Important Information. Please read carefully.

ARROX™

TABLET

COMPOSITION
Each tablet contains Meloxicam 7.5mg.

PHARMACODYNAMICS
Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties. The anti-inflammatory activity of meloxicam has been proven in classical models of inflammation. As with other NSAIDs, its precise mechanism of action remains unknown. However, there is at least one common mode of action shared by all NSAIDs (including meloxicam): inhibition of the biosynthesis of prostaglandins, known inflammation mediators.

PHARMACOKINETICS
Absorption: Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 89% following oral administration (capsule). Tablets, oral suspension and capsules were shown to be bioequivalent. Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 5-6 hours with capsules and 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 15 mg doses, respectively (C_{min} and C_{max} at steady state, respectively). Maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours. Continuous treatment for periods of more than one year results in similar drug concentrations to those seen once steady state is first achieved. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake.

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.

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 is about 20 hours. Total plasma clearance amounts on average 8 mL/min.

Special populations: *Hepatic/renal Insufficiency*: Neither hepatic, mild nor 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 (see section Recommended Dose). *Elderly:* Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

INDICATIONS
Symptomatic treatment of:
- painful osteoarthritis (arthrosis, degenerative joint disease)
- rheumatoid arthritis
- ankylosing spondylitis

RECOMMENDED DOSE:
Exacerbations of osteoarthrosis : 7.5 mg/day (one 7.5 mg tablet). If necessary, in the absence of improvement, the dose may be increased to 15 mg/day (two 7.5 mg tablets).
Rheumatoid arthritis, ankylosing spondylitis : 15 mg/day (two 7.5 mg tablets). (See also 'special populations'). According to the therapeutic response, the dose may be reduced to 7.5 mg/day (one 7.5 mg tablet). DO NOT EXCEED THE DOSE OF 15 MG/DAY. The total daily amount should be taken as a single dose, with water or another liquid, during a meal.

Special populations

Elderly patients and patients with increased risks for adverse reaction: The recommended dose for long term treatment of rheumatoid arthritis and ankylosing spondylitis in elderly patients is 7.5 mg per day. Patients with increased risks for adverse reactions should start treatment with 7.5 mg per day.

Renal impairment: In dialysis patients with severe renal failure, the dose should not exceed 7.5 mg per day. No dose reduction is required in patients with mild to moderate renal impairment (i.e. patients with a creatinine clearance of greater than 25 ml/min).

Hepatic impairment: No dose reduction is required in patients with mild to moderate hepatic impairment.

Children: Arrox should not be used in children aged under 15. This medicinal product exists in other dosages, which may be more appropriate.

Arrox should be used at the lowest effective dose for shortest possible time.

CONTRAINDICATIONS
This medicinal product is contra-indicated in the following situations:
- pregnancy and lactation (See section 'Pregnancy and lactation')
- hypersensitivity to meloxicam or to one of the excipients or hypersensitivity to substances with a similar action, e.g. NSAIDs, aspirin. Arrox should not be given to patients who have developed signs of asthma, nasal polyps, angioneurotic oedema or urticaria following the administration of aspirin or other NSAIDs.
- active gastro-intestinal ulcer or history of recurrent gastro-intestinal ulcer;
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy; active, or history of recurrent peptic ulcer/haemorrhage.
- severely impaired liver function;
- non-dialysed severe renal failure;
- gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders;
- severe uncontrolled heart failure.
- for the treatment of peri-operative pain in the setting of coronary artery bypass graft surgery.

WARNINGS AND PRECAUTIONS:
Cardiovascular Risk
NSAIDs may cause an increased 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.

Gastrointestinal Risk
NSAIDs cause an increased risk of gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms. Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events. If gastrointestinal bleeding or ulceration occurs in patients receiving meloxicam, the drug should be withdrawn.

Renal Effects
Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greater risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease
No information is available from controlled clinical studies regarding the use of Arrox in patients with advanced renal disease. Therefore, treatment with Arrox is not recommended in these patients with advanced renal disease. If therapy must be initiated, close monitoring of the patient's renal function is advisable.

In rare instances NSAIDs may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome. As with most NSAIDs, occasional increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen as well as other laboratory disturbances, have been reported. The majority of these instances involved transitory and slight abnormalities. Should any such abnormality prove significant or persistent, the administration of meloxicam should be stopped and appropriate investigations undertaken. Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics and consequently possible exacerbations of the condition of patients with cardiac failure or hypertension may occur with NSAIDs. NSAIDs inhibit the synthesis of renal prostaglandins involved in the maintenance of renal perfusion, in patients with decreased renal blood flow and blood volume. Administration of NSAIDs in such situations may result in the decompensation of latent renal failure. However, renal function returns to its initial status when treatment is withdrawn. This risk concerns all elderly individuals, patients with congestive cardiac failure, cirrhosis, nephrotic syndrome or renal failure as well as patients on diuretics or having undergone major surgery leading to hypovolemia. Careful monitoring of diuresis and renal function during treatment is necessary in such patients.

Adverse reactions are often less well tolerated in elderly, fragile or weakened individuals, who therefore require careful monitoring.

The possible occurrence of severe skin reactions and serious life threatening hypersensitivity reactions (i.e. anaphylactic reactions) is known to occur with NSAIDs including oxicams. In those cases, meloxicam should be withdrawn immediately and careful observation is necessary.

As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired.

The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven. In the absence of improvement after several days, the clinical benefit of the treatment should be reassessed.

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

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. In women who have difficulties conceiving, or who are undergoing investigation of infertility, withdrawal of meloxicam should be considered.

In rare cases, meloxicam has been associated with serious liver injury.

INTERACTIONS WITH OTHER MEDICAMENTS
Pharmacodynamic Interactions: *Other NSAIDs, including salicylates (acetylsalicylic acid ≥ 3 g/d)*: Administration of several NSAIDs together may increase the risk of gastrointestinal ulcers and bleeding, via a synergistic effect. The concomitant use of meloxicam with other NSAIDs is not recommended.

Diuretics: Treatment with NSAIDs is associated with potential for acute renal failure, notably in dehydrated patients. Patients receiving meloxicam and diuretics should be adequately hydrated and be monitored for renal function prior to initiating treatment.

Oral anticoagulants: Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. The concomitant use of NSAIDs and oral anticoagulants is not recommended. Careful monitoring of the INR is required if it proves impossible to avoid such combination.

Thrombolytics and antiplatelet drugs: Increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa.

ACE inhibitors and angiotensin II receptor antagonists: NSAIDs (including acetylsalicylic acid at doses ≥ 3g/d) and angiotensin-II receptor antagonists exert a synergistic effect on the decrease of glomerular filtration, which may be exacerbated when renal function is altered. When given to the elderly and/or dehydrated patients, this combination can lead to acute renal failure by acting directly on glomerular filtration. Monitoring of renal function at the beginning of the treatment is recommended as well as regular hydration of the patient. Additionally, concomitant treatment can reduce antihypertensive effect of ACE inhibitors and angiotensin II receptor antagonists, leading to partial loss of efficacy (due to inhibition of prostaglandins with vasodilatory effect).

Other antihypertensive drugs (e.g. Beta-blockers): As for the latter, a decrease of the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.

Cyclosporin: Nephrotoxicity of cyclosporin may be enhanced by NSAIDs via renal prostaglandin mediated effects. During combined treatment renal function is to be measured. A careful monitoring of the renal function is recommended, especially in the elderly.

Intrauterine devices: NSAIDs have been reported to decrease the efficacy of intrauterine devices. A decrease of the efficacy of intrauterine devices by NSAIDs has been previously reported but needs further confirmation.

Pharmacokinetic Interactions (Effect of meloxicam on the pharmacokinetics of other drugs):

Lithium: NSAIDs have been reported to increase blood lithium 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 (15mg/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 (see above).

Pharmacokinetic Interactions (Effect of other drugs on the pharmacokinetics of meloxicam)

Cholestyramine: Cholestyramine accelerates the elimination of meloxicam by interrupting the enterohepatic circulation so that clearance for meloxicam increases by 50% and the half-life decreases to 13±3 hrs. This interaction is of clinical significance. No clinically relevant pharmacokinetic drug-drug interactions were detected with respect to the concomitant administration of antacids, cimetidine and digoxin.

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PREGNANCY AND LACTATION:
Pregnancy: It is advisable to avoid the administration of meloxicam during the first two trimesters of pregnancy.

During the final three months, all prostaglandin synthesis inhibitors may expose the fetus to cardiopulmonary (pulmonary hypertension with premature closure of the ductus arteriosus) and renal toxicity or inhibit the contraction of the uterus. This effect on the uterus has been associated with an increase in the incidence of dystocia and delayed parturition in animals. Thus all NSAIDs are absolutely contra-indicated during the final three months.

Lactation: NSAIDs pass into mothers milk. Administration should therefore be avoided, as a precautionary measure, in women who are breast feeding.

SIDE EFFECTS
The following adverse events, which may be causally related to the administration of meloxicam, have been reported. The frequencies given below are based on corresponding occurrences reported in clinical trials, regardless of any causal relationship. Adverse reactions have been ranked under headings of frequency using the following convention: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥1/10000, < 1/1000); very rare (< 1/10000)

Blood and the lymphatic system disorders - Common: Anaemia.
Uncommon: Disturbances of blood count: leucocytopenia; thrombocytopenia; agranulocytosis.
Immune system disorders - Rare: Anaphylactic / anaphylactoid reactions.
Psychiatric disorders - Rare: Mood disorders, insomnia and nightmares.
Nervous system disorders - Common: Lightheadedness, headache.
Uncommon: Vertigo, tinnitus, drowsiness. Rare: Confusion.
Eye disorders - Rare: Visual disturbances including blurred vision.
Cardiac disorders - Uncommon: Palpitations.
Vascular disorders - Uncommon: Increase in blood pressure, flushes.
Respiratory, thoracic and mediastinal disorders - Rare: Onset of asthma attacks in certain individuals allergic to aspirin or other NSAIDs.
Gastrointestinal disorders - Common: Dyspepsia, nausea and vomiting symptoms, abdominal pain, constipation, flatulence, diarrhea.
Uncommon: Gastrointestinal bleeding, peptic ulcers, oesophagitis, stomatitis.
Rare: Gastrointestinal perforation, gastritis, colitis. The peptic ulcers, perforation or gastrointestinal bleeding, that may occur can be sometimes severe, especially in elderly.
Hepato-biliary disorders - Uncommon: Transitory disturbance of liver function test (e.g. raised transaminases or bilirubin). Rare: Hepatitis.
Skin and subcutaneous tissue disorders - Common: Pruritus, rash.
Uncommon: Urticaria. Rare: Stevens-Johnson Syndrome and toxic epidermal necrolysis, angioedema, bullous reactions such as erythema multiforme, photosensitivity reactions.
Renal and urinary disorders - Uncommon: Disturbances of laboratory tests investigating renal function (e.g. raised creatinine or urea). Rare: Renal failure
General disorders and administration site conditions - Common: Oedema including oedema of the lower limbs. Isolated cases of agranulocytosis have been reported in patients treated with meloxicam and other potentially myelotoxic drugs.

SYMPTOMS AND TREATMENT OF OVERDOSAGE:
Symptoms following acute NSAID 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.

Patients should be managed with symptomatic and supportive care following an NSAID overdose. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.

STORAGE CONDITION: Store below 30ºC.

SHELF LIFE: The expiry date is indicated on the packaging.

PRODUCT DESCRIPTION
Round, yellow color and normal convex tablet in 30's blister packs of 10's.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

For further information, please consult your pharmacist or physician.

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Manufacturer and Product Registration Holder (In Malaysia)
Xepa-Soul Pattinson (Malaysia) Sdn Bhd
1-5 Cheng Industrial Estate, 75250 Melaka, Malaysia.

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