PROFESSIONAL INFORMATION

FLEXOCAM RANGE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

FLEXOCAM 7,5 tablets

FLEXOCAM 15 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each FLEXOCAM 7,5 tablet contains 7,5 mg meloxicam.

Each FLEXOCAM 15 tablet contains 15 mg meloxicam.

Contains sugar (FLEXOCAM 7,5 mg contains 63,0 mg lactose monohydrate per tablet and FLEXOCAM 15 mg contains 126,0 mg lactose monohydrate per tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

FLEXOCAM 7,5 tablets:

Light yellow, round biconvex, bevelled-edged tablet with B and 18 debossed on one side and plain on the revers

FLEXOCAM 15 tablets:

Light yellow, round biconvex, bevelled-edged tablet with B and 19 debossed on either side of break-line on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FLEXOCAM is indicated for the symptomatic treatment of:

- rheumatoid arthritis
- painful osteoarthritis
- ankylosing spondylitis
- episodes of acute sciatica.

4.2 Posology and method of administration

For oral administration.

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

Adults

The maximum daily dose of FLEXOCAM 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 per day if necessary.

Rheumatoid arthritis: 15 mg once daily. Reduce dose if possible (provided therapeutic response is maintained).

Special populations

Patients with an 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/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 FLEXOCAM is contraindicated (see section 4.3).

End stage renal disease

The dose of FLEXOCAM 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).

Paediatric population

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

Method of administration

The tablet should be taken with a glass of water and together with a meal.

Missed dose

Doctors should advise patients who forget to take FLEXOCAM to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

4.3 Contraindications

- Hypersensitivity to meloxicam or to any of the ingredients of FLEXOCAM.
- Patients in whom attacks of asthma, urticaria, nasal polyps, angioedema or acute rhinitis are precipitated by acetylsalicylic acid (aspirin) or by other nonsteroidal anti-inflammatory medicines because of a potential cross-sensitivity.
- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Active peptic ulcer disease.
- Severe hepatic impairment.
- Severe non-dialysed renal impairment.
- Pregnancy and lactation (see section 4.6).
- History of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous

NSAIDs, including FLEXOCAM.

- 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.
- Perioperative analgesia in the setting of coronary artery bypass surgery (CABG).
- Children below the age of 18 years.

4.4 Special warnings and precautions for use

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

Elderly:

The elderly have an increased frequency of adverse reactions to NSAIDs including FLEXOCAM, especially gastrointestinal perforation, ulceration and bleeding (PUBs) which may be fatal.

Gastrointestinal perforation, ulceration and bleeding (PUBs):

- Any history of oesophagitis, gastritis and/or peptic ulcer must be sought in order to ensure their total cure before starting treatment with FLEXOCAM. Attention should routinely be paid to the possible onset of a recurrence in patients treated with FLEXOCAM and with a past history of this type.
- Patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesphageal reflux disease, angiodysplasia) should be monitored very carefully while on FLEXOCAM, as the condition may be exacerbated. When gastrointestinal bleeding or ulceration occurs in patients receiving FLEXOCAM, treatment with FLEXOCAM should be stopped (see section 4.3).
- The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of FLEXOCAM, in patients with a history of ulcers, and the elderly.

These patients should commence treatment on the lowest dose available. PUBs have been reported with all NSAIDs any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. Patients with a history of gastrointestinal toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially gastrointestinal bleeding), particularly in the initial stages of treatment.

- 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.
- 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, anticoagulants such as warfarin, other nonsteroidal anti-inflammatory medicines, or acetylsalicylic acid (aspirin) given at doses ≥ 500 mg as single intake or ≥ 3 g, as total daily amount, the combination with FLEXOCAM is not recommended (see section 4.5).

Skin:

- Serious skin reactions, which can be fatal, may occur and/or have been reported. Serious skin reactions may include exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis. FLEXOCAM should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as FLEXOCAM. 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 FLEXOCAM and evaluate the patient immediately.

Cardiovascular:

- There appears to be a higher risk for cardiovascular thrombotic events, myocardial infarction and stroke (which can be fatal) with higher doses and longer duration of treatment. Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2).
- Caution is advised when FLEXOCAM is prescribed to patients with cardiovascular risk factors (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking and hypercholesterolaemia), therapy should only be prescribed after careful consideration.
- Because of its lack of platelet effects, FLEXOCAM 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 FLEXOCAM, therefore FLEXOCAM 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 (see section 4.3).

Renal:

- By inhibiting the vasodilating effect of renal prostaglandins, FLEXOCAM may induce a functional renal failure by reduction of glomerular filtration. This adverse event is dose-dependent. 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:

  Patients who are elderly, dehydrated, have congestive heart failure, severe hepatic or renal dysfunction, taking diuretics, ACE inhibitors or angiotensin-II receptor antagonists or have undergone surgery leading to hypovolaemia.
- NSAIDs like FLEXOCAM may be the cause of interstitial nephritis, glomerulonephritis,

renal medullary necrosis or nephrotic syndrome.

- Hypokalaemia and renal tubular acidosis have been reported due to prolonged use of NSAIDS, such as FLEXOCAM, at higher than recommended doses. Presenting signs and symptoms included reduced level of consciousness and generalised weakness
- The dose of FLEXOCAM with end-stage renal failure on haemodialysis should not be higher than 7,5 mg. 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 patients with mild to moderate renal insufficiency receiving pemetrexed, FLEXOCAM 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).
- Induction of sodium, potassium and water retention and interference with natriuretic effects of diuretics may occur with FLEXOCAM. Cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result. For patients at risk, clinical monitoring is advised.

Other:

- 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, FLEXOCAM should be stopped and follow-up tests carried out. No dose reduction is required in patients with clinically stable liver cirrhosis.
- frail or debilitated patients may tolerate side effects less well and such patients should be carefully supervised. Caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function.
- FLEXOCAM may mask the symptoms of an underlying infectious disease.
- regular use of NSAIDs such as FLEXOCAM during the third trimester of pregnancy may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the newborn. The onset of labour may be

delayed, and its duration increased (see section 4.6).

- lithium: FLEXOCAM has been reported to increase plasma lithium levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and FLEXOCAM is not recommended. If this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of FLEXOCAM treatment.
- 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.
- some NSAIDs interfere with thyroid function tests by lowering serum-thyroid hormone concentrations.
- children under the age of 18 years - Safety and efficacy have not been established.
- FLEXOCAM should be used with caution in patients with asthma.

FLEXOCAM contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, or glucose-galactose malabsorption should not take FLEXOCAM. FLEXOCAM contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

Certain medicines or therapeutic groups may promote hyperkalaemia: potassium salts, potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, nonsteroidal anti-inflammatory medicines, 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 abovementioned medicines are co-administered with FLEXOCAM.

Other prostaglandin synthetase inhibitors (PSIs) including NSAIDs, glucocorticoids and salicylates (acetylsalicylic acid):

May result in increased gastric ulceration and/or bleeding via a synergistic effect and is not recommended. The concomitant use of FLEXOCAM and other NSAIDs is not recommended as it could result in an increase in side effects.

Concomitant administration of acetylsalicylic acid (aspirin) given at doses ≥ 500 mg as single intake or ≥ 3 g as total daily amount is not recommended (see section 4.4).

Because of its lack of platelet effects, FLEXOCAM 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 FLEXOCAM.

Oral anticoagulants, antiplatelet medicines, systemically administered heparin, thrombolytics and selective serotonin reuptake inhibitors (SSRIs):

Considerably increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa. FLEXOCAM may enhance the effects of anticoagulants, such as warfarin, clopidogrel, ticlopidine (see section 4.4).

The concomitant use of FLEXOCAM and anticoagulants or heparin administered in the elderly is not recommended. In remaining cases (e.g. preventive doses) 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.

Lithium:

May result in an increase in plasma lithium concentrations (via decreased renal excretion of lithium), which may reach toxic values. Monitor lithium plasma concentrations carefully when therapy with FLEXOCAM is initiated or withdrawn.

Methotrexate:

FLEXOCAM 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 FLEXOCAM is not recommended (see section 4.4). The risk of an interaction between FLEXOCAM and methotrexate, should be considered also in patients on low dosage of FLEXOCAM, 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 FLEXOCAM and methotrexate are given within 3 days, in which case the plasma level of FLEXOCAM may increase and cause increased toxicity.

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

Contraception:

FLEXOCAM may decrease the efficacy of intra-uterine devices.

Diuretics, ACE inhibitors and Angiotensin-II Antagonists:

NSAIDs, such as FLEXOCAM, 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 an ACE inhibitor or Angiotensin-II antagonists and medicines 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 (see section 4.4).

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

Other antihypertensive medicines (e.g. Beta-blockers):

A decrease of the antihypertensive effect of beta blockers (due to inhibition of prostaglandins with vasodilatory effect) can occur.

Cholestyramine:

May result in a reduced therapeutic effect of FLEXOCAM.

Calcineurin inhibitors (e.g. ciclosporin, tacrolimus):

Nephrotoxicity of calcineurin inhibitors may be enhanced by NSAIDs, like FLEXOCAM, 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.

Deferasirox:

The concomitant administration of meloxicam with deferasirox may increase the risk of gastrointestinal adverse reactions. Caution should be exercised when combining these medicinal products.

Pemetrexed:

For the concomitant use of FLEXOCAM with pemetrexed in patients with mild to moderate renal impairment (creatinine clearance from 45 - 79 mL/min), the administration of FLEXOCAM should be paused for 5 days before, on the day of, and 2 days following pemetrexed administration. If a combination of FLEXOCAM 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 FLEXOCAM with pemetrexed is not recommended.

In patients with normal renal function (creatinine clearance ≥ 80 mL/min), doses of 15 mg FLEXOCAM may decrease pemetrexed elimination and, consequently, increase the occurrence of pemetrexed adverse events. Therefore, caution should be exercised when administering 15 mg FLEXOCAM concurrently with pemetrexed to patients with normal renal function (creatinine clearance ≥ 80 mL/min).

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

Interactions with oral antidiabetics cannot be excluded.

FLEXOCAM 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 FLEXOCAM 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 FLEXOCAM. Patients concomitantly using FLEXOCAM with sulphonylureas or nateglinide should be carefully monitored for hypoglycaemia.

Alcohol:

Simultaneous intake may increase the risk of bleeding.

Corticosteroids:

Increased risk of gastrointestinal perforation, ulceration or bleeding (PUBs).

General:

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

4.6 Fertility, pregnancy and lactation

FLEXOCAM is contraindicated in pregnancy (see section 4.3).

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

Pregnancy

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 in early pregnancy. During the first and second trimester of pregnancy, FLEXOCAM should not be given.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors such as FLEXOCAM may expose the 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, FLEXOCAM is contraindicated during the third trimester of pregnancy (see sections 4.3 and 4.4).

Breastfeeding

While no specific experience exists for FLEXOCAM, NSAIDs are known to pass into mother's

milk. Administration of FLEXOCAM is therefore contraindicated in women who are breastfeeding.

Fertility

The use of FLEXOCAM may impair female fertility or may delay ovulation and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of FLEXOCAM should be considered.

4.7 Effects on ability to drive and use machines

FLEXOCAM is expected to have no or negligible influence on the ability to drive and use machines.

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

4.8 Undesirable effects

a. Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequent Less frequent	Anaemia Thrombocytopenia, neutropenia, eosinophilia, agranulocytosis, leukopenia, hyperkalaemia, hyponatraemia, cytopenia
Immune system disorders	Less frequent Frequency unknown	Allergic reactions other than anaphylactic or anaphylactoid reactions, angioedema Anaphylaxis, anaphylactoid reaction, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS)

Metabolism and nutrition disorders	Less frequent Frequency unknown	Weight decrease or increase Hypokalaemia*
Psychiatric disorders	Less frequent Frequency unknown	Mood altered, nightmares Confusional state, disorientation, depression
Nervous system disorders	Frequent Less frequent Frequency unknown	Headache, dizziness, light-headedness Drowsiness, insomnia, aseptic meningitis Cerebrovascular incidents (strokes)
Eye disorders	Less frequent	Visual disturbances, blurred vision, conjunctivitis, optic nerve reactions
Ear and labyrinth disorders	Frequent Less frequent	Hearing loss Vertigo, tinnitus
Cardiac disorders	Frequent Less frequent Frequency unknown	Peripheral oedema Palpitations, hypertension, angina pectoris, dysrhythmia, tachycardia Congestive heart failure, oedema, myocardial infarction, cardiovascular thrombotic events
Vascular disorders	Less frequent Frequency unknown	Hypertension, hypotension, flushing Aggravated hypertension
Respiratory, thoracic and mediastinal disorders	Frequent Less frequent	Bronchospasm Asthma in individuals allergic to aspirin or other NSAIDs

Gastrointestinal disorders	Frequent Less frequent Frequency unknown	Dyspepsia, nausea, vomiting, diarrhoea, flatulence, constipation, abdominal pain Gastrointestinal bleeding (sometimes fatal), perforation or ulceration (generally more serious in the elderly), induction or exacerbation of colitis, gastritis, eructation, oesophagitis, dry mouth, gastroesophageal reflux, dehydration, taste perversion, pancreatitis, flatulence Melaena, haematemesis, ulcerative stomatitis, peptic ulcers, exacerbation of Crohn's disease
Hepatobiliary disorders	Less frequent	Hepatitis, liver function disorder (e.g. raised transaminases or bilirubin), hepatotoxicity, idiosyncratic liver abnormality, jaundice
Skin and subcutaneous tissue disorders	Frequent Less frequent	Pruritus, rash Urticaria, stomatitis, photosensitivity, bullous dermatoses, including erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis, alopecia
Renal and urinary disorders	Less frequent Frequency unknown	Nephrotic syndrome, glomerulonephritis, interstitial nephritis and papillary necrosis, renal failure, sodium and water retention, hyperkalaemia, hyponatraemia, renal function test abnormal, micturition disorders, acute urinary retention, haematuria, albuminuria Renal tubular acidosis*

Reproductive system and breast disorders	Less frequent Frequency unknown	Delayed ovulation Female infertility
General disorders and administrative site conditions	Frequent	Oedema, fatigue

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use at higher than recommended doses.

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 online service for adverse drug reaction reporting by following the link: http://www.sahpra.org.za/document/adverse-drug-reactions-and-quality-problem-reporting-form/.

An email can also be sent directly to the company, pharmacovigilance@pharmadynamics.co.za to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Symptoms following acute FLEXOCAM 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. Exacerbation of asthma may occur in asthmatics. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs and may occur following an 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).

Management of overdose:

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
- Cholestyramine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-Steroidal Anti-Inflammatory agent, Oxicams

ATC code: M01AC06

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

Mechanism of action

Meloxicam, an oxicam (enolic acid) derivative, is a nonsteroidal 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

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 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).

Continuous treatment for longer periods (e.g. six months) did not point to any changes in pharmacokinetics compared to steady state pharmacokinetics after two weeks of oral treatment with 15 mg meloxicam/day.

The extent of absorption for meloxicam following oral administration is not altered by concomitant food intake.

Distribution:

Meloxicam is bound to plasma proteins, essentially albumin (99 %).

Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma.

Volume distribution is low, on average 11 L. Inter-individual variation is in the order of 30 – 40 %.

The volume of distribution following administration of multiple doses of meloxicam (7,5 to 15 mg) is about 16 L.

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 is 20 hours.

Total plasma clearance amounts on average to 8 mL/min.

Linearity/non-linearity:

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

Pharmacokinetics in special patient groups

Hepatic and renal insufficiency:

Mild or moderate hepatic insufficiency and mild or moderate renal insufficiency do not have 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 (see section 4.2).

Elderly:

Elderly male subjects exhibited similar mean pharmacokinetic parameters compared with those of young male subjects. Elderly female patients showed higher AUC-values, increased by 50 – 100 %, and longer elimination half-lives compared with those of young subjects of both genders.

Mean plasma clearance at steady state in elderly patients was slightly lower than that reported for younger patients.

5.3 Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crospovidone

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Silica colloidal anhydrous

Sodium citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

FLEXOCAM 7,5 tablets:

Hard Aluminium/opaque PVC blister packs of 30 tablets (strips of 10’s) in an outer carton.

FLEXOCAM 15 tablets:

Hard Aluminium/opaque PVC blister packs of 10 tablets or 30 tablets (strips of 10’s) in an outer carton.

Not all pack sizes are marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma Dynamics (Pty) Ltd

1st Floor, Grapevine House, Steenberg Office Park

Silverwood Close

Westlake, Cape Town

7945, South Africa

8. REGISTRATION NUMBER(S)

FLEXOCAM 7,5 tablets: A38/3.1/0497

FLEXOCAM 15 tablets: A38/3.1/0498

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration: 29 July 2005

10. DATE OF REVISION OF THE TEXT

17 August 2023

NAMIBIA:

FLEXOCAM 7,5: NS2 06/3.1/0205

FLEXOCAM 15: NS2 06/3.1/0204

BOTSWANA:

FLEXOCAM 7,5: NS2 BOT1101978

FLEXOCAM 15: NS2 BOT1101977A

FLEXOCAM 15: NS2 BOT1101977B