

Scheduling Status: S3

Proprietary Name (and dosage form):

COXFLAM 7.5 (Tablets) COXFLAM 15 (Tablets)

Composition:

Each **COXFLAM 7.5** tablet contains 7.5 mg meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1, 2-benzothiazine-3-carboxamide 1, 1-dioxide).

Each **COXFLAM 15** tablet contains 15 mg meloxicam (4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1, 2-benzothiazine-3-carboxamide 1,1,-dioxide).

Pharmacological Classification:

A 3.1 Anti-rheumatics (anti-inflammatory agents).

Pharmacological Action:

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties. It is one of the oxamic derivatives, a member of the enolic acids.

The action of meloxicam is due to its selective inhibiting effect on the enzyme cyclo-oxygenase-2 (COX-2) relative to cyclo-oxygenase-1 (COX-1), which are involved in the biosynthesis of prostaglandins. Prostaglandins play an important role in the mediation of inflammation, pain and fever.

Adverse gastro-intestinal and renal effects are associated with the inhibition of COX-1, while the selective inhibition of COX-2 is associated with the anti-inflammatory activity of meloxicam.

Pharmacokinetic properties:

Meloxicam is absorbed after oral administration (bioavailability ± 89%) and peak plasma concentration is achieved after 2 to 4 hours. After absorption, meloxicam is extensively (99%) bound to plasma proteins. A steady state concentration is achieved after three to five days and this steady state is maintained after prolonged continuous administration. The steady state concentration found in the synovial fluid is approximately half that found in the plasma. The rate or extent of the absorption of meloxicam is not influenced by the concomitant intake of food or antacids.

Once daily dosing leads to drug plasma concentrations with relatively small peak-trough fluctuations.

The major metabolic transformation in humans, is the oxidation of the methyl group on the thiazolyl ring of the active ingredient. The inactive metabolites are excreted in the urine and in the faeces (about half in each).

Less than 5% of meloxicam is excreted unchanged in the faeces, with only small amounts unchanged in the urine.

The mean elimination half life of meloxicam is 20 hours. The pharmacokinetics of meloxicam is not adversely affected by mild or moderate renal and hepatic insufficiency. Plasma clearance occurs at approximately 8 ml/minute and is halved in the elderly.

Indications:

For the symptomatic relief of painful and/or inflammatory conditions, including musculoskeletal and joint disorders such as osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.

Contra-Indications:

Known hypersensitivity to meloxicam, any other non-steroidal anti-inflammatory drugs (NSAIDs) or to aspirin. The potential for cross sensitivity to aspirin and other NSAIDs exists.

Meloxicam should not be administered to patients with a history of allergic reactions (such as skin rashes, urticaria, rhinitis, asthma, angioedema and anaphylactic shock) induced by aspirin or other NSAIDs. When aspirin-induced nasal polyps, associated with bronchospasm, are present, meloxicam should not be prescribed.

The use of meloxicam is contra-indicated in patients with peptic ulcerations or bleeding of the gastro-intestinal tract, severe hepatic insufficiency and non-dialysed severe renal insufficiency.

Patients whose renal functions are being maintained by prostaglandins should not use meloxicam. These may include patients on diuretics and patients with impaired circulation, renal vascular disease and heart failure.

NSAIDs may produce a high degree of gastro-

intestinal toxicity in children and should therefore not be prescribed to children under the age of 15 years. Safety during pregnancy and lactation has not been established (see "Warnings").

Warnings:

Regular use of NSAIDs during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus in utero and possibly in persistent pulmonary hypertension of the newborn. The onset of labour may be delayed and its duration increased.

The medication should be stopped and emergency treatment obtained if the following occurs: anaphylaxis, angioedema or bronchospasm. The medication should be stopped and a physician consulted if the following occurs: unexplained nosebleed, chest pain, spitting of blood, convulsions, fainting, gastrointestinal bleeding or ulceration and blood dyscrasias.

Dosage and Directions for Use:

Adults:

Rheumatoid arthritis: 15 mg meloxicam once daily.

The dose may be reduced to 7.5 mg daily according to the therapeutic response.

Osteo-arthritis: 7.5 mg meloxicam once daily.

In severe cases: 15 mg meloxicam once daily.

Ankylosing spondylitis: 15 mg once daily.

Elderly and other patients with increased risk for adverse reactions:

7.5 mg meloxicam daily initially.

Careful patient monitoring is recommended.

Dialysis patients: Do not exceed 7.5 mg meloxicam daily.

Maximum recommended dose: 15 mg meloxicam once daily.

Children under 15 years of age:

Not recommended. Safety and efficacy have not been established.

COXFLAM should be taken with water, with or after a

meal. Noticeable improvement in severe conditions may require 1 to 2 weeks of continuous use.

Side-effects and Special Precautions:

Side-effects:

Gastro-intestinal symptoms are the most common side-effects encountered.

NSAIDs may increase the incidence of bleeding in the upper gastro-intestinal tract and of perforation. The most important patient-related risk factors for upper gastro-intestinal toxicity are old age, a history of peptic ulcers or bleeding of the gastro-intestinal tract and the concomitant use of corticosteroids.

The following side-effects have been reported:

Gastro-intestinal/hepatobiliary: Abdominal pain, nausea and vomiting, constipation or diarrhoea, dyspepsia and flatulence have more frequently been reported. Oesophagitis, eructation, gastro-duodenal ulcer, and gastro-intestinal bleeding (occult or macroscopic) and abnormalities of liver function parameters (e.g. raised bilirubin or transaminases) are less frequently been reported. The induction or exacerbation of colitis, gastrointestinal perforation and hepatitis have occasionally been reported.

Neuropsychiatric: Dizziness, headache, tinnitus and drowsiness have been reported as well as nervousness, depression, insomnia, hearing loss, visual disturbances and vertigo.

Dermatological: Urticaria, pruritus and skin rashes may occur and less frequently stomatitis.

Occasionally photosensitivity, Stevens-Johnson syndrome, erythema multiforme and bullous reactions was reported.

Nephrological: Abnormal renal function parameters (increased serum creatinine and/or serum urea) may occur.

Renal failure may be provoked in patients with a pre-existing renal impairment.

Haematuria and fluid retention may occur.

Haematological: Anaemia, thrombocytopenia, neutropenia, oesinophilia and agranulocytosis, have been reported. The inhibition of platelet aggregation is reversible.

Concomitant administration of other potentially myelotoxic drugs, in particular methotrexate, can be a predisposing factor for the onset of cytopenia.

Cardiovascular: Oedema has more frequently been reported and less frequently, palpitations, flushes and increased blood pressure.

Respiratory: The onset of acute asthma has been reported in some patients following the administration of meloxicam.

Hypersensitivity reactions may occur occasionally and may include fever, angioedema, bronchospasm and rashes. Less frequently hepatotoxicity and aseptic meningitis may occur, which may also be hypersensitivity reactions.

Other less frequent adverse effects that occur with the use of non-steroidal anti-inflammatory agents may include alveolitis, pulmonary oesinophilia, and toxic epidermal necrolysis.

Special precautions:

Side-effects such as gastrointestinal ulceration and bleeding, are more likely to occur in the elderly, and are more likely to be of a serious nature, although they may occur at any time during treatment with or without warning symptoms or a previous history of serious gastro-intestinal events. Patients with a history of upper GIT disease and patients on anticoagulants should be treated with caution. Those with upper GIT symptoms should be monitored and COXFLAM treatment should be stopped if peptic ulceration or GIT bleeding occurs.

Age-related renal function impairment may increase the risk of NSAID-induced renal and hepatic toxicity, as well as the possible accumulation of the medication. Elderly patients should therefore be carefully monitored.

The bleeding time may be prolonged because of suppressed platelet aggregation. Caution should be used when prescribing meloxicam to patients with haemorrhagic disorders or patients on anticoagulants.

Due to the potential of meloxicam to 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, it may precipitate overt renal decompensation which is typically followed by recovery to pre-treatment state upon discontinuation of treatment in these patients. Patients at risk of such a reaction include dehydrated patients, those with congestive heart failure, liver cirrhosis, nephrotic syndrome and overt renal disease, those on diuretic therapy or those having undergone major surgical procedures, which have led to hypovolaemia. In such patients the extent of diuresis and the renal function should be monitored when therapy is initiated.

In rare instances NSAID's may cause interstitial nephritis, glomerulonephritis, papillary necrosis and the nephrotic syndrome. COXFLAM should be used with caution in patients with infections since meloxicam may mask symptoms like fever and inflammation.

The risk benefit should be considered in patients with mild allergic reactions, such as urticaria, skin rash and allergic rhinitis, induced by aspirin or other NSAID's. The risk benefit should also be considered in patients suffering from inflammatory or ulcerative diseases of the gastro-intestinal tract.

Patients suffering from bleeding problems (coagulation or platelet function disorders) or haemophilia should be carefully monitored and the associated risk considered.

In view of the product's inherent potential to cause fluid and electrolyte retention and its interference with the natriuretic effects of diuretics, heart failure or hypertension may be precipitated or exacerbated in susceptible patients.

Should mucocutaneous adverse events arise, the patient should be monitored, and discontinuation of COXFLAM should be considered. Severe skin reactions and serious life-threatening hypersensitivity reactions have occurred with NSAID's.

The effects on ability to drive and use machinery has not been studied with meloxicam, but should vertigo, visual disturbances, drowsiness or other central nervous system disturbances occur, it would be advisable to refrain from these activities.

Interactions:

An increased risk of gastro-intestinal ulceration and bleeding may occur with the concurrent administration of two or more NSAID's (including aspirin), due to the synergistic action produced.

The concomitant use of corticosteroids may increase the incidence of upper gastro-intestinal toxicity. The effects of oral anticoagulants, such as coumarin, indandion derivatives or heparin, may be enhanced. Meloxicam is bound in the gastro-intestinal tract by cholestyramine, and this leads to a faster elimination of meloxicam.

Increased plasma concentrations of lithium, methotrexate and cardiac glycosides may be present. The plasma levels of these medicines should be carefully monitored.

The hematologic toxicity of methotrexate may be increased. Strict monitoring of the blood cell count is therefore advised.

Acute renal insufficiency may occur in patients who are dehydrated. Patients who receive concurrent diuretics should be adequately hydrated and their renal function carefully monitored.

There may be an increased risk of nephrotoxicity when administered concomitantly with angiotensin converting enzyme inhibitors, cyclosporine and diuretics. An increased risk of hyperkalaemia may be present with angiotensin converting enzyme inhibitors, and potassium-sparing diuretics.

The effect of some anti-hypertensive agents, such as β-blockers, ACE-inhibitors, vasodilators and diuretics, may be affected due to the inhibition of vasodilating prostaglandins.

The concurrent administration of meloxicam and quinolones may cause convulsions.

The effect of phenytoin, and sulphonylurea anti-diabetics may be enhanced by meloxicam.

Prolonged concurrent use of meloxicam and paracetamol may increase the risk of adverse renal effects.

Potassium supplements may increase the risk of gastro-intestinal side-effects.

NSAID's may decrease the efficacy of intra-uterine devices.

Known Symptoms of Overdosage and Particulars of its Treatment:

See "Side-effects and special precautions". Treatment is symptomatic and supportive. Standard measures of gastric evacuation should be used in alert patients. Clinical trials have shown that cholestyramine accelerates the elimination of meloxicam.

Identification:

COXFLAM 7.5 : A yellow coloured, circular, flat, bevelled, uncoated tablet, with a central break-line on one side and plain on the other.

COXFLAM 15 : A yellow coloured, circular, flat, bevelled, uncoated tablet, with a central break-line on one side and '15' embossed on the other side.

Presentation:

COXFLAM 7.5 : Aluminium strips of 10 tablets packed in 10's, 30's or 100's.

COXFLAM 15 : Aluminium strips of 10 tablets packed in 10's, 20's, 30's or 50's.

Storage Instructions:

Store in well closed containers, below 25°C. KEEP OUT OF REACH OF CHILDREN.

Registration Numbers:

COXFLAM 7.5: 35/3.1/0055

COXFLAM 15: 35/3.1/0328

Name of Business and Address of Applicant:

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