SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ADCO-MELOXICAM 7,5 (7,5 mg tablets)

ADCO-MELOXICAM 15 (15 mg tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ADCO-MELOXICAM 7,5: Each tablet contains meloxicam 7,5 mg.

Excipient(s) with known effect:

Contains sugar (lactose monohydrate): 114,85 mg

ADCO-MELOXICAM 15: Each tablet contains meloxicam 15 mg.

Excipient(s) with known effect:

Contains sugar (lactose monohydrate): 106,81 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

Yellow, round, flat bevelled edged tablet with break-line on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADCO-MELOXICAM is indicated for the symptomatic treatment of:

- Rheumatoid arthritis
- Painful osteoarthritis
- Ankylosing spondylitis
- Episodes of acute sciatica.

4.2 Posology and method of administration

Posology

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

- *Adults:* The maximum daily dose of ADCO-MELOXICAM is 15 mg.
- *Acute sciatica:* 7,5 mg once daily. If there is no improvement the dose can be increased to 15 mg a day.
- *Ankylosing spondylitis:* 15 mg once daily. According to the therapeutic response, the dose may be reduced to 7,5 mg/day.
- *Osteoarthritis:* 7,5 mg once daily. Increase to 15 mg if necessary.
- *Rheumatoid arthritis:* 15 mg once daily. Reduce dose if possible (provided therapeutic response is maintained).

Special populations

In patients with an increased risk of adverse reactions, e.g. the elderly, a history of gastrointestinal disease or risk factors for cardiovascular disease, the treatment should be started at the dose of 7,5 mg/day (see section 4.4).

The dose of ADCO-MELOXICAM in patients with end stage renal disease on haemodialysis should not be greater than 7,5 mg/day. No dosage reduction is necessary in patients with mild to moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 mL/min).

Paediatric population

Safety and efficacy in children under the age of 18 years has not been established.

Method of administration

For oral administration.

ADCO-MELOXICAM should be taken with a glass of water and together with a meal.

4.3 Contraindications

- Hypersensitivity to ADCO-MELOXICAM or to any of the components listed in section 6.1.
- Patients in whom attacks of asthma, urticaria, nasal polyps or acute rhinitis are precipitated by acetylsalicylic acid (aspirin) or by other non-steroidal anti-inflammatory agents.

- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Perioperative analgesia in the setting of coronary artery bypass surgery (CABG).
- Active or history of recurrent ulcer/haemorrhage/perforations.
- Active inflammatory bowel disease (Crohn's disease or ulcerative colitis).
- Overt gastrointestinal bleeding, recent cerebrovascular bleeding or established systemic bleeding disorders.
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including ADCO-MELOXICAM.
- Severe hepatic impairment.
- Severe non dialysed renal impairment.
- Pregnancy (see section 4.6).
- Avoid use of NSAIDs in women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.4 and 4.6).

4.4 Special warnings and precautions for use

ADCO-MELOXICAM 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 ADCO-MELOXICAM is prescribed to patients with cardiovascular risk factors e.g. hypertension, diabetes, smoking and hypercholesterolaemia.
- Because of its lack of platelet effects, ADCO-MELOXICAM is not a substitute for aspirin for cardiovascular prophylaxis.
- Due to inhibition of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking ADCO-MELOXICAM, therefore ADCO-MELOXICAM should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.
- Patients who are elderly, dehydrated, have a heart failure, hepatic or renal dysfunction, taking diuretics, ACE inhibitors or angiotensin-II receptor antagonists, or have undergone surgery

leading to hypovolaemia, are at particular risk of renal decompensation and renal function should be carefully monitored.

- Hyperkalaemia can be favoured by diabetes or concomitant treatment known to increase kalaemia (see section 4.5). Regular monitoring of potassium values should be performed in such cases.
- The elderly have an increased frequency of adverse reactions to NSAIDs including ADCO-MELOXICAM, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.
- When gastrointestinal bleeding or ulceration occurs in patients receiving ADCO-MELOXICAM, treatment with ADCO-MELOXICAM should be stopped.
- ADCO-MELOXICAM should be given with caution to patients with a history of gastrointestinal disease (e.g. hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated.
- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolyis have been reported. ADCO-MELOXICAM should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
- Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as ADCO-MELOXICAM. Some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue ADCO-MELOXICAM and evaluate the patient immediately.
- Regular use of NSAIDs such as ADCO-MELOXICAM 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 new-born. The onset of labour may be delayed and its duration increased.
- Foetal Toxicity: Limit use of NSAIDs, including ADCO-MELOXICAM, between 20 and 30 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction. Avoid use of NSAIDs in women around 30 weeks gestation and later in pregnancy due to the risks of

oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus.

- If NSAID treatment is necessary between 20 weeks and 30 weeks gestation, limit ADCO-MELOXICAM use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if ADCO-MELOXICAM treatment extends beyond 48 hours. Discontinue ADCO-MELOXICAM if oligohydramnios occurs and follow up according to clinical practice (see section 4.3 and 4.6).
- ADCO-MELOXICAM may mask symptoms of an underlying infectious disease.

ADCO-MELOXICAM contains lactose

ADCO-MELOXICAM contains lactose and this should be taken into account in patients with diabetes mellitus.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ADCO-MELOXICAM (see sections 2 and 6.1).

4.5 Interactions with other medicines and other forms of interaction

- Acetylsalicylic acid/aspirin and other NSAIDS: use of two or more NSAIDs concomitantly could result in an increase in side effects such as an increase in gastric ulceration and/or bleeding. There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with ADCO-MELOXICAM.

  Because of its lack of platelet effects, ADCO-MELOXICAM is not a substitute for aspirin for cardiovascular prophylaxis.
- Oral anticoagulants, systemically administered heparin, thrombolytics: ADCO-MELOXICAM may enhance the effects of anticoagulants such as warfarin, with an increased risk of bleeding. If such co-prescribing cannot be avoided, close monitoring of their effects on coagulation is required.
- Corticosteroids: increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).
- Antiplatelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.
- Lithium: may result in an increase in lithium plasma concentrations. Monitor lithium plasma concentrations carefully when therapy with ADCO-MELOXICAM is initiated or withdrawn.
- Methotrexate: may result in increased haematological toxicity due to methotrexate toxicity.

- Angiotensin-converting enzyme (ACE) inhibitors and other antihypertensive agents: may result in a decrease in antihypertensive effects and an increased risk of renal failure.
- Colestyramine: may result in a reduced therapeutic effect of ADCO-MELOXICAM.
- Calcineurin inhibitors (e.g. ciclosporin, tacrolimus): increases the risk of nephrotoxicity.
- Alcohol: simultaneous intake may increase the risk of bleeding.
- Diuretics: may result in renal impairment if the patient is dehydrated (see section 4.4).
- Probenecid: concomitant treatment with probenecid leads to reduced excretion and thereby increased effects of ADCO-MELOXICAM.
- Pemetrexed: in patients with creatinine clearance from 45 to 79 mL/min, the administration of ADCO-MELOXICAM should be paused for 5 days before, on the day of, and 5 days following pemetrexed administration. If a combination of ADCO-MELOXICAM with pemetrexed is necessary, patients should be closely monitored, especially for myelosuppression and gastrointestinal adverse reactions. In patients with creatinine clearance below 45 mL/min the concomitant administration of ADCO-MELOXICAM with pemetrexed is not recommended.
- Intrauterine devices: NSAID's may decrease the efficacy of intrauterine devices.

ADCO-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 ADCO-MELOXICAM and medicines known to inhibit, or to be metabolised by CYP 2C9 and/or CYP 3A4 are administered concurrently. Interactions via CYP 2C9 can be expected in combination with medicinal products such as oral antidiabetics (sulphonylureas, nateglinide), which may lead to increased plasma levels of these medicines and ADCO-MELOXICAM. Patients concomitantly using ADCO-MELOXICAM with sulphonylureas or nateglinide should be carefully monitored for hypoglycaemia.

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

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation has not been established. The use of ADCO-MELOXICAM during the third trimester is not recommended because of possible adverse effects

on the foetus, such as premature closure of the *ductus arteriosus*, which may lead to persistent pulmonary hypertension in the newborn (see section 4.3).

Use of NSAIDs, including ADCO-MELOXICAM, can cause premature closure of the foetal ductus arteriosus and foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, the use of ADCO-MELOXICAM dose and duration between 20 and 30 weeks of gestation should be limited and avoided at around 30 weeks of gestation and later in pregnancy (see section 4.3 and 4.4).

Fertility

No data on male and female fertility is available.

4.7 Effects on ability to drive and use machines

ADCO-MELOXICAM has a moderate influence on the ability to drive and use machines (see section 4.8).

Patients should not operate machinery or drive a vehicle if they experience drowsiness, blurred vision or any other central nervous system effect.

It is not always possible to predict to what extent ADCO-MELOXICAM may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which ADCO-MELOXICAM affects them.

4.8 Undesirable effects

a. Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature.

b. Tabulated summary of adverse reactions

SYSTEM ORGAN CLASS	**FREQUENCY**	**ADVERSE REACTIONS**
	Frequent	Anaemia

Blood and lymphatic system disorders	Less frequent	Thrombocytopenia, neutropenia, eosinophilia, agranulocytosis, leucopenia
Nervous system disorders	Frequent	Headache, dizziness, light-headedness
	Less frequent	Vertigo, confusion, drowsiness, insomnia, nightmares
	Frequency unknown	Cerebrovascular incidents (stroke)
Eye disorders	Less frequent	Visual disturbances (such as blurred vision), conjunctivitis
Cardiac disorders	Less frequent	Palpitations, oedema, hypertension and cardiac failure
	Frequency unknown	Dysrhythmia, tachycardia, myocardial infarction, cardiovascular thrombotic events
Vascular disorders	Frequency unknown	Aggravated hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	[1]Bronchospasm
Gastrointestinal disorders	Frequent	Dyspepsia, nausea and vomiting, diarrhoea, flatulence, constipation and abdominal pain
	Less frequent	Gastrointestinal bleeding, perforation or ulceration (generally more serious in the elderly), induction or exacerbation of colitis, and gastritis, ulcerative stomatitis, eructation, oesophagitis
	Frequency unknown	Pancreatitis
Hepatobiliary disorders	Less frequent	Hepatitis, abnormal liver function test (e.g. raised transaminases or bilirubin)

Skin and subcutaneous tissue disorders	Frequent	Pruritus, rash
	Less frequent	Flushing, urticaria, stomatitis, photosensitivity, bullous dermatoses, including erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4)
Renal and urinary disorders	Less frequent	Nephrotic syndrome, glomerulonephritis, and papillary necrosis interstitial nephritis, renal failure, abnormal renal function test (increased serum creatinine and/or serum urea), micturition disorders including acute urinary retention, hyperkalaemia
Investigations	Less frequent	Elevated blood pressure

c. Description of selected adverse reactions

[1] Other:

Less frequent:

Tinnitus, hypersensitivity reactions including anaphylaxis, angioedema and bronchospasm (especially if patient is aspirin-sensitive and has asthma and/or nasal polyps, ADCO-MELOXICAM should be withdrawn immediately).

d. Paediatric population

No information available.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug**

Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms of overdosage

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Treatment of overdosage

Treatment is symptomatic and supportive as there is no known antidote.

Absorption should be reduced by:

- Activated charcoal if patients presents 1 to 2 hours after overdose.
- Colestyramine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 3.1 Antirheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Non-steroidal anti-inflammatory agents, oxicams. ATC code: M01 AC06

Meloxicam, an oxicam (enolic acid) derivative, is a non-steroidal anti-inflammatory compound (NSAID) with analgesic, antipyretic and anti-inflammatory activities.

The action of meloxicam is related to inhibition of the enzyme cyclo-oxygenase (COX), resulting in the decreased formation of prostaglandins (mediators of inflammation) and thromboxanes. A selective COX-2 inhibitory (anti-inflammatory) effect *in vitro* in relation to COX-1 has been demonstrated. Inhibition of COX-1 (gastrointestinal, renal and platelet effects) *in vivo* occurs.

It is suggested that the extent of inhibition of COX-1 *in vivo* is a function of dose and inter-individual variability of meloxicam concentrations.

5.2 Pharmacokinetic properties

The extent of absorption after oral administration is 89 % and concomitant administration with food does not affect absorption. Meloxicam is 99 % protein bound and has an elimination half-

life of 15 to 20 hours. Meloxicam is extensively metabolized in the liver (mainly by oxidation) and less than 5 % of the daily dose is excreted unchanged in the faeces and urine.

5.3 Preclinical safety data

No information available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silicon dioxide
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Povidone cross-linked (Crospovidone)
Povidone
Sodium lauryl sulphate
Pregelatinised starch

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

ADCO-MELOXICAM 7,5: 24 months
ADCO-MELOXICAM 15: 24 months

6.4 Special precautions for storage

Store at or below 25 °C in a well-closed container. Protect from direct sunlight.

6.5 Nature and contents of container

10, 30, 100 and 300 tablets

- The tablets are packed in a white opaque polypropylene cylindrical securitainer with a white opaque low density polyethylene (LDPE) to medium density polyethylene snap on lid and a clean white, circular polyether polyurethane flexible cellular foam insert or a white bleached, non-absorbent cotton wool wadding.

- The tablets are packed in a crystal clear, rigid PVC multiple unit blister packs heat-sealed with silver-coloured, plain, hard temper, laminated aluminium foil packed into a cardboard carton.

Not all pack types and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER(S)

ADCO-MELOXICAM 7,5: 37/3.1/0234
ADCO-MELOXICAM 15: 37/3.1/0235

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 July 2005

10. DATE OF REVISION OF THE TEXT

10 November 2022

ADCO-MELOXICAM 7,5: Namibia: NS2 12/3.1/0001
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