PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

XEFO® 8 IV/IM

8,0 mg Lornoxicam powder for reconstitution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 8 mg lornoxicam.

Contains sugar: 100,0 mg/vial mannitol

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

XEFO 8 IV/IM: Yellow freeze-dried powder in an amber coloured glass vial.

XEFO Water for Injection: A clear, colourless liquid in a clear glass ampoule.

When reconstituted the medicine is a yellow, clear liquid free of visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short term treatment of mild to moderate pain when oral administration is inappropriate (e.g., after dental surgery).

4.2 Posology and method of administration

Posology

Lornoxicam should be given in doses of 8 mg, and the daily dose should in general not exceed 16 mg. In some patients a further 8 mg given within the first 24 hours could be needed.

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

Special Populations

Children and adolescents

Lornoxicam is not recommended for use in children and adolescents below age 18 due to a lack of data on safety and efficacy.

Elderly

Lornoxicam should be administered with caution in the elderly as gastrointestinal adverse effects are less well tolerated in this group (see section 4.4).

Renal impairment

For patients with mild to moderate renal impairment dose reduction should be considered (see section 4.4).

Hepatic impairment

For patients with moderate hepatic impairment dose reduction should be considered (see section 4.4).

This medicine is for single use only.

The solution for injection is prepared by dissolving the contents of one vial in Water for Injection (2 ml) or in the accompanying ampoule immediately prior to use.

The route of administration is intravenous (IV) or intramuscular injection (IM). When given as IV injection, the time of injection should be at least 15 seconds, and for IM injection, at least 5 seconds.

After preparation of the solution, the needle should be changed. For IM injection use a sufficiently long needle for a deep intramuscular injection.

For further instructions on handling of the product before administration, see section 6.6.

4.3 Contraindications

XEFO is contra-indicated in the following groups of patients:

- those allergic to lornoxicam, or to any of the excipients in XEFO (see section 6.1)

- those who have suffered hypersensitivity reactions (bronchospasm, rhinitis, angioedema or urticaria) to other non-steroidal anti-inflammatory medicines, including acetylsalicylic acid
- those with hypovolaemia or dehydration
- those with confirmed or suspected cerebrovascular bleeding
- those with bleeding and coagulation disorders
- those with active peptic ulcer or history of recurrent peptic ulceration/haemorrhage/perforations
- those with severe liver impairment
- those with severe renal impairment (serum creatinine > 700 µmol/l or creatinine clearance < 30 ml/min)
- those with thrombocytopenia
- heart failure
- the elderly (> 65 years)
- those that are pregnant or lactating
- those under 18 years of age

4.4 Special warnings and precautions for use

In patients with the following disorders, XEFO should only be administered after careful risk-benefit assessment.

Elderly patients (65 years or above):

There is no clinical experience with this dosage form in this patient group. The elderly has an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation which may be fatal (see section 4.3).

Monitoring of renal and hepatic function is recommended. Precaution is advised in elderly postoperative patients.

Gastrointestinal bleeding, ulceration and perforation: Gastrointestinal (GI) bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs, such as lornoxicam as in XEFO, at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

The risk of gastrointestinal bleeding, ulceration or perforation is higher with increasing doses of XEFO, in patients with a history of ulcers, particularly if complicated with haemorrhage or perforation (see section 4.3), 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 in patients requiring concomitant low dose acetylsalicylic acid or other medicines likely to increase gastrointestinal risk (see section 4.5). Clinical monitoring at regular intervals is recommended.

Caution is advised in patients receiving concomitant medicines that could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors, or anti-platelet medicines such as acetylsalicylic acid (see section 4.5).

XEFO 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 4.8)

Patients developing peptic ulceration and/or gastro-intestinal bleeding while taking XEFO should discontinue medicine administration with appropriate therapeutic actions being taken.

Previous cerebrovascular haemorrhage; SLE; porphyria; haematopoietic disorders; patients with reduced cardiac function.

Appropriate monitoring and advice is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with XEFO therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for XEFO.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with XEFO after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Hepatic impairment (e.g., liver cirrhosis): Clinical monitoring and laboratory assessments at regular intervals should be considered in patients with hepatic impairment as accumulation of lornoxicam (increase in AUC) may occur after treatment with daily doses of 12 mg to 16 mg. Apart from that, hepatic impairment does not seem to affect pharmacokinetic parameters of lornoxicam as compared to healthy subjects.

Concomitant treatment with NSAIDs, and heparin in the context of a spinal or epidural anaesthesia increases the risk of spinal/epidural haematoma (see section 4.5).

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. Patients appear to be at highest risk of these reactions early during therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. XEFO should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Renal Impairment: Patients with *mild* renal impairment (serum creatinine 150 - 300 µmol/l) should be monitored quarterly, patients with *moderate* renal impairment (serum creatinine 300 - 700 µmol/l) should be monitored at 1-to-2-month intervals. Should renal function deteriorate during treatment, XEFO should be discontinued.

Renal functions should be monitored in patients who

- undergo major surgery,
- with cardiac failure,
- receiving treatment with diuretics,
- receiving concomitant treatment with medicines that are suspected to or known to be able to cause kidney damage (see section 4.5)

Patients with coagulation disorders: Careful clinical monitoring and laboratory assessment is recommended (e.g., PTT).

XEFO reduces platelet aggregation and prolongs bleeding time and consequently care should be taken when administering to patients with increased bleeding tendency.

Long term treatment (longer than 3 months):

A regular laboratory assessment of haematology (haemoglobin), renal function (creatinine) and liver enzymes is recommended.

The use of XEFO with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided.

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

Concomitant treatment of XEFO and tacrolimus may increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. Renal function must therefore be monitored closely in patients receiving combination therapy (see section 4.5).

As with most NSAIDs occasional increase in serum transaminases level, increase in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea nitrogen as well as other laboratory abnormalities have been reported. Should any such abnormality prove significant or persist the administration of XEFO should be stopped and appropriate investigations prescribed.

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

4.5 Interaction with other medicines and other forms of interaction

- Anti-coagulants: XEFO may enhance the effects of anti-coagulants such as Warfarin (see section 4.4). Careful monitoring of INR should be undertaken.
- sulphonylureas (e.g., glibenclamide): may increase the hypoglycaemic effect.

- other non-steroidal anti-inflammatory medicines and aspirin: increased risk of adverse reactions including an increased risk of gastrointestinal bleeding or ulceration.

- diuretics: decreased diuretic and antihypertensive effect of loop diuretics, thiazide diuretics and potassium sparing diuretics (increased risk of hyperkalaemia and nephrotoxicity).; NSAIDs counteract the diuretic effect of furosemide.

- ACE inhibitors: the effect of the ACE inhibitor may decrease and there is a risk of acute renal insufficiency.

- lithium: might lead to an increase of the lithium peak concentration and thus to a possible increase in adverse events. Therefore, serum lithium levels require monitoring, especially during initiation, adjustment and withdrawal of treatment. Avoid concomitant use if frequent analysis of lithium concentration in plasma cannot be performed.

- methotrexate: increased serum concentration of high dose methotrexate; avoid concomitant use. Special care must be taken if both NSAID and methotrexate are administered within 24 hours. Increased toxicity may result.

- cimetidine: higher plasma concentrations of lornoxicam. (No interaction between XEFO and ranitidine, or XEFO and antacids has been demonstrated).

- digoxin: decreased renal clearance of digoxin.

- cyclosporine: Increased serum concentration of cyclosporine. Nephrotoxicity of cyclosporine may be enhanced via renal prostaglandin mediated effects. During combined treatment renal function should be monitored

- Corticosteroids: increased risk of gastrointestinal ulceration or bleeding (see section 4.4)

- Antiplatelet medicines and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding (see section 4.4).

Phenprocoumon: Decreased effect of phenprocoumon treatment.

Heparin: NSAIDs increase the risk of spinal or epidural haematoma when given concomitantly to heparin in the context of spinal or epidural anaesthesia.

Beta-adrenergic blockers: Decreased antihypertensive efficacy.

Quinolone antibiotics (e.g., levofloxacin, ofloxacin): Increased risk of seizures.

Known inducers and inhibitors of CYP2C9 isoenzymes: Lornoxicam has interactions with known inducers and inhibitors of CYP2C9 isoenzymes such as phenytoin, amiodarone, miconazole, tranylcypromine, and rifampicin. See section 5.2.

Tacrolimus: Increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. During combined treatment renal function should be monitored.

4.6 Fertility, pregnancy and lactation

Pregnancy

Lornoxicam is contraindicated in the third trimester of pregnancy and should not be used during pregnancy in the first and second trimesters and delivery as no clinical data on exposed pregnancies are available.

There are no adequate data from the use of lornoxicam, as in XEFO, in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

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 after use of a prostaglandin synthesis inhibitor in early pregnancy. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryofoetal lethality. During the first and second trimester of pregnancy, prostaglandin synthesis inhibitors should not be given unless clearly necessary.

From the 20th week of pregnancy, the use of lornoxicam can initiate a fetal renal dysfunction triggered oligohydramnios. This may occur shortly after the start of the treatment and is usually reversible after discontinuation of treatment. In addition, after treatment in the second trimester of pregnancy, cases reported of a narrowing of the ductus arteriosus in most cases resolves after discontinuation of the treatment. Thus, lornoxicam should not be used during the first and second trimesters unless absolutely necessary.

If lornoxicam is used in a woman who is trying to become pregnant or who is in the first and second trimester of pregnancy, the dose should be as low as possible, and the duration of treatment should be

kept as short as possible. After several days of use of lornoxicam from the 20th week of pregnancy onwards, prenatal monitoring for oligohydramnios and a narrowing of the ductus arteriosus should be done. Lornoxicam should be discontinued if oligohydramnios or narrowing of the ductus arteriosus is noted.

Prostaglandin synthesis inhibitors administered during the third trimester of pregnancy may expose the foetus to cardiopulmonary toxicity (premature closure of the ductus arteriosus and pulmonary hypertension) and renal dysfunction which may lead to renal failure and hence a reduced quantity of amniotic fluid. At the end of pregnancy, prostaglandin synthesis inhibitors may expose the mother and the foetus to increased bleeding time and inhibition of uterine contractions, which may delay or prolong the labour. Therefore, the use of XEFO is contraindicated during the third trimester of pregnancy (see section 4.3).

Breastfeeding

There are no data on the excretion of lornoxicam, as in XEFO, in human breastmilk. Lornoxicam, as in XEFO, is excreted in milk of lactating rats in relatively high concentrations. Therefore, XEFO should not be used in breastfeeding women.

Fertility

The use of lornoxicam, as in XEFO, 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, withdrawal of XEFO should be considered.

4.7 Effects on ability to drive and use machines

Patients showing dizziness and/or sleepiness under treatment with XEFO should refrain from driving or operation machinery.

4.8 Undesirable effects

a) Summary of the safety profile

The most commonly observed adverse events are gastrointestinal in nature.

Peptic ulcers, perforation, or GI bleeding, sometimes fatal, particularly in the elderly, may occur (see section 4.4).

Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration of NSAIDs, such as lornoxicam, as in XEFO. Less frequently, gastritis has been observed.

Approximately 20 % of patients treated with lornoxicam, as in XEFO, can be expected to experience adverse reactions. The most frequent adverse effects of lornoxicam, as in XEFO, include nausea, dyspepsia, indigestion, abdominal pain, vomiting, and diarrhoea. These symptoms have generally occurred in less than 10 % of patients in available studies.

Oedema, hypertension, and cardiac failure have been reported in association with NSAID, such as lornoxicam, as in XEFO, treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs, such as lornoxicam, as in XEFO, (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

NSAIDs, such as ZEFO, can cause Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4).

Listed below are undesirable effects which generally occurred in more than 0.05% of the 6.417 patients treated in clinical phase II, III and IV trials.

Very common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1000, <1/100); rare (≥1/10.000, <1/1.000); Very rare (<1/10.000).

b) Tabulated summary of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Infections and infestations	Rare	Pharyngitis.
Blood and the lymphatic system disorders	Rare	Anaemia, prolonged bleeding time, thrombocytopenia, leukopenia.
	Very rare	Ecchymosis.

		It has been reported that that NSAIDs have potentially severe haematological class effects such as neutropenia, agranulocytosis, aplastic anaemia, and hemolytic anaemia.
Immune system disorders	Rare	Hypersensitivity. Including anaphylactoid reactions and anaphylaxis.
Metabolism and nutritional disorders	Uncommon	Anorexia, weight changes.
Psychiatric disorders	Uncommon	Depression, insomnia.
	Rare	Confusion, nervousness, agitation.
Nervous system disorders	Common	Mild and transient headache, dizziness
	Rare	Migraine, paraesthesia, taste perversion, tremor, somnolence.
Eyes disorders	Uncommon	Conjunctivitis
	Rare	Visual disturbances.
Ear and labyrinth disorders	Uncommon	Vertigo, tinnitus
Cardiac disorders	Uncommon	Palpitations, tachycardia, oedema, cardiac failure.
Vascular disorders	Uncommon	Flushing, oedema.
	Rare	Hypertension, hot flush, haemorrhage, haematoma
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinitis.
	Rare	Dyspnoea, cough, bronchospasm.
	Unknown	Symptoms of irritation in upper respiratory tract.
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, dyspepsia, nausea, vomiting.
	Uncommon	Constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, abdominal pain upper, duodenal ulcer, mouth ulceration.

	Rare	Melaena, haematemesis, stomatitis, oesophagitis, gastroesophageal reflux, dysphagia, aphthous stomatitis, glossitis, perforated peptic ulcer, gastrointestinal bleeding.
	Unknown	ulcerative stomatitis, exacerbation of colitis and Crohn's disease, haemorrhoidal or rectal bleeding.
Hepatobiliary disorders	Uncommon	Increase in liver function tests, SGPT (ALT) or SGOT (AST).
	Very rare	Hepatotoxicity, e.g., liver failure, hepatitis, jaundice and cholestasis.
Skin and subcutaneous tissue disorders	Uncommon	Rash, pruritus, hyperhidrosis, rash erythematous, urticaria, angioedema, alopecia.
	Rare	Dermatitis, purpura.
	Very rare	Oedema and bullous reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia
	Rare	Bone pain, muscle spasms, myalgia.
	Unknown	Cramps in leg
Renal and urinary disorders	Rare	Micturition disorders, nocturia, increase in blood urea nitrogen and creatinine levels
	Very rare	XEFO may cause acute renal failure in patients with existing renal impairment, triggering by renal prostaglandins for the preservation of renal blood flow (see Section 4.4). Various forms of nephrotoxicity including nephritis and nephrotic syndrome relates to NSAIDs as a class effect
	Uncommon	Malaise, face oedema.
	Rare	Asthenia.

General disorders and administrative site conditions	Unknown	Injection site reactions (e.g., pain, rubor, stinging, tension), sedation, changes in appetite, debility

Reporting of suspected adverse reactions

Reporting of Suspected Adverse Reactions Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety App (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. You can also report side effects to Acino Pharma via email on drugsafety_ZA@acino.swiss.

4.9 Overdose

Overdose may cause nausea and vomiting, cerebral symptoms (dizziness, disturbances in vision). Severe symptoms are ataxia, ascending to coma and cramps, liver and kidney damage, coagulation disorders.

In the case of an actual or suspected overdose, the medicine should be withdrawn. Treatment is symptomatic and supportive.

Due to its short half-life, lornoxicam, as in XEFO, is rapidly excreted. Lornoxicam is not dialysable. No specific antidote is known to date. Gastrointestinal disorders can for example be treated with a prostaglandin analogue or ranitidine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 3.1 Antirheumatics (anti-inflammatory agents)

Lornoxicam is a non-steroidal anti-inflammatory drug with analgesic properties and belongs to the class oxicams. The mode of action of lornoxicam is partly based on inhibition of prostaglandin synthesis (inhibition of the cyclo-oxygenase enzyme).

In vitro the inhibition of cyclo-oxygenase does not result in an increase in leukotriene formation.

The mechanism of the analgesic action of lornoxicam has not been fully determined.

5.2 Pharmacokinetic properties

Absorption

XEFO 8 IV/IM is intended for intravenous or intramuscular administration. After intramuscular injection maximum plasma concentrations are achieved after approximately 20-25 minutes. The absolute bioavailability (calculated on AUC) after intramuscular injection is 97 %.

Distribution

Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The plasma protein binding of lornoxicam is 99% and not concentration dependent.

Biotransformation

Lornoxicam is extensively metabolised in the liver. The hydroxylated metabolite exhibits no pharmacological activity. Lornoxicam is metabolised completely, and approximately 2/3 is eliminated via the liver and 1/3 via the kidneys as inactive substance.

Elimination

The mean elimination half-life of the parent compound is 3 to 4 hours. The elimination half-life of 5-hydroxylornoxicam is about 9 hours after a parenteral single or twice daily dose.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Lornoxicam caused renal toxicity and gastrointestinal ulceration single- and repeat-dose toxicity studies in several species.

In animals, administration of prostaglandin synthesis inhibitor has been shown to result in increased pre- and post- implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

In rat, lornoxicam impaired fertility (effects on ovulation and implantation) and affected the pregnancy and delivery. In rabbit and rat, lornoxicam caused premature closure of the ductus arteriosus due to inhibition of cyclooxygenase.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Disodium edetate, mannitol, trometamol.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

XEFO IV/IM: 36 months

6.4 Special precautions for storage

Store at room temperature at or below 25 ºC.

Do not use the preparation later than 24 hours after reconstitution.

6.5 Nature and contents of container

A vial containing freeze-dried powder and a 2 ml glass ampoule with Water for Injection packed as a set in one pack or a vial containing freeze dried powder only.

Package sizes available: 1 set, 5 sets. Vial only: 5 vials per pack.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

If visible signs of deterioration are seen in the medicinal product, the product must be disposed of in accordance with local requirements.

Lornoxicam has shown compatibility with 0,9 % NaCl, 5 % dextrose (glucose) and Ringer's solution.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Acino Pharma (Pty) Ltd

106 16th Road

Midrand

8 REGISTRATION NUMBERS:

XEFO 8 IV/IM: 33/3.1/0249

XEFO Water for Injection: 33/34/0250

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 October 1998

10 DATE OF REVISION OF THE TEXT

31 October 2024

Registration No.:
Namibia (NS2): 04/3.1/0752