be measured during combination therapy.
Diuretics: NSAIDS therapy results in decreased renal prostaglandin synthesis with consequent decreased glomerular filtration resulting in an elevated risk of acute renal failure in dehydrated patients. Use of meloxicam with a diuretic means it is essential to ensure the patient is adequately hydrated and to closely monitor renal function at the initiation of such therapy.

Low dosage methotrexate, less than 15 mg / week: NSAIDS decrease the renal clearance of methotrexate resulting in increased haematological toxicity of methotrexate. Blood count should be monitored weekly during the first few weeks of such combination therapy. In elderly patients, and those with even slight renal impairment, require increased monitoring and close supervision.
Pentoxifylline: There is an increased risk of bleeding, and general clinical monitoring and verification of bleeding time should be of increased frequency.
Zidovudine: Due to effects on the reticulocytes there is an increased risk of greater red cell line toxicity effects, with severe anaemia resulting one week after NSAID therapy is initiated. The CBC and reticulocyte count should be checked one or two weeks post NSAID therapy initiation.
Simulataneous administration of meloxicam with the drugs itemised in this section requires caution and the taking of appropriate precautions:
Antihypertensives (beta - blockers, angiotensin converting enzyme inhibitors, diuretics): NSAIDS therapy inhibits prostaglandin synthesis and may result in a decrease of the antihypertensive effect.
Intra Uterine Devices (IUD): There is a possible risk of impaired efficacy, and additional contraceptive precautions may be required.
Thrombolytics: There is an elevated risk of bleeding.

Other drug interactions:
Antacids, H2- receptor agonists (cimetidine, ranitidine)furosemide, beta acetyl digoxin: Concomitant administration with meloxicam has not resulted in any significant pharmacokinetic interactions.
Cholestyramine: The elimination of meloxicam is accelerated due to binding in the digestive tract.
Oral anti - diabetics: The possibility of interactions cannot be excluded, and such patients should be closely monitored and supervised.

Pregnancy and Lactation
Pregnancy: Lethal effects on the foetus have been reported in animal studies using doses higher than those administered clinically. It is recommended that the use of meloxicam be avoided during pregnancy. Use of NSAIDs at about 20 weeks gestation or later in pregnancy may cause foetal renal dysfunction leading to oligohydramnios and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. In the final trimester of pregnancy the use of any prostaglandin synthesis inhibitor may result in foetal cardiopulmonary toxicity, pulmonary hypertension and premature closure of the ductus arteriosus, and renal toxicity. Uterine contraction may also be inhibited, and in animals this has been associated with dystocia incidence elevation and delayed parturition. Meloxicam, in common with all NSAIDS, is absolutely contraindicated during the final trimester of pregnancy.

Lactation: NSAIDS are excreted in maternal breast milk, therefore administration should be avoided in women who are breast feeding as a precaution.

Effects on Ability to Drive and Use Machines
Patients may experience drowsiness, vertigo, visual disturbances, and other central nervous system disturbances during meloxicam therapy (see Undesirable Effects). Patients should be cautioned as to the possibility of such effects, and advised not to drive or operate machinery if such disturbances occur.

Undesirable Effects
Cardiovascular system: oedema, lower limb oedema, elevated blood pressure (see also Special Warnings and Precautions), palpitations, and flushes.
Central Nervous System: Drowsiness, headache, lightheadedness, tinnitus, and vertigo may occur. Rare instances of confusion, insomnia, and nightmares.
Dermatological: Reports of skin rash, pruritus, urticaria, and photosensitivity reactions. Very rarely, erythema multiforme, Stevens Johnson syndrome, and toxic epidermal necrolysis, or other bullous reactions.
Gastrointestinal system: Abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, nausea, oesophagitis, stomatitis, and vomiting may occur. Rare instances of peptic ulceration, perforation, or gastrointestinal bleeding, sometimes severe, particularly in the elderly (see also Special Warnings and Precautions for Use). Reports of rare cases of gastritis.
Genitourinary system: Laboratory tests of renal function may be disturbed, such as elevated creatinine or urea.
Haematological system: Reports of blood count disturbances in patients taking meloxicam, some of which have been attributed to therapy; anaemia, leucocytopenia, and thrombocytopenia. There are isolated reports of agranulocytosis in patients taking meloxicam and other drugs with myelotoxic potential.
Hepatic system: Liver function tests may show transitory disturbance, such as elevation of bilirubin or transaminase levels.
Immunological: Rare reports of angioedema, and anaphylactic or anaphylactoid reactions.
Pulmonary system: patients allergic to aspirin or other NSAIDS have experienced asthma attacks.
Sensory systems: Rare reports of visual disturbances, including blurred vision.

Overdose
Symptoms: Symptoms following acute NSAIDS overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse, and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDS, and may occur following an overdose.

Treatment: There is no known antidote to meloxicam, and therefore treatment of overdose is symptomatic and supportive. Cholestyramine administration, 4 g three times a day, may enhance the elimination of meloxicam. Antacids and H2 - receptor antagonists may be used for the treatment of severe gastrointestinal lesions. In cases of acute overdose, gastric lavage followed by activated charcoal is recommended. Gastric lavage performed more than one hour after overdose has little benefit in the treatment of overdose. 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. Forced diuresis, alkalinization of urine, haemodialysis, or haemoperfusion may not be useful due to high protein binding of meloxicam.

Pharmacology

Pharmacodynamics: Pharmacotherapeutic group: Non - steroidal anti - inflammatory drug (NSAID)
Meloxicam is a NSAID of the oxicam group, possessing analgesic, anti - inflammatory, and anti - pyretic activity. In common with other NSAIDS, although the exact mechanism of action remains unknown, it is known that the inhibition of prostaglandin synthesis, known inflammation mediators, plays a role in the anti - inflammatory activity.

Pharmacokinetics: Following oral administration, meloxicam is well absorbed from the gastrointestinal tract, and it has an absolute bioavailability of about 90 %. Peak serum levels are reached after 7 - 8 hours following a single oral dose, with steady state concentration being achieved after 3 - 5 days administration. Plasma concentrations are proportional to dose over the 7.5 mg - 15 mg dosage range.
Plasma protein binding, principally to albumin, is high, 99 %.
Meloxicam undergoes extensive metabolism, principally via oxidation of the methyl group of the thiazolyl ring.
Excretion of administered dose is 50 % in the urine and 50 % in the faeces, principally as metabolites, with only about 3 % of the dose being excreted as unchanged meloxicam.
Mean elimination half life is approximately 20 hours. Mean plasma clearance is about 8 ml / minute, and clearance is reduced in the elderly. Meloxicam has a low volume of distribution, about 11 L, although there is considerable interindividual variation.
Patients with terminal renal failure have an increased volume of distribution, and the stipulated maximum daily dosage of 7.5 mg must not be exceeded.

Preclinical Safety Data: Meloxicam exhibits a similar toxicological profile to other NSAIDS. Preclinical studies in animals using chronic administration of high doses resulted in gastrointestinal erosion and ulceration, and renal papillary necrosis. Depending upon the animal species, non toxic doses were 3 - 10 times greater than those used clinically.
Reproductive toxicological studies in animals demonstrated foetotoxic effects at doses greatly in excess of those used clinically. Foetotoxic effects at the end of the gestation period common to all prostaglandin synthesis inhibitors were found, cardiopulmonary and renal toxic effects.
In vitro and in vivo studies have not shown any eveidence of mutagenic or carcinogenic potential.

List of Excipients
Melox 7.5 mg tablets also contain sodium citrate, lactose, microcrystalline cellulose, colloidal silicon dioxide, povidone, crospovidone, and magnesium stearate.
Melox 15 mg tablets also contain sodium citrate, lactose, microcrystalline cellulose, colloidal silicon dioxide, povidone, crospovidone, and magnesium stearate.

Storage conditions
Store below 25°C, in the original blister.
Shelf Life: Twenty four (24) months.

Packing and pack sizes
Tablets are packaged in PVC/PVDC-Alu blisters.
Melox 7.5 mg tablets: Boxes of 10, 100 and 1000 tablets.
Melox 15 mg tablets: Boxes of 10, 100 and 1000 tablets.
Not all presentations are available locally.

Product Owner:

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MEL/.....
SINGAPORE

160 x 270 mm