

SCHEDULING STATUS: S3

PROPRIETARY NAME (and dosage form):

XEFO[®] 4 Tablets

XEFO[®] 8 Tablets

COMPOSITION:

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

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

PHARMACOLOGICAL CLASSIFICATION:

A 3.1 Antirheumatics (anti-inflammatory agents)

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

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.

Pharmacokinetic properties:

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 on AUC) of XEFO film-coated tablets is 90-100%. No first-pass effect was observed. The mean elimination half-life is 3 to 4 hours.

Lornoxicam is found in the plasma in unchanged form and as its hydroxylated metabolite. The hydroxylated metabolite exhibits no pharmacological activity.

The plasma protein binding of lornoxicam is 99% and not concentration-dependent.

Lornoxicam is metabolized completely, and approximately 2/3 is eliminated via the liver and 1/3 via the kidneys as inactive substance.

Lornoxicam is metabolized by cytochrome P450 2C9. Due to genetic polymorphism slow and rapid metabolisers exist for this drug, which could result in markedly increased plasma levels of lornoxicam in slow metabolisers.

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 %.

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

In elderly subjects 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, or in patients with mild hepatic or kidney dysfunction.

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.

CONTRA-INDICATIONS:

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

- those allergic to lornoxicam, or any of its excipients
- those who have suffered hypersensitivity reactions (bronchospasm, 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
- those who are pregnant or lactating
- those under 18 years of age

WARNINGS:

In patients with the following disorders, XEFO should only be administered after careful risk-benefit assessment (see also Special precautions):

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

The risk of gastrointestinal bleeding or perforation is higher with increasing doses of XEFO in patients with a history of ulcers, and the elderly.

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

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

Previous cerebrovascular haemorrhage; SLE; porphyria; haematopoietic disorders; patients with reduced cardiac function. When treating patients with mild to moderate cardiac failure, attention must be paid to the risk of fluid retention and decreased renal function.

Caution 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.

Liver diseases (e.g. liver cirrhosis).

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. XEFO should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

DOSAGE AND DIRECTIONS FOR USE:

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

XEFO is not recommended for use in children under 18 years. No special dosage modification is required for elderly patients (> 65 years), unless renal or hepatic function is impaired, in which case the daily dosage should be restricted (see Special precautions).

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.

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.

Rheumatoid Arthritis and Osteoarthritis:

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

Dose reduction in special groups

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). For details see Special precautions.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

General: Headache, dizziness, somnolence, changes in appetite, increased sweating, loss of weight, oedema, allergic reactions, debility, weight increase.

Central nervous system (CNS): Depression, insomnia.

Eyes: Conjunctivitis, vision disorders.

Gastro-intestinal: The most commonly observed adverse events are gastrointestinal in nature. Abdominal pain, diarrhoea, dyspepsia, nausea, vomiting, flatulence, dysphagia, constipation, gastritis, dry mouth, ulcerative stomatitis, gastro-esophageal reflux, peptic ulceration, perforation or gastrointestinal bleeding, melaena, haematemesis, exacerbation of colitis and Crohn's disease, esophagitis, haemorrhoidal or rectal bleeding.

Haematological: Anemia, ecchymosis, prolonged bleeding time, thrombocytopenia.

Liver: Increased transaminases.

Musculo-skeletal: Cramps in leg, myalgia.

Neurological: Migraine, paraesthesia, taste perversion, tinnitus and tremor.

Respiratory: Dyspnoea, symptoms of irritation in upper respiratory tract.

Skin: Allergic skin reactions such as dermatitis, flushing and pruritus, loss of hair. Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Urogenital: Micturition disorders.

Cardiovascular: Palpitations, tachycardia, hypertension and cardiac failure.

Special precautions:

Gastro-intestinal ulceration and bleeding in medical history:

Clinical monitoring at regular intervals is recommended. Patients developing peptic ulceration and/or gastro-intestinal bleeding while taking XEFO should discontinue medicine administration with appropriate therapeutic actions being taken.

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.

Patients with coagulation disorders:

Careful clinical monitoring and laboratory assessment is recommended (e.g. PTT).

Liver diseases (e.g. liver cirrhosis):

Clinical monitoring and laboratory assessment at regular intervals is recommended (e.g. liver enzymes).

Long term treatment (longer than 3 months):

Regular laboratory assessments of haematology (haemoglobin), renal functions (creatinine) and liver enzymes is recommended.

Elderly patients (65 years or above):

There is no clinical experience with this dosage form in this patient group.

It is important to monitor renal function in patients:

- who are to undergo major surgery
- with compromised renal function e.g. as a result of significant blood loss or severe dehydration
- with cardiac failure
- receiving concomitant treatment with diuretics
- receiving concomitant treatment with medicines that are nephrotoxic

Interactions:

- Concomitant administration of XEFO and anticoagulants or platelet aggregation inhibitors may prolong the bleeding time.
- sulphonylureas : may increase the hypoglycaemic effect.
- other non-steroidal anti-inflammatory medicines and aspirin: increased risk of adverse reactions.
- diuretics: decreased efficacy of loop diuretic drugs; 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. 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 NSAIDs and methotrexate are administered within 24 hours.
- 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.
- cyclosporin: increased renal toxicity.
- Corticosteroids: increased risk of gastrointestinal ulceration or bleeding
- Anti-coagulants: XEFO may enhance the effects of anti-coagulants such as Warfarin.
- Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Overdose may cause nausea and vomiting, dizziness, ataxia, coma and cramps, liver and kidney damage, coagulation disorders.

In the case of a real or suspected overdose, the medication should be withdrawn. Treatment is symptomatic and supportive.

IDENTIFICATION:

XEFO 4: White to yellowish, oblong, film-coated tablet, with imprint "L04"

XEFO 8: White to yellowish, oblong, film-coated tablet, with imprint "L08"

PRESENTATION:

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.

STORAGE INSTRUCTIONS:

Store below 25 °C.

Keep out of reach of children.

REGISTRATION NUMBERS:

XEFO 4: 33/3.1/0247

XEFO 8: 33/3.1/0248

NAME AND BUSINESS ADDRESS OF THE APPLICANT:

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