PROFESSIONAL INFORMATION

SCHEDULING STATUS: S3

1 NAME OF THE MEDICINE

XEFO®4, 4 mg film-coated tablets

XEFO® 8, 8 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

XEFO 4 tablets: Each film-coated tablet contains 4 mg lornoxicam

Contains sugar: Lactose monohydrate 94 mg

XEFO 8 tablets: Each film-coated tablet contains 8 mg lornoxicam

Contains sugar: Lactose monohydrate 90 mg

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets

XEFO 4: White to yellowish oblong film-coated tablet with imprint “L04”

XEFO 8: White to yellowish oblong film-coated tablet with imprint “L08”

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short-term treatment of mild to moderate pain associated with extra articular inflammation.

Symptomatic treatment of pain and inflammation in osteoarthritis and rheumatoid arthritis.

4.2 Posology and method of administration

Posology

For all patients the appropriate dosing regimen should be based upon individual response to treatment.

Use the lowest effective dose for the shortest possible duration of treatment necessary to control symptoms, (see section 4.4)

Treatment of pain:

8 mg to 16 mg per day given in 2 to 3 divided doses. The total daily dose should not exceed 16 mg.

Osteoarthritis and rheumatoid arthritis:

Initial recommended total daily dose is 12 mg divided in two or three doses. Maintenance dose should not exceed 16 mg per day.

Special populations

Paediatric population

XEFO is not recommended for use in children under 18 years of age.

Elderly

No special dosage modification is required for elderly patients (> 65 years of age), unless renal or hepatic function is impaired, in which case the daily dosage should be restricted, (see section 4.4).

Renal or hepatic impairment

For patients with renal or hepatic impairment, the maximal recommended daily dose is reduced to 12 mg (one film-coated tablet XEFO 4 mg tid) see section 4.4

Method of administration

XEFO film-coated tablets are supplied for oral administration and should be taken before meals with a sufficient quantity of liquid.

4.3 Contraindications

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

- Hypersensitivity to the active substance, lornoxicam, or any of the excipients listed in section 6.1.
- those who have suffered hypersensitivity reactions (bronchospasm, asthma, rhinitis, angioedema or urticaria) to other non-steroidal anti-inflammatory medicines, including, acetylsalicylic acid

- history of gastro-intestinal bleeding or perforation related to previous NSAID use
- 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)
- those with thrombocytopenia
- heart failure
- the elderly (> 65 years), those weighing less than 50 kg and those undergoing acute surgery
- Pregnancy, due to the risk of foetal renal dysfunction, leading to oligohydramnios and, in some cases, neonatal renal impairment associated with the use of NSAIDs during pregnancy, and lactation
- those under 18 years of age

4.4 Special warnings and precautions for use

Lornoxicam reduces platelet aggregation and prolongs bleeding time. Consequently, caution should be taken when administering to patients with increased bleeding tendency.

XEFO should only be administered after careful risk-benefit assessment in patients with:

- Renal impairment: XEFO should be administered with caution in patients with mild (serum creatinine 150 – 300 µmol/L) to moderate (serum creatinine 300 – 700 µmol/L) renal impairment due to dependence on renal prostaglandins for maintenance of renal blood flow (see section 4.2). Treatment with XEFO should be discontinued if renal function deteriorates during treatment.
- Renal function should be monitored in patients:
    - who undergo major surgery
    - with cardiac failure
    - receiving concomitant treatment with diuretics or medicinal products that are suspected to, or known to be able to cause kidney damage (see section 4.5).
- Patients with blood coagulation disorders: careful clinical monitoring and laboratory assessment is recommended (e.g. APTT).

- Hepatic impairment (e.g. liver cirrhosis): clinical monitoring and laboratory assessments are recommended in patients with hepatic impairment, as accumulation of lornoxicam (increase in AUC) may occur (see section 5.2*)* after treatment with daily doses of 12-16 mg. Apart from that, hepatic impairment does not seem to affect pharmacokinetic parameters of lornoxicam as compared to healthy subjects.
- Patients receiving long term treatment (longer than 3 months): with NSAIDs should be monitored regularly for renal and hepatic function and haematology.
- In elderly patients above 65 years of age: monitoring of renal and hepatic function is recommended. Caution is advised in elderly postoperative patients.

Concomitant NSAID use

The use of lornoxicam with concomitant NSAIDs (including cyclooxygenase-2 selective inhibitors) should be avoided (see section 4.5).

Minimisation of undesirable effects

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 below).

Drug Reaction with Eosinophillia 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. Eosinophillia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue XEFO and evaluate the patient immediately

Gastrointestinal bleeding, ulceration and perforation

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

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, 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 (see section 4.2). Combination therapy with

gastroprotective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose acetylsalicylic acid or other medicinal products likely to increase gastrointestinal risk (see below and section 4.5). Clinical monitoring at regular intervals is recommended.

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

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

When GI bleeding or ulceration occurs in patients receiving XEFO, treatment should be withdrawn.

NSAIDs should be given with caution to patients with a history of GI disease (e.g. ulcerative colitis, Crohn's disease) as their condition may be exacerbated (see section 4.8).

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation, which may be fatal (see section 4.2).

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of or present hypertension and/or mild to moderate congestive heart failure, as fluid retention and oedema have been reported in association with NSAID 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 an increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for lornoxicam.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with Lornoxicam 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).

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).

Skin disorders

Serious skin reactions, some of which are fatal, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported very rarely in association with the use of NSAIDs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of reactions occurring within the first month of treatment in the majority of cases. Lornoxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Respiratory disorders

Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma as NSAIDs have been reported to precipitate bronchospasm in such patients.

Systemic Lupus Erythematosus and mixed connective tissue disease

Caution is required in patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders, as there may be an increased risk of aseptic meningitis.

Nephrotoxicity

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

Laboratory abnormalities

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

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

Fertility

The use of lornoxicam, as with any drug known to inhibit cyclooxygenase / prostaglandin synthesis, 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 lornoxicam should be considered (see section 4.6).

Pregnancy

The use of NSAIDs during pregnancy is associated with a risk of foetal renal dysfunction, leading to oligohydramnios and, in some cases, neonatal renal impairment.

Varicella

Exceptionally, varicella can be at the origin of serious cutaneous and soft tissues infectious complications.

To date, the contributing role of NSAIDs in the worsening of these infections cannot be ruled out. Thus, it is advisable to avoid use of lornoxicam in case of varicella.

4.5 Interaction with other medicinal products and other forms of interaction

- Concomitant administration of XEFO and anticoagulants or platelet aggregation inhibitors may prolong the bleeding time.
- Sulphonylureas (e.g. glibenclamide): May increase the hypoglycaemic effect.
- Other non-steroidal anti-inflammatory medicines and aspirin: increased risk of adverse reactions such as gastrointestinal bleeding or ulceration.
- Diuretics: Decreased diuretic and antihypertensive effect of loop diuretics, thiazide diuretics, and with potassium sparing diuretics (increased risk of hyperkalaemia and nephrotoxicity)
- ACE inhibitors: The antihypertensive effect of the ACE inhibitor may decrease and there is a risk of acute renal insufficiency.
- Lithium: NSAIDs inhibit renal clearance of lithium, thus the serum concentration of lithium may increase above toxicity limits. Therefore, serum lithium levels require monitoring, especially during initiation, adjustment and withdrawal of treatment.
- Methotrexate: Increased serum concentration of methotrexate. Increased toxicity may result. When concomitant therapy has to be used careful monitoring should be undertaken.
- Cimetidine: Increased plasma concentrations of lornoxicam, which may increase the risk of adverse effects of XEFO. (No interaction between XEFO and ranitidine, or XEFO and antacids has been demonstrated)
- Digoxin: Decreased renal clearance of digoxin, which increases risk of digoxin toxicity.
- Cyclosporin: Increased serum concentration of cyclosporin. Nephrotoxicity of cyclosporin 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).

- Anti-coagulants: XEFO may enhance the effects of anti-coagulants such as Warfarin (see section 4.4). Careful monitoring of INR should be undertaken.
- Antiplatelet agents (e.g. clopidogrel) and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding see section 4.4.
- Known inducers and inhibitors of CYP2C9 isoenzymes: Lornoxicam (as other NSAIDs depending on the cytochrome P450 2C9 [CYP2C9 isoenzyme]) has interactions with known inducers and inhibitors of CYP2C9 isoenzymes (see section 5.2. Biotransformation).
- Phenprocoumon: Decreased effect of phenprocoumon treatment.
- Heparin: NSAIDs increase the risk of bleeding and spinal or epidural haematomas when given concomitantly to heparin in the context of spinal or epidural anaesthesia (see section 4.4).
- Beta-adrenergic blockers: Decreased antihypertensive efficacy.
- Angiotensin II receptor blocker: Decreased antihypertensive efficacy
- Quinolone antibiotics (e.g. levofloxacin, ofloxacin): Increased risk of seizures.
- Tacrolimus: Increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. During combined treatment renal function should be monitored (see section 4.4).
- Pemetrexed: NSAIDs may reduce renal clearance of pemetrexed resulting in increased renal and gastrointestinal toxicity, and myelosuppression.

XEFO film-coated tablets show a delayed absorption of lornoxicam when given with food. Therefore, XEFO film-coated tablets should not be taken with food when a quick onset of efficacy (relief of pain) is required.

Food may decrease the absorption with about 20 % and increase T_{max} (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

XEFO should not be used during pregnancy.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or 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 embryo-foetal lethality.

The use of NSAIDs around 20 weeks gestation or later in pregnancy may cause a rare but serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis, in some cases (see section 4.3).

Breastfeeding

There are no data on the excretion of lornoxicam in human breast milk.

Lornoxicam is excreted in milk of lactating rats in relatively high concentrations.

Lornoxicam should not be used in breastfeeding women.

Fertility

The use of lornoxicam, as with any medicine known to inhibit cyclooxygenase / prostaglandin synthesis, 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 lornoxicam should be considered.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most commonly observed adverse events of NSAIDs 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. Less frequently, gastritis has been observed.

Approximately 20 % of patients treated with lornoxicam can be expected to experience adverse reactions. The most frequent adverse effects of lornoxicam 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 treatment.
Clinical trial and epidemiological data suggest that use of some NSAIDs (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).
Exceptionally, occurrence of serious cutaneous and soft tissues infectious complications during varicella.
NSAIDs, such as XEFO, can cause Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see Section 4.4)
Listed below in table 1 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.
The following convention is used for the classification of the frequency of an adverse drug reaction: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).
Table 1: Adverse effects

System organ class	Frequency	Adverse reaction(s)
Infections and infestations	Rare	Pharyngitis
Blood and lymphatic system disorders	Rare	Anaemia, thrombocytopenia, leucopenia, prolonged bleeding time
	Very rare	Ecchymosis. NSAIDs have been reported to cause potentially severe haematological disorders like neutropenia, agranulocytosis, aplastic anaemia, and haemolytic anaemia as class effects
Immune system disorders	Rare	Hypersensitivity including anaphylactoid reactions and anaphylaxis
Metabolism and nutrition	Uncommon	Anorexia, weight changes

System organ class	Frequency	Adverse reaction(s)
disorders		
Psychiatric disorders	Uncommon	Insomnia, depression
	Rare	Confusion, nervousness, agitation
Nervous system disorders	Common	Mild and transient headache, dizziness
	Rare	Somnolence, paraesthesia, dysgeusia, tremor, migraine
	Very rare	Aseptic meningitis in patients with SLE and mixed connective tissue disorder (see section 4.4)
Eye disorders	Common	Conjunctivitis
	Rare	Visual disturbances
Ear and labyrinth disorders	Uncommon	Vertigo, tinnitus
Cardiac disorders	Uncommon	Palpitations, tachycardia, oedema, cardiac failure (see section 4.4)
Vascular disorders	Uncommon	Flushing, oedema
	Rare	Hypertension, hot flush, haemorrhage, haematoma
Respiratory, thoracic and mediastinal disorders	Uncommon	Rhinitis
	Rare	Dyspnoea, cough, bronchospasm
Gastrointestinal disorders	Common	Nausea, abdominal pain, dyspepsia, diarrhoea, vomiting
	Uncommon	Constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, upper abdominal pain, duodenal ulcer, mouth ulceration
	Rare	Melaena, haematemesis, oesophagitis, gastro-oesophageal reflux, dysphagia, aphthous stomatitis, glossitis, perforated peptic ulcer, gastrointestinal haemorrhage

System organ class	Frequency	Adverse reaction(s)
Hepatobiliary disorders	Uncommon	Increase in liver function tests, SGPT (ALT) or SGOT (AST)
	Very rare	Hepatotoxicity resulting in e.g. hepatic failure, hepatitis, jaundice and cholestasis
Skin and subcutaneous tissue disorders	Uncommon	Rash, pruritus, hyperhidrosis, rash erythematous, urticaria, angioedema, alopecia
	Rare	Dermatitis, and eczema, 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
Renal and urinary disorders	Rare	Nocturia, micturition disorders, increase in blood urea nitrogen and creatinine levels
	Very rare	Lornoxicam may precipitate acute renal failure in patients with pre-existing renal impairment, who are dependent on renal prostaglandins for maintenance of renal blood flow (see section 4.4). Nephrotoxicity in various forms including nephritis and nephrotic syndrome has been associated with NSAIDs as class effect
General disorders and administration site conditions	Uncommon	Malaise, face oedema
	Rare	Asthenia

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 asked 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

At this time, there is no experience of overdose to permit definition of the consequence of an overdose, or to suggest specific management. However, it can be expected that after an overdose with lornoxicam, the following symptoms may be observed: nausea, vomiting, cerebral symptoms (dizziness, disturbances in vision). Severe symptoms such as ataxia (ascending to coma and cramps), liver and kidney damage and potentially coagulation disorders may also occur.

In the case of a real or suspected overdose, the medicinal product should be withdrawn. Due to its short half-life, lornoxicam is rapidly excreted. Lornoxicam is not dialysable. No specific antidote is known to date. The usual emergency measures should be considered. Based on principles, only administering activated charcoal immediately after the intake of lornoxicam can lead to diminished absorption of the preparation. Gastrointestinal disorders can for example be treated with a prostaglandin analogue or ranitidine.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC code: M01 AC05.

Mechanism of action

Lornoxicam is a non-steroidal anti-inflammatory drug with analgesic properties and belongs to the class of oxicams. Lornoxicams mode of action is mainly related to inhibition of prostaglandin synthesis (inhibition of the cyclo-oxygenase enzyme), leading to desensitisation of peripheral nociceptors and consequently inhibition of inflammation. A central effect on nociception, which seems to be independent of anti-inflammatory effects has also been suggested.

Pharmacodynamic effects

Lornoxicam has no effect on vital signs (e.g. body temperature, respiratory rate, heart rate, blood pressure, ECG, spirometry).

Clinical efficacy and safety

The analgesic properties of lornoxicam have been demonstrated successfully in several clinical trials during development of the drug.

Due to a local gastrointestinal irritation and a systemic ulcerogenic effect related to the inhibition of prostaglandin (PG)-synthesis, gastrointestinal sequela are common undesirable effects after treatment with lornoxicam as seen with other NSAIDs.

5.2 Pharmacokinetic properties

Absorption

Lornoxicam is absorbed rapidly and almost completely from the gastro-intestinal tract. Maximum plasma concentrations are achieved after approximately 1 to 2 hours. The absolute bioavailability (calculated using AUC) of XEFO film-coated tablets is 90 - 100 %. No first-pass effect was observed.

Simultaneous intake of lornoxicam with meals reduced C_{max} by approximately 30 %. T_{max} was increased from 1,5 to 2,3 hours. The absorption of lornoxicam (calculated on AUC) can be reduced by up to 20 %.

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. It is also found in synovial fluid after repeated dosing.

Biotransformation

Lornoxicam is extensively metabolised in the liver, primarily to the inactive 5-hydroxylornoxicam by hydroxylation. CYP2C9 is involved in biotransformation of lornoxicam. Due to genetic polymorphism, slow and extensive metabolisers exist for this enzyme, which could result in markedly, increased plasma levels of lornoxicam in slow metabolisers. 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.

When tested in animal models, lornoxicam did not induce liver enzymes. From clinical trial data there is no evidence of accumulation of lornoxicam after repeated administrations, when given according to recommended dosage. This finding was supported by drug monitoring data from one year studies.

Elimination

The mean elimination half-life of the parent compound is 3 to 4 hours.

After oral administration, about 50 % is excreted in the faeces and 42 % through the kidneys, mainly as 5-hydroxylornoxicam. The elimination half-life of 5-hydroxylornoxicam is approximately 9 hours after a parenteral single or twice daily dose. There is no evidence that elimination rate changes with repeat dose administration.

In elderly patients above age 65, the clearance is reduced by 30 to 40 %. Apart from this reduced clearance there is no significant change in the kinetic profile of lornoxicam in elderly patients.

There is no significant change in the kinetic profile of lornoxicam in patients with renal or hepatic failure, except for accumulation in patients with chronic liver disease after 7 days of treatment with daily doses of 12 and 16 mg.

Simultaneous intake with antacids has no effect on the pharmacokinetics of lornoxicam.

5.3 Preclinical safety data

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

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

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

In animals, administration of prostaglandin synthesis inhibitors 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Lactose monohydrate

Cellulose, microcrystalline

Povidone K 30

Croscarmellose sodium

Magnesium stearate

Film:

Macrogol 6 000

Titanium dioxide (E171)

Talc

Methylhydroxypropyl cellulose 5

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store at or below 25 ºC.

6.5 Nature and contents of container

XEFO 4 film-coated tablets: blister pack of opaque PVC foil with silver-coloured aluminium foil. Each blister strip contains 10 film-coated tablets.

XEFO 8 film-coated tablets: blister pack of opaque PVC foil with gold-coloured aluminium foil. Each blister strip contains 10 film-coated tablets.

Package sizes: packages with 20 and 100 film-coated tablets.

6.6 Special precautions for disposal

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

ACINO PHARMA (PTY) LTD.

106 16th Road

Midrand

1685

087 742 1860

8 REGISTRATION NUMBERS

XEFO 4: 33/3.1/0247

XEFO 8: 33/3.1/0248

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

XEFO 4: 29 October 1999

XEFO 8: 14 April 1998

10 DATE OF REVISION OF THE TEXT

13 February 2025