PROFESSIONAL INFORMATION FOR

COXFLAM 7,5 / 15

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

COXFLAM 7,5 (Tablets).

COXFLAM 15 (Tablets).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

COXFLAM 7,5: Each tablet contains 7,5 mg meloxicam.
Contains sugar (lactose monohydrate 43 mg per tablet).

COXFLAM 15: Each tablet contains 15 mg meloxicam.
Contains sugar (lactose monohydrate 86 mg per tablet).

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Tablets

COXFLAM 7,5: A yellow coloured, circular, flat, bevelled, uncoated tablet, with a central break-line on one side and plain on the other side.

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.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

COXFLAM is indicated for the symptomatic relief of painful and/or inflammatory conditions, including musculoskeletal and joint disorders such as osteoarthritis, rheumatoid arthritis, acute sciatica and ankylosing spondylitis.

4.2. Posology and method of administration

Posology

Use the lowest effective dose for the shortest possible duration of treatment.

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.
Acute sciatica:	7,5 mg once daily. The dose may be increased to 15 mg once daily according to the therapeutic response.

Special populations

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.

Paediatric population

Children under 12 years *of age:*	Contraindicated (see **section 4.3**). Safety and efficacy have not been established.

Method of administration

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.

4.3. Contraindications

COXFLAM is contraindicated in:

- Patients with a known hypersensitivity to meloxicam or any of the excipients in COXFLAM (see **section 6.1**) any other non-steroidal anti-inflammatory medicines(NSAIDs) or to aspirin. The potential for cross sensitivity to aspirin and other NSAIDs exists.
- Patients with a history of allergic reactions (such as skin rashes, urticaria, rhinitis, asthma, angioedema and anaphylactic shock) induced by aspirin or other NSAIDs.
- Patients with aspirin-induced nasal polyps, associated with bronchospasm.
- Patients with peptic ulcerations or bleeding of the gastrointestinal tract, active inflammatory bowel disease (Crohn’s disease or ulcerative colitis), severe hepatic insufficiency, non-dialysed severe renal insufficiency, recent cerebrovascular bleeding or established systemic bleeding disorders, peripheral arterial disease, established ischaemic heart disease and uncontrolled heart failure.
- The treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.
- Patients whose renal functions are being maintained by prostaglandins. These may include patients on diuretics and patients with impaired circulation, renal vascular disease and heart failure (see **section 4.5**).

- Children under the age of 12 years, as NSAIDs may produce a high degree of gastrointestinal toxicity in children.
- Pregnancy (see **section 4.6**).

4.4. Special warnings and precautions for use

COXFLAM may predispose to cardiovascular events, gastrointestinal events, or cutaneous reactions which may be fatal.

There appears to be a higher risk for cardiovascular events with higher doses and longer duration of treatment. Caution is advised when COXFLAM is prescribed to patients with cardiovascular risk factors e.g. hypertension, diabetes, smoking and hypercholesterolaemia.

Gastrointestinal tract (GIT) 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. Patients with a history of ulcers and the elderly are more susceptible to GIT side effects with increasing doses. GIT side effects may occur at any time during treatment with or without warning symptoms or a previous history of serious gastrointestinal events. Patients with a history of upper GIT disease and symptoms should be monitored and COXFLAM treatment should be stopped if peptic ulceration or GIT bleeding occurs.

Serious skin reactions, which can be fatal, may occur. Skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis and exfoliative dermatitis have been reported. The highest risk for occurrence of skin reactions is within the first weeks of treatment. COXFLAM should be discontinued if a mucocutaneous adverse event arises and the patient should be monitored.

Because of its lack of platelet effects, COXFLAM is not a substitute for aspirin for cardiovascular prophylaxis.

Patients with pre-existing congestive heart failure or hypertension should be closely monitored as fluid retention and oedema have been reported.

COXFLAM should be given with care to patients with a history of gastrointestinal disease such as Crohn's disease, gastro-oesophageal reflux disease, ulcerative colitis, angiodysplasia or hiatus hernia as the condition may be exacerbated (see **section 4.2**).

Serious life-threatening hypersensitivity reactions have occurred with the use of NSAID's. 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 (see **section 4.2**).

Due to inhibition of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking COXFLAM, therefore COXFLAM should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Renal prostaglandins play an important supportive role in the maintenance of renal perfusion. The inhibition of renal prostaglandin synthesis may precipitate overt renal decompensation which is typically followed by recovery to pre-treatment state upon discontinuation of treatment. Patients at risk of such a reaction include elderly, dehydrated patients, those with congestive cardiac failure, liver cirrhosis or dysfunction, nephrotic syndrome and overt renal disease, those on concurrent diuretics, sartans, angiotensin-II receptor antagonist or ACE-inhibitor treatment or those that are hypovolaemic (regardless the cause). In such patients careful monitoring of diuresis and the kidney function at the start of treatment is recommended.

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. In rare instances NSAID's may cause interstitial nephritis, glomerulonephritis, papillary necrosis and the nephrotic syndrome.

The dose of COXFLAM should be restricted to 7,5 mg daily in haemodialysed patients with terminal kidney disease. Patients with mild or moderate renal impairment (creatinine clearance > 25 mL/min) or clinically stable liver cirrhosis do not require dose reduction.

Occasional elevations of serum transaminases or other indicators 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, COXFLAM treatment should be discontinued and appropriate medical action taken.

In view of COXFLAM’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.

Caution should be used when prescribing COXFLAM to patients with haemorrhagic disorders (coagulation or platelet function disorders or haemophilia) or patients on anticoagulants as the bleeding time may be prolonged because of suppressed platelet aggregation (see **section 4.5**). These patients should be carefully monitored and the associated risk considered.

COXFLAM should be used with caution in patients with infections, since meloxicam may mask symptoms like fever and inflammation.

COXFLAM should not be used during pregnancy and lactation (see **section 4.3** and **4.6**).

Risk of renal tubular acidosis and hypokalaemia are associated with non-steroidal anti-inflammatory medicine (NSAID) usage.

Lactose

COXFLAM contains lactose monohydrate. Patients with rare hereditary conditions of galactose intolerance e.g., galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption should not take COXFLAM.

4.5. Interaction with other medicines and other forms of interaction

Because of its lack of platelet effects, COXFLAM is not a substitute for aspirin for cardiovascular prophylaxis.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with COXFLAM.

An increased risk of gastrointestinal 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 gastrointestinal toxicity.

The effects of oral anticoagulants, such as coumarin, indandion derivates or systemically administered heparin, thrombolytics and selective serotonin reuptake inhibitors may lead to an increased risk of bleeding by inhibition of platelet function.

Meloxicam is bound in the gastrointestinal tract by cholestyramine, and this leads to a faster elimination of COXFLAM.

Increased plasma concentrations of lithium (via decreased renal excretion of lithium) and methotrexate (via decreased renal tubular secretion of methotrexate) may be present with concomitant use of COXFLAM. The plasma levels of these medicines should be carefully monitored if treatment with COXFLAM is unavoidable.
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, angiotensin-II receptor antagonists, ciclosporin and diuretics.
An increased risk of hyperkalaemia may be present with angiotensin converting enzyme inhibitors, angiotensin-II receptor antagonists, NSAIDs, heparins, ciclosporin, tacrolimus, trimethoprim and potassium-sparing diuretics.

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

The concurrent administration of COXFLAM and quinolones may cause convulsions.

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

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

Potassium supplements may increase the risk of gastrointestinal side effects.

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

Concomitant treatment with probenecid leads to reduced excretion and thereby increased effects of COXFLAM.

COXFLAM should not be used in combination with tacrolimus.

COXFLAM 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 COXFLAM and medicines known to inhibit, or to be metabolised by CYP 2C9 and/or CYP 3A4 are administered concurrently.

No significant medicine interaction exists between cimetidine, furosemide, digoxin and antacids.

Simultaneous use of COXFLAM and alcohol increases the risk of bleeding.

4.6. Fertility, pregnancy and lactation

Pregnancy

COXFLAM is contraindicated in pregnancy (see **section 4.3**).

In early pregnancy, an increased risk of miscarriage, cardiac malformation and gastrochisis exists.

Regular use of NSAIDs during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus *in utero*, renal dysfunction with possible renal failure with oligohydramnios and persistent pulmonary hypertension of the newborn. The inhibition of prostaglandin synthesis may prolong bleeding time and inhibit uterine contractions at the end of pregnancy. The onset of labour may be delayed and its duration increased.

Use of NSAIDs, such as COXFLAM, around 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis, in some cases.

Breastfeeding

It is not known whether COXFLAM is excreted in breast milk, however NSAIDs are known to pass into breast milk. Therefore, the use of COXFLAM during breastfeeding is not advised.

Fertility

COXFLAM may reduce female fertility and is not recommended in women attempting to conceive. Women who have difficulties conceiving, or who are undergoing investigation of infertility should not use COXFLAM.

4.7. Effects on ability to drive and use machines

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.

4.8. Undesirable effects

Blood and lymphatic system disorders

Less frequent: Anaemia, abnormal blood count, leukopenia and thrombocytopenia.

Frequency unknown: Agranulocytosis. Concomitant administration of other potentially myelotoxic medicines, in particular methotrexate, can be a predisposing factor for the onset of cytopenia.

Immune system disorders

Less frequent: Allergic reactions.

Frequency unknown: Anaphylactic reactions, anaphylactoid reaction and other immediate hypersensitivity.

Metabolism and nutrition disorders

Frequency unknown: Hypokalaemia.

Psychiatric disorders

Less frequent: Altered mood and nightmares.

Frequency unknown: Disorientation and confusion.

Nervous system disorders

Frequent: Headache.

Less frequent: Dizziness, somnolence.

Frequency unknown: Cerebrovascular incidents (strokes) and insomnia.

Eye disorders

Less frequent: Visual disturbances (including blurred vision) and conjunctivitis.

Ear and labyrinth disorders

Less frequent: Tinnitus and vertigo.

Cardiac disorders

Less frequent: Palpitations.

Frequency unknown: Peripheral oedema, dysrhythmia, tachycardia, congestive cardiac failure, myocardial infarction, cardiovascular thrombotic events.

Vascular disorders

Less frequent: Increased blood pressure, flushing.

Frequency unknown: Aggravated hypertension and hypertension.

Respiratory, thoracic and mediastinal disorders

Less frequent: Asthma in individuals allergic to aspirin or other NSAIDs.

Gastrointestinal disorders

Frequent: Dyspepsia, nausea, diarrhoea, vomiting, constipation, flatulence and abdominal pain.

Less frequent: Gastrointestinal perforation, gastroduodenal ulcer, colitis, oesophagitis, gastritis, eructation, occult or macroscopic gastrointestinal haemorrhage and stomatitis.

Frequency unknown: Melaena, Crohn's disease, peptic ulcers, haematemesis.

Potentially fatal side effects include gastrointestinal ulceration or perforation and haemorrhage.

Hepatobiliary disorders

Less frequent: Hepatitis, abnormal liver function tests (e.g. raised bilirubin or transaminases).

Skin and subcutaneous tissue disorders

Less frequent: Dermatitis bullous, erythema multiforme, urticaria, Stevens-Johnson syndrome, toxic epidermal necrolysis, pruritus, rash and angioedema.

Frequency unknown: Photosensitivity reaction.

Renal and urinary disorders

Less frequent: Micturition disorders (including acute urinary retention), acute renal failure, sodium and water retention, hyperkalaemia and abnormal renal function parameters (increased serum creatinine and/or serum urea) may occur.

Frequency unknown: Renal tubular acidosis.

General disorders and administration site conditions

Less frequent: Oedema including oedema of the lower limbs.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 and to Cipla Medpro (Pty) Ltd by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9. Overdose

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see **section 4.4** and **section 4.8**)

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. Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day was demonstrated in a clinical trial.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacological classification A 3.1 Antirheumatics (anti-inflammatory agents).

Pharmacodynamic effects

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) with analgesic, anti-inflammatory and antipyretic properties. It is one of the oxicam 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 gastrointestinal 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.

5.2. Pharmacokinetic properties

Absorption

The rate or extent of the absorption of meloxicam is not influenced by the concomitant intake of food or antacids. Meloxicam is absorbed after oral administration (bioavailability ± 89 %) and peak plasma concentration is achieved after 5 to 6 hours. 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. Once daily dosing leads to drug plasma concentrations with relatively small peak-trough fluctuations.

Distribution

After absorption, meloxicam is extensively (99 %) bound to plasma proteins and penetrates into synovial fluid. The volume of distribution is low, averaging at 11 L (interindividual variation 7 to 20 %).

Biotransformation and elimination

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. Plasma clearance occurs at approximately 8 mL/minute on average and is halved in the elderly.

Linearity/non-linearity

Following oral or intramuscular administration of meloxicam, a linear pharmacokinetic profile is shown at the therapeutic dosage range of 7,5 mg to 15 mg.

Special populations

Hepatic and renal insufficiency

The pharmacokinetics of meloxicam is not adversely affected by mild or moderate renal and hepatic insufficiency. A significantly higher total meloxicam clearance may present in patients with moderate renal insufficiency. An increase in the volume of distribution in end stage renal disease may result in higher free meloxicam concentrations, and a daily dose of 7,5 mg must not be exceeded.

Elderly patients

The average plasma clearance at steady state was reported as being lower compared to younger individuals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

**Colloidal anhydrous silica

*Colloidal silicon dioxide

Lactose monohydrate

*Low substituted hydroxypropyl cellulose

Magnesium stearate

Maize starch

Microcrystalline cellulose

*Povidone

**Pregelatinised starch

Sodium citrate dihydrate.

*Only present in COXFLAM 7,5.

**Only present in COXFLAM 15.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store at or below 30 °C.

Keep the blisters in the outer carton until required for use.

6.5. Nature and contents of container

COXFLAM 7,5: Aluminium foil/amber PVC/PVDC film blister strips of 10 tablets packed in cartons of 10's, 30's or 100's.

COXFLAM 15: Aluminium foil/amber PVC/PVDC film blister strips of 10 tablets packed in cartons of 10's, 20's or 50's.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9,

Parc du Cap,

Mispel Street,

Bellville,

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

COXFLAM 7,5: 35/3.1/0055

COXFLAM 15: 35/3.1/0328

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 May 2002.

10. DATE OF REVISION OF THE TEXT

26 October 2023