1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

LOXIFLAM 7,5 mg tablets

LOXIFLAM 15 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of LOXIFLAM 7,5 mg contains 7,5 mg meloxicam.

Contains sugar: Lactose monohydrate 163,5 mg

Each tablet of LOXIFLAM 15 mg contains 15 mg meloxicam.

Contains sugar: Lactose monohydrate 156,0 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets.

LOXIFLAM 7,5 mg tablet is a round, pale yellow, flat bevelled tablet, bisected on one side.

LOXIFLAM 15 mg tablet is a round, pale yellow, biconvex tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

LOXIFLAM is indicated for use in patients aged 12 years and older for:

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

4.2. Posology and method of administration

Posology

Adults

The maximum recommended dose of LOXIFLAM is 15 mg daily.

Combined administration: The total daily dosage of LOXIFLAM administered as tablets, suppositories and injections should not exceed 15 mg.

Use the lowest effective dose for the shortest possible duration of treatment as the potential for adverse reactions increases with dose and duration of exposure.

Rheumatoid arthritis:

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

Ankylosing spondylitis:

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

Painful osteoarthritis:

7,5 mg/day. If necessary, the dose may be increased to 15 mg/day.

Episodes of acute sciatica:

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

Special populations

Elderly population

In patients with an increased risk of adverse reactions, such as the elderly, start treatment with a dose of 7,5 mg/day.

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 LOXIFLAM is contraindicated (section 4.3). In patients with end-stage renal failure on haemodialysis the maximum daily dose should not exceed 7,5 mg/day.

Paediatric population

LOXIFLAM is contraindicated in children under the age of 12 years (see section 4.3).

Method of administration

For oral administration.

The total daily dose of LOXIFLAM tablets should be taken as a single dose and should be swallowed with water or other fluid in conjunction with food. The maximum recommended daily dose regardless of formulation, is 15 mg (see section 4.4).

4.3. Contraindications

LOXIFLAM is contraindicated in:

- Patients with known hypersensitivity to LOXIFLAM or any of the excipients in LOXIFLAM (see section 6.1).
- Patients with a history of hypersensitivity reactions to aspirin or other nonsteroidal anti-inflammatory agents, including those in whom attacks of asthma, anaphylaxis, angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID.
- Patients who have aspirin-induced nasal polyps associated with bronchospasm.
- Patients in renal failure unless receiving dialysis.
- Patients with severe hepatic failure / insufficiency.
- Patients with bleeding disorders.
- Patients with overt gastrointestinal bleeding, recent cerebrovascular bleeding or established systemic bleeding disorders.
- Patients with established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Patients who have had perioperative analgesia administered in the setting of coronary artery bypass surgery (CABG).

- Patients with heart failure.
- Patients with active or a history of recurrent ulcer/haemorrhage/perforations (see section 4.4).
- Patients with active inflammatory bowel disease (Crohn's disease or ulcerative colitis) (see section 4.4).
- Patients with a history of gastrointestinal bleeding, ulceration or perforation related to previous NSAIDS use.
- Children under the age of 12 years (see section 4.2 and 4.4).
- Pregnancy and lactation (see section 4.6).
- In case of rare hereditary conditions that may be incompatible with an excipient of LOXIFLAM, the use of LOXIFLAM is contraindicated.

4.4. Special warnings and precautions for use

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

Skin reactions

Serious skin reactions, which may be fatal, including exfoliate dermatitis, Steven-Johnson syndrome and toxic epidermal necrolysis, may occur. Patients appear to be at the highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. LOXIFLAM should be discontinued at the first appearance of skin rash, mucosal lesions or any sign of hypersensitivity.

Most patients recovered from skin reactions when LOXIFLAM was withdrawn.

In patients reporting mucocutaneous adverse events, special attention should be paid and

consideration given to discontinuation of LOXIFLAM.

Drug Reaction with Eosinophilia and Systemic Symptoms

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as LOXIFLAM. 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 LOXIFLAM and evaluate the patient immediately.

Gastrointestinal effects

LOXIFLAM should not be given to patients with gastrointestinal bleeding, peptic ulcers or perforation (see section 4.3).

The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal.

Perforation can occur at any time during treatment .There is a higher risk for cardiovascular and gastrointestinal bleeding or perforation events with higher doses and longer duration of treatment in patients with a history of ulcers and the elderly.

Patients with gastrointestinal symptoms should be monitored.

When gastrointestinal bleeding or ulceration occurs in patients receiving LOXIFLAM, treatment with LOXIFLAM should be stopped.

Gastrointestinal bleeding, ulceration or perforation can occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. The consequences of such events are generally more serious in the elderly.
LOXIFLAM should be given with caution to patients with a history of gastrointestinal disease (e.g., ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated (see section 4.3).
Special precautions must also be taken in patients with a history of peptic ulcers or bleeding of the gastrointestinal tract, and concomitant use of corticosteroids (see section 4.5).
Caution should be exercised in patients receiving treatment with anticoagulants.
To reduce the risk of gastrointestinal effects, LOXIFLAM may be taken with or after food or milk. However, food and milk may reduce the rate and extent of medicine absorption.

Cardiovascular and cerebrovascular effects
Caution is advised when LOXIFLAM is prescribed to patients with cardiovascular risk factors e.g., hypertension, diabetes, smoking and hypercholesterolaemia, as fluid retention and oedema have been reported in association with LOXIFLAM therapy. In view of LOXIFLAM's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.
LOXIFLAM may increase the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use.
Due to the inhibition of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking meloxicam, as in LOXIFLAM therefore, LOXIFLAM should be used with caution in patients with compromised cardiac function and other predisposing to, or worsened by, fluid retention. Patients with pre-existing congestive heart failure or hypertension should be closely monitored.

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

Use in pregnancy

Regular use of NSAIDs 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.).

Elderly

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

Gastrointestinal bleeding, ulceration or perforation, potentially fatal, can occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. The consequences of such events are generally more serious in the elderly.

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of LOXIFLAM, in patients with a history of ulcers, and the elderly. LOXIFLAM should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastroesophageal reflux disease, angiodysplasia), as the condition may be exacerbated (see section 4.3).

Special precautions must be taken in the elderly patient, as LOXIFLAM can increase the

need for antihypertensive therapy.

LOXIFLAM should be used with caution in the elderly and may need to be given in reduced doses.

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.

Fluid retention may occur, which may precipitate congestive heart failure in elderly patients. Long-term use or abuse of analgesics, including NSAIDs such as LOXIFLAM has been associated with nephropathy.

Renal impairment

LOXIFLAM inhibits the synthesis of renal prostaglandins which play a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients' administration of LOXIFLAM may precipitate overt renal decompensation which is typically followed by recovery to pre-treatment state upon discontinuation of therapy.

Patients at greatest risk of such reactions are dehydrated patients, those with congestive heart failure, liver cirrhosis, nephritic syndrome and overt renal disease, those receiving a diuretic or those having undergone major surgical procedures which led to hypovolaemia. In such patients the volume of diuresis and the renal function should be carefully monitored at the beginning of therapy.

The dose of LOXIFLAM in patients 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).

LOXIFLAM may cause interstitial nephritis, glomerulonephritis, papillary necrosis, nephrotic syndrome and lupus nephropathy.

Hepatic impairment

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, LOXIFLAM should be stopped and follow up tests carried out.

No dose reduction is required in patients with clinically stable liver cirrhosis.

General

Induction of sodium, potassium and water retention and interference with natriuretic effects of diuretics may occur with LOXIFLAM. Cardiac failure or hypertension may be precipitated or exacerbated in susceptible patients as a result.

LOXIFLAM should be used with caution in patients with infections, since symptoms such as fever and inflammation may be masked, and also used with caution in patients with asthma or allergic disorders.

Other general precautions to be observed include administration to patients with haemorrhagic disorders, hypertension, and impaired renal, hepatic or cardiac function.

Patients undergoing therapy with LOXIFLAM may need to be monitored for the development of blood, kidney, liver, or eye disorders.

LOXIFLAM can interfere with thyroid function tests by lowering serum-thyroid hormone concentrations.

Damage to the distal small intestine and colon can also occur.

Lithium

LOXIFLAM 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 LOXIFLAM is not recommended. If this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of LOXIFLAM treatment (see section 4.5).

Paediatric population

LOXIFLAM should not be used in children under 12 years of age (see section 4.3).

Excipients

Lactose warning:

Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency, or glucose-galactose malabsorption should not take LOXIFLAM.

4.5. Interaction with other medicines and other forms of interaction.

Notable interactions involving NSAIDs such as LOXIFLAM include enhancement of the effects of anticoagulants and increased plasma concentrations of lithium, methotrexate, and digoxin.

Lithium:

LOXIFLAM 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 LOXFIFLAM is not recommended. If this combination appears necessary, it is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing LOXIFLAM treatment (see section 4.4).

Methotrexate:

LOXIFLAM may increase the haematological toxicity of methotrexate. In this situation strict monitoring of blood cell count is recommended.

LOXIFLAM 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 LOXIFLAM is not recommended.The risk of an interaction between LOXIFLAM and methotrexate should be considered, also in patients on a low dosage of methotrexate, especially in patients with impaired renal function. When combination treatment is necessary, the blood cell count and renal functionshould be monitored. When LOXIFLAM and methotrexate are given within 3 days of each other, the plasma level of methotrexate may increase and cause increased toxicity.

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

Aspirin and other NSAIDs may result in an increase in gastric ulceration and/or bleeding via a synergistic effect. Concomitant use of LOXIFLAM with other NSAID administration is not recommended. The concomitant use of more than one NSAID (including aspirin and LOXIFLAM) should be avoided because of the increased risk of adverse effects.

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

Oral anticoagulants:

LOXIFLAM may enhance the effects of anti-coagulants 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.

An increased risk of bleeding through inhibition of platelet functions and irritation of the gastroduodenal mucosa may occur when LOXIFLAM is co-administered with oral anticoagulants, parenterally administered heparin, thrombolytics and ticlopidine.

Interactions with warfarin have been reported with meloxicam as in LOXIFLAM. If such a co-prescription cannot be avoided, close monitoring of the effects of the anticoagulants is required.

ACE-inhibitors:

The risk of nephrotoxicity may be increased if given with ACE inhibitors, ciclosporin, tacrolimus, or diuretics. Effects on renal function may lead to reduced excretion of some medicines. There may also be an increased risk of hyperkalaemia with ACE inhibitors and potassium-sparing diuretics. The antihypertensive effects of some antihypertensives including ACE inhibitors, beta-blockers, and diuretics may be reduced.

ACE inhibitors can also produce impairment and combined use with LOXIFLAM should be undertaken with great care. Prostaglandin inhibition may also lead to salt and water retention particularly when there is pre-existing hypertension or renal impairment.

LOXIFLAM and angiotensin-II receptor antagonists as well as ACE inhibitors exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment this may lead to acute renal failure.

Diuretics:

NSAIDs such as LOXIFLAM, therefore, tend to counteract the action of diuretics and antihypertensives. There have been reports of severe hyponatraemia and other symptoms resembling the syndrome of inappropriate antidiuretic hormone secretion in

patients taking meloxicam as in LOXIFLAM. Hyperkalaemia is more likely to occur in patients with specific risk factors such as those receiving potassium supplements or potassium-sparing diuretics. Patients receiving LOXIFLAM and diuretics should be adequately hydrated and be monitored for renal function prior to initiating treatment. Treatment with LOXIFLAM is associated with the potential for acute renal insufficiency in patients who are dehydrated.

Probenecid:

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

Oxpentifylline:

There may be an increased risk of bleeding during concomitant use of LOXIFLAM and oxpentifylline.

Contraception:

Meloxicam, as in LOXIFLAM, has been reported to decrease the efficacy of the intrauterine devices.

Cholestryramine:

Cholestyramine binds LOXIFLAM in the gastrointestinal tract leading to a faster elimination of LOXIFLAM.

Ciclosporin:

Nephrotoxicity of ciclosporin may be enhanced by LOXIFLAM via renal prostaglandin mediated effects. During combined treatment renal function should be assessed regularly.

Quinolone antibiotics:

Convulsions may occur due to an interaction with quinolones.

Sulphonylureas:

LOXIFLAM may enhance the effects of phenytoin and sulphonylurea antidiabetics.

Moclobemide:

The effects of LOXIFLAM might be enhanced by use with moclobemide.

Corticosteroids, alcohol, bisphosphonates:

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) associated with LOXIFLAM is increased when used with corticosteroids (see section 4.4) or possibly, alcohol, bisphosphonates.

Mifepristone:

NSAIDs or aspirin should be avoided for 8 to 12 days after mifepristone use because of a theoretical risk that these prostaglandin synthetase inhibitors may alter the efficacy of mifepristone.

Tacrolimus:

Tacrolimus should not be combined with LOXIFLAM.

Pemetrexed:

For the concomitant use of LOXIFLAM with pemetrexed in patients with creatinine

clearance from 45 to 79 mL/min, the administration of LOXIFLAM should be paused for 5 days before, on the day of, and 5 days following pemetrexed administration. If a combination of LOXIFLAM 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 LOXIFLAM with pemetrexed is not recommended.

Antiplatelet medicines, and selective serotonin reuptake inhibitors (SSRIs):
Increased risk ofgastrointestinal bleeding, via inhibition of platelet function.

CYP2C9 inhibitors
LOXIFLAM 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 LOXIFLAM 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 LOXIFLAM. Patients concomitantly using LOXIFLAM 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

LOXIFLAM is contraindicated in pregnancy and lactation (see section 4.3).

Regular use of NSAIDs, such as LOXIFLAM , 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.

Pregnancy

Inhibition of prostaglandin synthesis may adversely affect 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, LOXIFLAM should not be given.

Regular use of NSAIDs 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),
- renal dysfunction, which may progress to renal failure with oligohydramnios (see section 4.4);

and may expose the mother and the neonate, at the end of pregnancy to:

- 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.

Breasfeeding

LOXIFLAM is contraindicated in women who are breastfeeding (see section 4.3)

Fertility

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

4.7. Effects on ability to drive and use machines

LOXIFLAM has a minor influence on the ability to drive or operate machinery.
Since adverse reactions such as light-headedness, drowsiness and blurred vision have been reported in patients taking LOXIFLAM, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that LOXIFLAM does not adversely affect their ability to do so (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature. Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis.

b) Tabulated list of adverse reactions

System organ class	**Frequent**	**Less Frequent**	**Frequency Unknown** (cannot be estimated from available data)
Blood and the lymphatic system	Anaemia.	Differential white cell count, leucopenia, agranulocytosis,	

disorders		thrombocytopenia, pancytopenia[1].	
Immune system disorders	Fever, angioedema, bronchospasm, rashes, anaphylactoid reactions.	Hepatotoxicity, aseptic meningitis[2].	Anaphylactic reaction[3]
Psychiatric disorders	Altered mood.		Confusion, disorientation, insomnia, nightmares.
Nervous system disorders	Light-headedness, headache.	Drowsiness, dizziness.	
Eye disorders			Blurred vision, conjunctivitis.
Ear and labyrinth disorders		Vertigo, tinnitus.	
Cardiac disorders			Dysrhythmia, tachycardia, congestive cardiac failure, myocardial infarction, cardiovascular thrombotic events.
Vascular disorders	Peripheral oedema.	Aggravated hypertension, palpitations, flushes.	Cerebrovascular incidents (strokes).
Respiratory, thoracic and mediastinal disorders	Asthma[4].	Alveolitis, pulmonary eosinophilia.	
Gastrointestinal disorders	Dyspepsia, nausea, abdominal pain, vomiting, diarrhoea, constipation, flatulence, stomatitis, eructation, occult or macroscopic gastrointestinal bleeding.	Oesophagitis, gastroduodenal ulcer, pancreatitis, gastrointestinal perforation, colitis, peptic ulcer, gastritis.	Melaena, haematemesis, relapse of Crohn's disease.
Hepatobiliary disorders		Abnormalities of liver function parameters[5].	Hepatitis.
Skin and subcutaneous tissue disorders	Pruritus, skin rash.	Urticaria, toxic epidermal necrolysis, bullous reactions, Stevens-Johnson syndrome.	Photosensitivity, erythema multiforme.
Renal and urinary disorders		Abnormal renal function test, micturition disorders[6].	Interstitial nephritis, nephrotic syndrome, renal failure, haematuria. acute renal failure.
Reproductive system and breast disorders		Delayed ovulation.	Female infertility.

c) Description of selected adverse reactions

Blood and the lymphatic system disorders

[1]Disturbances of blood count, including differential white cell count, leucopenia, agranulocytosis and thrombocytopenia. Concomitant administration of a potentially myelotoxic medicine, in particular methotrexate, appears to be a predisposing factor to

the onset of pancytopenia.

Immune system disorders

[2]Hepatotoxicity, aseptic meningitis, may also be hypersensitivity reactions.

[3] anaphylactic reaction, including anaphylactic shock, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4).

Respiratory, thoracic and mediastinal disorders

[4]Asthma in individuals allergic to aspirin or other NSAIDs.

Hepatobiliary disorders

[5]Abnormalities of liver function parameters (e.g., raised transaminases or bilirubin)

Renal and urinary disorders

[6]Abnormal renal function test (increased serum creatinine and/or serum urea. Micturition disorders including acute urinary retention

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 providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088 / +27 (0)11 239-6200

4.9. Overdose

Symptoms

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

Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAID and may occur following an overdose.

Treatment

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

It has been shownin a clinical trial that cholestyramine accelerates the elimination of LOXIFLAM.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, Oxicams

ATC code: M01AC06

Mechanism of action

Meloxicam is a non-steroidal anti-inflammatory medicine (NSAID) of the enolic acid class which has shown anti-inflammatory, analgesic and antipyretic properties. A common mechanism for the above effects may exist in the ability of meloxicam to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.

The discovery of an inducible form of cyclooxygenase 2 (COX-2) whose expression is enhanced by inflammatory mediators has suggested that the COX-2 isoform might be responsible for production of prostaglandins at inflammatory sites.

Selective inhibition of COX-2 is anticipated to be related to the anti-inflammatory effect.

A selective inhibition of cyclo-oxygenase-2 (COX-2) relative to cyclo-oxygenase-1 (COX-1) by meloxicam has been demonstrated.

COX-2 inhibition relates to the anti-inflammatory effects of NSAIDs whereas inhibition of constitutive COX-1 is thought to be responsible for gastric and renal side-effects.

5.2. Pharmacokinetic properties

Absorption

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

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

Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake or the use of inorganic antacids.

Dose linearity was demonstrated after oral administration in the therapeutic dose range of 7,5 to 15 mg. With multiple dosing, steady state conditions were reached within 3 to 5

days.

Once daily dosing leads to mean meloxicam plasma concentrations with a relatively small peak-trough fluctuation in the range of 0,4 to 1,0 µg/mL for 7,5 mg doses and 0,8 to 2,0 µg/mL for 15 mg doses, respectively (C_{min} and C_{max} at steady state, correspondingly). Mean maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours

Distribution

Steady state conditions are achieved in three to five days. 99 % is bound to plasma proteins. Meloxicam penetrates into synovial fluid to give concentrations approximately half those in plasma.

Volume of distribution is low, i.e. approximately 11 L after i.m. or i.v. administration, and shows interindividual variation in the order of 7 to 20 %.

The volume of distribution following administration of multiple oral doses of meloxicam (7,5 to 15 mg) is about 16 L with coefficients of variation ranging from 11 to 32 %.

Biotransformation

Meloxicam is extensively metabolised. The major metabolic pathway is the oxidation of the methyl group of the thiazoolyl-moeity. Neither hepatic, nor mild or moderate renal insufficiency does substantially affect meloxicam's pharmacokinetics.

Meloxicam undergoes extensive hepatic biotransformation. Four different metabolites of meloxicam were identified in urine, which are all pharmacodynamically inactive.

Elimination

Less than 5 % of the daily dose is excreted unchanged in the faeces, while only traces of the unchanged compound are excreted in the urine. Meloxicam is eliminated from the

body with a mean half-life of 20 hours. Plasma clearance is on average 8 ml/min. Clearance is halved in the elderly.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

LOXIFLAM 7,5 tablets

Croscarmellose sodium, lactose monohydrate, povidone K25, sodium stearyl fumarate, trisodium citrate dihydrate

LOXIFLAM 15 mg tablets:

Croscarmellose sodium, lactose monohydrate, povidone K25, sodium stearyl fumarate, trisodium citrate dihydrate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C in well-closed containers.

Keep in original packaging until required for use.

6.5. Nature and contents of container

LOXIFLAM 7,5 mg:30 tablets are packed in a clear or red polyvinyl chloride,

polyvinylidene chloride or a clear polyvinyl chloride, polyethylene, polyvinylidene chloride film sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

LOXIFLAM 15 mg:

10 or 30 tablets are packed in a polyvinyl chloride, polyethylene, polyvinylidene chloride or red polyvinyl chloride, polyvinylidene chloride film sealed with an aluminium foil backing. The blister strips are packed into an outer cardboard carton together with a leaflet.

Not all packs and pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBERS

LOXIFLAM 7,5 mg: 36/3.1/0101

LOXIFLAM 15 mg: 36/3.1/0102

9. DATE OF FIRST AUTHORISATION

05 September 2003

10. DATE OF REVISION OF TEXT

04 January 2023

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

Namibia:	NS2
LOXIFLAM 7,5 mg:	05/3.1/0242
LOXIFLAM 15 mg:	05/3.1/0241

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