**1.5 Product Information**

**1.5.1 Summary of Product Characteristics**

**1. Name of the Medicinal Product**

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|---|---|---|
| **1.1 Trade Name** | **:** | **ZIMOXICAM 7.5** (Meloxicam Tablets BP 7.5 mg) |
| **1.2 Strength** | **:** | 7.5 mg |
| **1.3 Pharmaceutical Form** | **:** | Tablet |

**2. Pharmaceutical Form**

**Dosage form:** Tablet

**Physical Description:** Pale yellow, circular, slightly biconvex, uncoated tablet plain on both sides.

**3. Clinical Particulars**

**3.1 Therapeutic indications**

Meloxicam is indicated for;

• Short-term symptomatic treatment of exacerbations of osteoarthritis.

• Long-term symptomatic treatment of rheumatoid arthritis or ankylosing spondylitis.

**3.2 Posology and method of administration**

**Posology**

*Exacerbations of osteoarthritis:* 7.5 mg daily dose (one 7.5 mg tablet). If necessary, in the absence of improvement, the dose may be increased to 15 mg daily dose (two 7.5 mg tablets).

• *Rheumatoid arthritis, ankylosing spondylitis:* 15 mg daily dose (two 7.5 mg tablets).

According to the therapeutic response the dose may be reduced to 7.5 mg daily dose (one 7.5 mg tablet).

**Do Not Exceed The Dose of 15 mg/Day.**

***Special populations***

***Elderly patients and patients with increased risks for adverse reactions:*** 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 risk 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 greater than 25 ml/min)

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

***Children and adolescents:*** This medicinal product should not be used in children and adolescents aged under 16 years.

***Method of administration***

Oral use

The total daily amount should be taken as a single dose, with water or another liquid, during a meal.

**3.3 Contraindication**

This medicinal product is contraindicated in the following situations:

- Third trimester of pregnancy and lactation.
- Children and adolescents aged under 16 years
- Hypersensitivity to meloxicam or to one of the excipients or hypersensitivity to substances with a similar action, e.g. NSAIDs, aspirin. This medicinal product 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.
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Active intestinal inflammatory disease (Crohn´s disease, ulcerative colitis)
- Severely impaired liver function.
- Non-dialysed severe renal failure.
- Gastrointestinal bleeding, cerebrovascular bleeding or other bleeding disorders.
- Severe heart failure
- Meloxicam is contraindicated in treatment of perioperative pain after coronary artery bypass surgery (CABG)

**3.4 Special warnings and special precautions for use**

Undesirable effects may be minimized by using the lowest effective dose for the shortest duration necessary to control symptoms.

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. The use of meloxicam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

Any history of oesophagitis, gastritis and/or peptic ulcer must be sought in order to ensure their total cure before starting treatment with meloxicam. Attention should routinely be paid to the possible onset of a recurrence in patients treated with meloxicam and with a past history of this type.

***Gastrointestinal effects:*** Gastrointestinal bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.
The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk.
Caution is advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as heparin as a curative treatment or given in geriatrics, anticoagulants such as warfarin or other non-steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥ 1g as single intake or ≥ 3g as total daily amount).
When gastrointestinal bleeding or ulceration occurs in patients receiving meloxicam, the product should be withdrawn.

***Cardiovascular and cerebrovascular effects:*** Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.
Clinical monitoring of blood pressure for patients at risk is recommended at baseline and especially during treatment initiation of meloxicam.

The use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for meloxicam.
Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with meloxicam after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking).

***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 NSAIDSs. Patients appear to be at highest risk for 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.

***Parameters of liver and renal function:*** 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 results, 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.

***Functional renal failure:*** NSAIDS, by inhibiting the vasodilating effect of renal prostaglandins, may induce a functional renal failure by reduction of glomerular filtration. This adverse event is dose dependant. At the beginning of the treatment, or after dose increase, careful monitoring of diuresis and renal function is recommended in patients with the following risk factors:

- Elderly
- Concomitant treatments such as ACE inhibitors, Angiotensin-II-antagonists, sartans, diuretics
- Hypovolaemia (whatever the cause)
- Congestive heart failure
- Renal failure
- Nephrotic syndrome
- Lupus nephropathy
- Severe hepatic dysfunction (serum albumin < 25g/l or Child-Pugh score ≥ 10).

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 7.5mg. 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).

***Sodium, potassium and water retention:*** Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with NSAIDs.

Furthermore, a decrease of the antihypertensive effect of antihypertensive drugs can occur. Consequently, oedema, cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. Clinical monitoring is therefore necessary for patients at risk.

***Hyperkalaemia:*** Hyperkalaemia can be associated with diabetes or concomitant treatment known to increase kalaemia. Regular monitoring of potassium values should be performed in such cases.

Adverse reactions are often less tolerated in elderly, fragile or weakened individuals, who therefore require careful monitoring. As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired.
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal.

Meloxicam, as other NSAIDs, may mask symptoms of an underlying infectious disease. The use of meloxicam, as with any substance 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.

Lactose: Use with caution with the advice of physician in case of lactase insufficiency, galactosaemia or glucose/galactose malabsorption syndrome.

**3.5 Interaction with other medicinal products and other forms of interaction**
Interaction studies have only been performed in adults.
***Pharmacodynamic interactions:***
• *Other non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid ≥ 3 g/day:* Combination with other non-steroidal anti-inflammatory drugs, including acetylsalicylic acid given at anti-inflammatory doses (≥1g as single intake or ≥ 3g as total daily amount) is not recommended.
• *Corticosteroids (e.g. Glucocorticoids):* The concomitant use with corticosteroids requests cautions because of an increased risk of bleeding or gastrointestinal ulceration.
• *Anticoagulant or heparin administered in geriatrics or at curative doses:* Considerably increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. NSAIDs may enhance the effects of anticoagulants, such as warfarin. The concomitant use of NSAIDs and anticoagulants or heparin administered in geriatrics or at curative doses is not recommended. In remaining cases of heparin use,

caution is necessary due to an increased bleeding risk. 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.

• *Selective serotonin reuptake inhibitors (SSRIs):* Increased risk of gastrointestinal bleeding.

• *Diuretics, ACE inhibitors and Angiotensin-II Antagonists:* NSAIDs may reduce the effect of diuretics and other antihypertensive drugs. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function) the co-administration of an ACE inhibitor or Angiotensin-II antagonist and agents that inhibit cyclo-oxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

• *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.

• *Calcineurin inhibitors (e.g. ciclosporin, tacrolimus):* Nephrotoxicity of calcineurin inhibitors 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 (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.

***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 hours. 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.

**3.6 Fertility, pregnancy and lactation**
Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or embryo/ foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis 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 prostaglandin synthesis inhibitor has been shown to result in increased 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 first and second trimesters of pregnancy, meloxicam should not be given unless clearly necessary. If meloxicam is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible

- During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose t*he 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.
Consequently, meloxicam is contraindicated during the third trimester of pregnancy.

***Lactation:*** While no specific experience exists for meloxicam, NSAIDs pass into mother's milk. Meloxicam is therefore contradicted during breast-feeding.

**3.7 Effects on ability to drive and use machines**

Some undesirable effects like visual disturbances or drowsiness, vertigo or other central nervous system disturbances occur, it is advisable to refrain from driving and operating machinery.

**3.8 Undesirable effects**

The most commonly-observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease have been observed in study of following administration. Less frequently, gastritis has been observed.
The following adverse reaction observed while taking Meloxicam. The frequency grouping is defined using the following convention: 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) and Not known (cannot be estimated from the available data).

***Blood and lymphatic system disorders***
*Uncommon:* Anaemia
*Rare:* Blood count abnormal (including differential white cell count), leukopenia, thrombocytopenia

***Immune system disorders***
*Uncommon:* Hypersensitivity, allergic reactions other than anaphylactic or anaphylactoid reactions
*Not known:* Anaphylactic reaction, anaphylactoid reaction

***Psychiatric disorders***
*Rare:* Mood altered, nightmares
*Not known:* Confusional state, disorientation

***Nervous system disorders***
*Common:* Headache
*Uncommon:* Dizziness, somnolence

***Eye disorders***
*Rare:* Visual disturbance including vision blurred; conjunctivitis

***Ear and labyrinth disorders***
*Uncommon:* Vertigo

*Rare:* Tinnitus

***Cardiac disorders***

*Rare:* Palpitations

***Vascular disorders***

*Uncommon:* Blood pressure increased, flushing

***Respiratory, thoracic and mediastinal disorders***

*Rare:* Asthma in individuals allergic to aspirin or other NSAIDs

***Gastrointestinal disorders***

*Very common:* Dyspepsia, nausea, vomiting, abdominal pain, constipation, flatulence, diarrhoea

*Uncommon:* Occult or macroscopic gastrointestinal haemorrhage, stomatitis, gastritis, eructation

*Rare:* Colitis, gastroduodenal ulcer, oesophagitis

*Very rare:* Gastrointestinal perforation

*Not known:* Pancreatitis

***Hepatobiliary disorders***

*Uncommon:* Liver function disorder (e.g. raised transaminases or bilirubin)

*Very rare:* Hepatitis

***Skin and subcutaneous tissue disorders***

*Uncommon:* Angioedema, pruritus, rash

*Rare:* Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria

*Very rare:* Dermatitis bullous, erythema multiforme

*Not known:* Photosensitivity reaction

***Renal and urinary disorders***

*Uncommon:* Sodium and water retention, hyperkalaemia, renal function test abnormal (increased serum creatinine and/or serum urea)

*Very rare:* Acute renal failure in particular in patients with risk factors

***General disorders and administration site conditions***

*Uncommon:* Oedema including oedema of the lower limbs.

**3.9 Overdose**

*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.
*Treatment:* 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.

**4. Pharmacological Properties**

**4.1 Pharmacodynamics properties**

*Pharmacotherapeutic group*: Non-Steroidal Anti-Inflammatory agent, Oxicams
ATC code: M01AC06
*Mechanism of action:* Meloxicam is a non-steroidal anti-inflammatory substance (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 NSAID, its precise mechanism of action remains unknown. However, there is at least one common mode of action shared by all NSAID (including meloxicam): Inhibition of the biosynthesis of prostaglandins, known inflammation mediators.

**4.2 Pharmacokinetic Properties**

*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 5-6 hours with solid oral dosage forms. With multiple dosing, steady state conditions were reached within 3-5 days. Maximum plasma concentrations of meloxicam at steady state, are achieved within 5-6 hours. 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. Volume of distribution is low, on average 11 l. Inter-individual 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).

*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 to 8 ml/min.

Special populations

Hepatic/renal insufficiency: Neither hepatic, nor mild nor moderate renal insufficiency has 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.

**5. Pharmaceutical Particulars**

**5.1 List of excipients**

Colloidal Anhydrous Silica
Lactose Monohydrate
Sodium Starch Glycolate (Type A)
Microcrystalline Cellulose
Povidone
Polysorbate 80
Croscarmellose Sodium
Sodium Lauryl Sulfate
Purified Talc
Magnesium Stearate

**5.2 Incompatibilities**

Not Applicable

**5.3 Shelf life**

36 Months

**5.4 Special precautions for storage**

Store at a temperature not exceeding 30°C. Protect from moisture.

**5.5 Nature and contents of container**

1 x 10 Alu-Alu Blister

**5.6 Special precautions for disposal and other handling**

No special requirements.

**6. Marketing Authorization Holder and Manufactured By**

**ZIM Laboratories Limited**

B-21/22, MIDC Area,
Kalmeshwar, Nagpur 4401501,
Maharashtra State, India.

**7. Marketing Authorization Number**

TAN 22 HM 0370

**8. Date of First Registration / Renewal of the Registration**

21/09/2022

**9. Date of Revision of the Text**

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