PACKAGE INSERT TEMPLATE FOR MELOXICAM TABLET & MELOXICAM CAPSULE

Brand or Product Name
[Product name] Tablet 7.5mg
[Product name] Tablet 15mg
[Product name] Capsule 7.5mg
[Product name] Capsule 15mg

Name and Strength of Active Substance(s)
Meloxicam 7.5mg
Meloxicam 15mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc) eg :
Tablet - White, circular flat beveled edge tablets marked '15' on one side
Capsule - Yellow opaque cap and body, oblong hard gelatin capsules filled with white powder]

Pharmacodynamics
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 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.

This improved safety profile is thought to be related to a selective inhibition of COX-2 relative to COX-1. The selective inhibition of COX-2 relative to COX-1 by meloxicam has been demonstrated in vitro on various cell systems: guinea pig macrophages, bovine aortic endothelial cells (for testing for COX-1 activity), mouse macrophages (for testing for COX-2 activity), and human recombinant enzymes expressed in cos-cells. Evidence is now accumulating that COX-2 inhibition provides the therapeutic effects of NSAIDs whereas inhibition of constitutive COX-1 is responsible for gastric and renal side effects. Clinical studies demonstrated a lower incidence of gastrointestinal adverse events including perforations, ulcers or bleeds with the recommended doses of meloxicam than standard doses of other NSAIDs.

Pharmacokinetics
Absorption
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 2 hours for the suspension and within 5-6 hours with solid oral dosage forms (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 - 1.0µg/mL for 7.5mg doses and 0.8 - 2.0µg/mL for 15mg doses, respectively (C_{min} and C_{max} at steady state, respectively). Mean maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours for the tablet and the oral suspension, respectively.

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. 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. The volume of distribution following administration of multiple oral doses of meloxicam (7.5 to 15mg) is about 16L with coefficients of variation ranging from 11 to 32%.

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.

Linearity/non-linearity
Meloxicam demonstrates linear pharmacokinetics in the therapeutic dose range of 7.5 mg to 15 mg following per oral 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.

Indication
Meloxicam is a non-steroidal anti-inflammatory drug indicated for:
- symptomatic treatment of painful osteoarthritis (arthrosis, degenerative joint disease)
- symptomatic treatment of rheumatoid arthritis
- symptomatic treatment of ankylosing spondylitis

Recommended Dosage
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.

Ankylosing spondylitis
15 mg/day. According to the therapeutic response, the dose may be reduced to 7.5 mg/day

In patients with increased risks of adverse reactions: start treatment at the dose of 7.5 mg/day.
In dialysis patients with severe renal failure: the dose should not exceed 7.5 mg/day.

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 general, usage should be restricted to adults. The maximum recommended daily dose of meloxicam is 15 mg. Tablets and capsules should be swallowed with water or other fluid in conjunction with food.

Mode of Administration
Oral

Contraindications
Known hypersensitivity to meloxicam or any excipient of the product. There is a potential for cross sensitivity to acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (NSAIDs).
Meloxicam should not be given to patients who have developed signs of asthma, nasal polyps, angio-oedema or urticaria following the administration of acetylsalicylic acid 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 systemic bleeding disorders
- Severe uncontrolled heart failure
- Children under 12 years, except when approved for use in Juvenile Rheumatoid Arthritis
- Pregnancy or breastfeeding

Meloxicam is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Warnings and Precautions
[Specific package insert requirement for NSAID]

WARNING

RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAID

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAID therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in theraphy, 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 GI events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking, and 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.

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

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.

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 a 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 meloxicam in patients with end-stage renal failure on haemodialysis should not be higher than 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).

As with 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, meloxicam should be stopped and follow up tests carried out. No dose reduction is required in patients with clinically stable liver cirrhosis.

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

Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with NSAIDs. Cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. For patients at risk, clinical monitoring is recommended.

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.

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

Effects on the ability to drive and use machines
There are no specific studies about effects on the ability to drive vehicles and to use machinery. Patients who experience visual disturbances, drowsiness or other central nervous system disturbances should refrain from these activities.

Interactions with Other Medicaments

Other Prostaglandin Synthetase Inhibitors (PSI) including glucocorticoids and salicylates (acetylsalicylic acid)

Co-administration of PSIs may increase the risk of gastro-intestinal ulcers and bleeding, via a synergistic effect, and is not recommended. The concomitant use of meloxicam with other NSAIDs is not recommended.

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

Increased risk of bleeding, via inhibition of platelet function. If such co-prescribing cannot be avoided, close monitoring of the effects of anticoagulants is required.

Lithium

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

Methotrexate

NSIDs 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) was 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 gastro-intestinal tract leading to a faster elimination of meloxicam.

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

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.

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

Interactions with oral antidiabetics cannot be excluded.

Statement on Usage During Pregnancy and Lactation

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 and gastrochisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation 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

While no specific experience exists for meloxicam, NSAIDs are known to pass into mother's milk. Administration should therefore be avoided in women who are breastfeeding.

Adverse Effects / Undesirable Effects

Blood and lymphatic system disorders
Blood count abnormal (including differential white cell count), leukopenia, thrombocytopenia, anaemia. Concomitant administration of a potentially myelotoxic drug, in particular methotrexate, appears to be a predisposing factor to the onset of a cytopenia.

Immune system disorders
Anaphylactic reaction, anaphylactoid reaction, and other immediate hypersensitivity

Psychiatric disorders
Confusional state, disorientation, mood altered

Nervous system disorders
Dizziness, somnolence, headache

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

Gastrointestinal disorders
Gastrointestinal perforation, occult or macroscopic gastrointestinal haemorrhage, gastroduodenal ulcer, colitis, gastritis, oesophagitis, stomatitis, abdominal pain, dyspepsia, diarrhoea, nausea, vomiting, constipation, flatulence, eructation. Gastrointestinal haemorrhage, ulceration or perforation may potentially be fatal.

Hepatobiliary disorders
Hepatitis, liver function test abnormal (e.g. raised transaminases or bilirubin)

Skin and subcutaneous tissue disorders
toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, dermatitis bullous, erythema multiforme, rash, urticaria, photosensitivity reaction, pruritus

Renal and urinary disorders
Renal failure acute, renal function test abnormal (increased serum creatinine and/or serum urea) The use of NSAIDs may be related to micturition disorders, including acute urinary retention.

General disorders and administration site conditions
Oedema

Overdose and Treatment
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.

Storage Conditions
Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]