Professional information for M-CAM

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

M-CAM 7,5 mg tablets

M-CAM 15 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

M-CAM 7,5 mg: Each tablet contains 7,5 mg meloxicam.

M-CAM 15 mg: Each tablet contains 15 mg meloxicam.

Excipients with known effect:

Contains sugar (M-CAM 7,5 mg contains 63 mg and M-CAM 15 mg contains 126 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

M-CAM 7,5 mg tablets: Light yellow, round, biconvex, bevelled edged tablet embossed with “B” and “18” on one side.

M-CAM 15 mg tablets: Light yellow, round, biconvex, bevelled edged tablet with breakline on one side, with “B” and “19” embossed on one side of tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

M-CAM 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

As the potential for adverse reactions increases with dose and duration of exposure, the lowest effective daily dose should be used for the shortest possible duration of treatment.

The maximum recommended daily dose regardless of formulation is 15 mg.

Rheumatoid arthritis

15 mg once daily. According to the therapeutic response, the dose may be reduced to 7,5 mg per day.

Episodes of acute sciatica

7,5 mg once daily. If necessary, in the absence of improvement, the dose may be increased to 15 mg per day.

Ankylosing spondylitis

15 mg once daily. According to the therapeutic response, the dose may be reduced to 7,5 mg per day.

Painful osteoarthritis

7,5 mg once daily. If necessary, the dose may be increased to 15 mg per day.

Special populations

Elderly population and patients with increased risk of adverse reactions

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 per day (see section 4.4).

Renal impairment

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). In non-dialysed patients with severe renal impairment M-CAM is contraindicated (see section 4.3).

In patients with end-stage renal disease on haemodialysis the maximum daily dose should not exceed 7,5 mg per day.

Paediatric population

M-CAM tablets are contraindicated in children below 12 years of age because the strengths of the tablets do not allow appropriate dosing in this age group (see section 4.3).

Method of administration

Oral administration.

The total daily dose of M-CAM tablets should be taken as a single dose and should be swallowed with water or other fluid in conjunction with food.

4.3 Contraindications

- Hypersensitivity to meloxicam or to any of the excipients of M-CAM listed in section 6.1.
- Patients who have developed signs of asthma, urticaria, nasal polyps, angioedema or acute rhinitis following the administration of acetylsalicylic acid (aspirin) or by other nonsteroidal anti-

inflammatory drugs (NSAIDs), because of a potential cross-sensitivity.

- Peri-operative analgesia in the setting of coronary artery bypass graft (CABG) surgery.
- Active or history of recurrent gastrointestinal ulceration/perforation/haemorrhage.
- Active inflammatory bowel disease (Crohn's disease or ulcerative colitis).
- Severe hepatic impairment.
- Severe non-dialysed renal impairment.
- Overt gastrointestinal bleeding, recent cerebrovascular bleeding or established systemic bleeding disorders.
- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs, including M-CAM.
- Pregnancy and lactation (see section 4.6).
- Use in children under 12 years of age.
- In case of rare hereditary conditions that may be incompatible with an excipient of M-CAM (see section 4.4), the use of M-CAM is contraindicated.

4.4 Special warnings and precautions for use

M-CAM may predispose to cardiovascular events, gastrointestinal events, or cutaneous reactions which may be fatal.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and gastrointestinal (GI) and cardiovascular risks below).

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 M-CAM with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

M-CAM is not appropriate for the treatment of patients requiring relief from acute pain.

In the absence of improvement after several days, the clinical benefit of the treatment with M-CAM should be reassessed.

Elderly patients

Adverse reactions are often less well tolerated in the elderly 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, such as M-CAM, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.2).

Gastrointestinal (GI) effects

Any history of oesophagitis, gastritis and/or peptic ulcer must be sought before starting treatment with M-CAM (see section 4.3).

GI bleeding, ulceration or perforation, which can be fatal, have been reported with all NSAIDs, such as M-CAM, at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective medicines (e.g. misoprostol or proton pump inhibitors) should be

considered for these patients, and also for patients requiring concomitant low dose aspirin, or other medicines likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as heparin, as curative treatment or given in the elderly, oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or other NSAIDs, including aspirin, given at anti-inflammatory doses (≥ 500 mg per dose or ≥ 3 g as total daily amount) (see section 4.5).

When GI bleeding or ulceration occurs in patients taking M-CAM, the treatment should be stopped.

NSAIDs, such as M-CAM, should be given with care to patients with a history of gastrointestinal disease (Crohn's disease or ulcerative colitis), and should not be given to patients with an active inflammatory bowel disease (see section 4.3).

Cardiovascular and cerebrovascular effects

There appears to be a higher risk for cardiovascular events with higher doses and longer duration of treatment.

Due to inhibition of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking M-CAM, therefore M-CAM should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention. Patients with hypertension should be closely monitored.

Clinical monitoring of blood pressure for patients at risk is recommended at baseline and especially

during treatment initiation with M-CAM.

Caution is advised when M-CAM is prescribed to patients with cardiovascular risk factors (e.g. diabetes, smoking and hypercholesterolaemia).

Because of its lack of platelet effects, M-CAM is not a substitute for aspirin for cardiovascular prophylaxis (see section 4.5).

Skin reactions

Serious skin reactions, which can be fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), may occur (see section 4.8). Patients appear to be at highest risk for these reactions early during therapy. The onset of the reaction occurring in most cases within the first month of treatment.

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

If the patient has developed SJS or TEN with the use of M-CAM, therapy with M-CAM must not be re-started in this patient at any time.

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs, such as M-CAM. 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. Eosinophilia 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 M-CAM and evaluate the patient immediately.

Parameters of liver and renal function

Increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea and other laboratory disturbances, have been reported. If the abnormality is significant or persistent, M-CAM should be stopped, and follow-up tests carried out.

Functional renal failure

NSAIDs, such as M-CAM, may cause a dose dependent inhibition of the synthesis of renal prostaglandins involved in the maintenance of renal perfusion. In patients with decreased renal blood flow and blood volume, taking M-CAM may result in the decompensation of latent renal failure. However, renal function returns to its initial status when treatment is stopped.
This particularly concerns patients with the following risk factors where monitoring of diuresis and renal function during treatment is necessary (see sections 4.2 and 4.3):

- Elderly patients.
- Dehydrated patients.
- Concomitant treatment with medicines such as ACE inhibitors, angiotensin-II antagonists, sartans or diuretics (see section 4.5).
- Hypovolaemia (whatever the cause).
- Renal failure.
- Nephrotic syndrome.
- Lupus nephropathy.

NSAIDs, such as M-CAM, may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.

Sodium, potassium and water retention

Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with M-CAM. Furthermore, a decrease of the antihypertensive effect of antihypertensive medicines may occur (see section 4.5). Oedema or hypertension may be precipitated or exacerbated. Clinical monitoring is therefore necessary for patients at risk. In view of the product's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients (see sections 4.2 and 4.3).

Hyperkalaemia

Hyperkalaemia can be favoured by diabetes or concomitant treatment known to increase serum potassium levels (see section 4.5). Regular monitoring of potassium values should be performed in such cases.

Combination with pemetrexed

In patients with mild to moderate renal insufficiency receiving pemetrexed, M-CAM should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.5).

Underlying infections

M-CAM, as any other NSAID, may mask the symptoms of an underlying infectious disease.

Fertility

M-CAM can inhibit cyclooxygenase / prostaglandin synthesis, which 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, M-CAM should be stopped (see section 4.6).

Excipient warning

M-CAM contains lactose monohydrate. Patients with rare hereditary problems of galactose

intolerance, total lactase deficiency or glucose-galactose malabsorption should not take M-CAM.

4.5 Interaction with other medicines and other forms of interaction

Risks related to hyperkalaemia

Certain medicines or therapeutic groups may promote hyperkalaemia: Potassium salts, potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, NSAIDs, (low-molecular-weight or unfractionated) heparins, ciclosporin, tacrolimus and trimethoprim.

The onset of hyperkalaemia may depend on whether there are associated factors. This risk is increased when the above-mentioned medicines are co-administered with M-CAM.

Antiplatelet medicines and other NSAIDs

Concomitant use of M-CAM with other NSAIDs and antiplatelet medicines, including aspirin (acetylsalicylic acid) given at anti-inflammatory doses (≥ 500 mg per dose or ≥ 3 g as total daily amount) is not recommended, as it may increase the risk of gastrointestinal ulcers and bleeding (see section 4.4), via inhibition of platelet function and damage to the gastroduodenal mucosa.

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

Because of its lack of platelet effects, M-CAM is not a substitute for aspirin for cardiovascular prophylaxis (see section 4.4).

Corticosteroids (e.g. glucocorticoids)

The concomitant use of M-CAM with corticosteroids may increase the risk of gastrointestinal side effects, such as bleeding or gastrointestinal ulceration. Use with caution.

Anticoagulants, heparin and thrombolytics

M-CAM may enhance the effects of oral anticoagulants, such as warfarin, thrombolytics and heparin, with an increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. The concomitant use of M-CAM and anticoagulants or heparin administered in the elderly or at curative doses is not recommended (see section 4.4).

In remaining cases of heparin use, caution is necessary due to an increased bleeding risk. Careful monitoring of the international normalized ratio (INR) is required if it proves impossible to avoid such combination.

Selective serotonin reuptake inhibitors (SSRIs)

Concomitant use of M-CAM with SSRIs may increase the risk of gastrointestinal bleeding.

Antihypertensive medicines

NSAIDs, such as M-CAM, may reduce the effect of diuretics and other antihypertensive medicines. In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II antagonists and medicines that inhibit cyclooxygenase 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 (see section 4.4).

Concomitant use may decrease the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect).

Probenecid

Concomitant treatment with probenecid may lead to reduced excretion and thereby increase the

effects of M-CAM.

Calcineurin inhibitors (e.g. ciclosporin, tacrolimus)

Nephrotoxicity of calcineurin inhibitors may be enhanced by NSAIDs, such as M-CAM, via renal prostaglandin mediated effects. During combined treatment, renal function should be monitored regularly, especially in the elderly.

Deferasirox

Concomitant treatment of M-CAM and deferasirox may increase the risk of gastrointestinal adverse reactions. Caution is advised when combining these medicines.

Mifepristone

M-CAM should not be used for 8 – 12 days after taking mifepristone as it can reduce the effect of mifepristone.

Intrauterine devices

M-CAM may decrease the efficacy of intrauterine devices.

Quinolone antibiotics

Concomitant use with quinolone antibiotics may have an increased risk of developing convulsions.

Zidovudine

There is an increased risk of haematological toxicity when M-CAM is taken with zidovudine.

Lithium

M-CAM may increase blood lithium levels (via decreased renal excretion of lithium), which may reach toxic values. Concomitant use is not recommended. Lithium plasma concentrations should be monitored carefully when treatment with M-CAM is initiated, adjusted or withdrawn.

Methotrexate

M-CAM 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 M-CAM is not recommended.

The risk of an interaction between M-CAM and methotrexate should be considered, also in patients on low dosage of methotrexate, especially in patients with impaired renal function. When combination treatment is necessary, the blood cell count and renal function should be monitored. When M-CAM and methotrexate are given within 3 days of each other, the plasma level of methotrexate may increase and cause increased toxicity.

Although the pharmacokinetics of methotrexate (15 mg/week) may not relevantly be affected by concomitant M-CAM treatment, it should be considered that the haematological toxicity of methotrexate can be amplified by treatment with M-CAM.

Pemetrexed

For the concomitant use of M-CAM with pemetrexed in patients with mild to moderate renal impairment (creatinine clearance from 45 to 79 mL/min), M-CAM treatment should be discontinued for at least five days before, on the same day, and at least two days following pemetrexed administration. If a combination of M-CAM with pemetrexed is necessary, patients should be closely monitored, especially for myelosuppression and gastrointestinal adverse reactions. In patients with severe renal impairment (creatinine clearance below 45 mL/min), the concomitant administration of M-CAM with pemetrexed is not recommended.

In patients with normal renal function (creatinine clearance ≥ 80 mL/min), doses of 15 mg meloxicam (as in M-CAM) may decrease the elimination of pemetrexed and therefore increase the occurrence of adverse events due to pemetrexed. Therefore, caution should be taken when co-

administering 15 mg doses of meloxicam with pemetrexed in patients with normal renal function (creatinine clearance ≥ 80 mL/min).

Cholestyramine

Cholestyramine accelerates the elimination of meloxicam (as in M-CAM), by interrupting the enterohepatic circulation so that clearance for meloxicam increases and may result in a reduced therapeutic effect of M-CAM.

Medicines known to inhibit, or to be metabolised by cytochrome (CYP) 2C9 and/or CYP 3A4

M-CAM 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 considered when M-CAM 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 medicines such as oral antidiabetics (sulphonylureas, nateglinide), which may lead to increased plasma levels of these medicines and M-CAM. Patients concomitantly using M-CAM with sulphonylureas or nateglinide should be carefully monitored for hypoglycaemia.

Alcohol

Simultaneous intake of alcohol and M-CAM may increase the risk of bleeding.

Other medicines

No relevant pharmacokinetic interactions were detected with respect to the concomitant administration of antacids, cimetidine, digoxin and furosemide, but increased serum levels of digoxin may occur.

4.6 Fertility, pregnancy and lactation

Pregnancy

M-CAM is contraindicated during pregnancy (see section 4.3).

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the 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 (such as M-CAM) in early pregnancy.

During the third trimester of pregnancy, prostaglandin synthesis inhibition may expose the foetus to:

- Cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension in the newborn).
- Renal dysfunction, which may progress to renal failure with oligohydramnios.

At the end of pregnancy, M-CAM may expose the mother and the neonate to the following:

- 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.

Breastfeeding

M-CAM is contraindicated during lactation (see section 4.3).

NSAIDs, such as M-CAM, are known to pass into mother’s milk.

Fertility

M-CAM can inhibit cyclooxygenase / prostaglandin synthesis, which may impair fertility and is not recommended in women attempting to conceive. M-CAM may delay ovulation. In women who have difficulties conceiving, or who are undergoing investigation of infertility, M-CAM should be stopped (see section 4.4).

4.7 Effects on ability to drive and use machines

M-CAM may cause side effects, such as visual disturbances including blurred vision, dizziness, drowsiness, vertigo and other central nervous system disturbances (see section 4.8) and therefore affect the ability to drive a vehicle or use machinery. Caution is advised before driving a vehicle or operating machinery until the effects of M-CAM are known.

4.8 Undesirable effects

Summary of the safety profile

NSAIDs, such as M-CAM, particularly at high doses and in long term treatment may be associated with an increased risk of arterial thrombotic events (such as myocardial infarction or stroke) (see section 4.4).

Oedema, hypertension and cardiac failure have been reported in association with NSAID treatment (such as M-CAM).

The most commonly observed adverse events are gastrointestinal in nature. Gastroduodenal ulcers, perforation or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4). Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, anorexia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported. Less frequently, gastritis, glossitis, pancreatitis, oesophagitis and oesophageal lesions have been observed.

Severe cutaneous adverse reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN), have been reported (see section 4.4).

List of adverse reactions

Blood and lymphatic system disorders

Frequent: anaemia.

Less frequent: abnormal blood count (including differential white cell count), thrombocytopenia, neutropenia, eosinophilia, agranulocytosis, leukopenia.

Immune system disorders

Less frequent: hypersensitivity reactions including anaphylaxis, angioedema and bronchospasm (especially if patient is aspirin-sensitive and has asthma and/or nasal polyps, M-CAM should be withdrawn immediately).

Frequency unknown: anaphylactoid reactions.

Psychiatric disorders

Less frequent: altered mood, confusional state, insomnia, nightmares.

Frequency unknown: disorientation.

Nervous system disorders

Frequent: headache, dizziness, light-headedness.

Less frequent: drowsiness.

Frequency unknown: cerebrovascular incidents (strokes).

Eye disorders

Less frequent: visual disturbances (such as blurred vision), conjunctivitis.

Ear and labyrinth disorders

Less frequent: vertigo, tinnitus.

Cardiac disorders

Less frequent: palpitations.

Frequency unknown: dysrhythmia, tachycardia, congestive cardiac failure, myocardial infarction,

cardiovascular thrombotic events.

Vascular disorders

Less frequent: elevated blood pressure (hypertension), flushing.

Frequency unknown: aggravated hypertension.

Respiratory, thoracic and mediastinal disorders

Less frequent: bronchospasm (see **Immune system disorders**), asthma in individuals allergic to aspirin or other NSAIDs.

Gastrointestinal disorders

Frequent: dyspepsia, nausea, vomiting, diarrhoea, flatulence, constipation, abdominal pain.

Less frequent: occult or macroscopic gastrointestinal haemorrhage, perforation or ulceration (generally more severe and potentially fatal, especially in the elderly), induction or exacerbation of colitis, stomatitis, gastritis, eructation, oesophagitis.

Frequency unknown: pancreatitis.

Hepatobiliary disorders

Less frequent: hepatitis, liver function disorder (e.g. raised transaminases or bilirubin).

Skin and subcutaneous tissue disorders

Frequent: pruritus, rash.

Less frequent: urticaria, angioedema, photosensitivity reaction, bullous dermatoses, including erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis (see section 4.4).

Renal and urinary disorders

Less frequent: nephrotic syndrome, glomerulonephritis, interstitial nephritis and papillary necrosis, acute renal failure (particularly in patients with risk factors – see section 4.4), sodium and water retention, hyperkalaemia (see sections 4.4 and 4.5), abnormal renal function test (increased serum creatinine and/or serum urea), micturition disorders including acute urinary retention.

Reproductive system and breast disorders

Frequency unknown: female infertility, delayed ovulation.

General disorders and administration site conditions

Frequent: peripheral oedema.

Post-marketing experience

Skin and subcutaneous tissue disorders

Drug reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4).

Description of selected adverse reactions

Very rare cases of agranulocytosis have been reported in patients treated with meloxicam (as in M-CAM) and other potentially myelotoxic medicines (see section 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of M-CAM is important. It allows continued monitoring of the benefit/risk balance of M-CAM. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (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

Symptoms following acute NSAID (such as M-CAM) overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which may be 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 (such as M-CAM) and may occur following an overdose.

Treatment

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

Absorption should be reduced by:

- Activated charcoal if patient presents 1 to 2 hours after overdose.
- Accelerated removal of meloxicam by 4 g oral doses of cholestyramine given three times a day has been demonstrated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 3.1 Antirheumatics (anti-inflammatory agents).

Pharmacotherapeutic group: Nonsteroidal anti-inflammatory agent; Oxicams.

ATC code: M01AC06.

Mechanism of action

Meloxicam, an oxicam (enolic acid) derivative, is a nonsteroidal anti-inflammatory drug (NSAID) with analgesic, antipyretic and anti-inflammatory activities. The action of meloxicam is related to inhibition of the enzyme cyclooxygenase (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

Absorption

Meloxicam is well absorbed from the gastrointestinal tract, which is reflected by a high absolute bioavailability of 90 % following oral administration.

Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 5 to 6 hours.

With multiple dosing, steady state conditions were reached within 3 to 5 days. Once daily dosing leads to medicine plasma concentrations with a relatively small peak-trough fluctuation in the range of 0,4 – 1,0 µg/mL for 7,5 mg doses and 0,8 – 2,0 µg/mL for 15 mg doses, respectively (C_{min} and C_{max} at steady state, respectively). 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 after administration of multiple oral doses of meloxicam (7,5 mg to 15 mg) is approximately 16 L with coefficients of variation ranging from 11 % to 32 %.

Biotransformation

Meloxicam undergoes extensive hepatic biotransformation. Four different metabolites were

identified in urine, which were 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 varies between 13 and 25 hours after oral, IM and IV administration. Total plasma clearance is 7 to 12 mL/min after a single dose.

Linearity/non-linearity

Meloxicam demonstrates linear pharmacokinetics in the therapeutic dose range of 7,5 mg to 15 mg following oral administration.

Special populations

Hepatic/renal impairment

Neither hepatic nor mild or moderate renal impairment have a substantial effect on meloxicam pharmacokinetics. Moderate renal impairment had significantly higher total medicine clearance. Protein binding is reduced in patients with end stage renal disease. 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 (see section 4.2).

Elderly population

Elderly males exhibited mean pharmacokinetic parameters similar to those of young males. Elderly females showed higher AUC values and longer elimination half-life compared to younger subjects of both sexes. Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Crospovidone

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

M-CAM 7,5 mg: White opaque PVC/PVDC/aluminium blister strips containing 10 tablets. 3 blister strips are packed in an outer carton.

Pack size: 30 tablets.

M-CAM 15 mg: White opaque PVC/PVDC/aluminium blister strips containing 10 tablets. 3 blister strips are packed in an outer carton.

Pack size: 30 tablets.

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

Unichem SA (Pty) Ltd

San Domenico

Ground Floor, Unit G4

10 Church Street

Durbanville

7551 Cape Town

8. REGISTRATION NUMBERS

M-CAM 7,5 mg: 37/3.1/0255

M-CAM 15 mg: 37/3.1/0269

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 29 July 2005

10. DATE OF REVISION OF THE TEXT

10 October 2023