

Xefo 8mg Tablets

Summary of product characteristics

1. Name of the medicinal product

XEFO 8 mg film coated tablets

2. Qualitative and quantitative composition

1 film-coated tablet contains 8 mg lornoxicam

Excipients: Lactose monohydrate 90 mg

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablets

White to yellowish oblong film coated tablets, with imprint "LO8"

4. Clinical particulars

4.1. Therapeutic indications

- Short term treatment of moderate pain such as pain after dental surgery
- Treatment of pain associated with acute lumbo-sciatica
- Symptomatic treatment of pain and inflammation in osteoarthritis and rheumatoid arthritis

4.2. Posology and method of administration

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

Pain

8-16 mg lornoxicam daily divided into 2 or 3 doses. Maximum recommended daily dose is 16 mg.

Osteoarthritis and Rheumatoid arthritis

Initial recommended dose is 12 mg lornoxicam daily divided into 2 or 3 doses. Maintenance dose should not exceed 16 mg lornoxicam daily.

Xefo film-coated tablets are supplied for oral use and should be taken with a sufficient quantity of liquid.

Additional information on special populations

Dosage for children and elderly patients:

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

No special dosage modification is required for elderly patients above age 65 unless renal or hepatic function is impaired. Lornoxicam should be administered with precaution 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 the maximum recommended daily dose is 12 mg divided in 2 or 3 doses (see section 4.4).

Hepatic impairment

For patients with moderate hepatic impairment the maximum recommended daily dose is 12 mg divided in 2 or 3 doses (see section 4.4).

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4.).

4.3 Contraindications

- Hypersensitivity to lornoxicam, or any of its excipients
- hypersensitivity (symptoms like asthma, rhinitis, angioedema or urticaria) to other non steroidal anti-inflammatory drugs, including acetylic salicylic acid.
- gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- active or history of recurrent peptic ulceration/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- severe hepatic impairment
- severe renal impairment (Serum creatinine > 700 µmol/L)
- thrombocytopenia
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- severe heart-failure
- The third trimester of pregnancy (see section 4.6)

4.4 Special warnings and special precautions for use

For the following disorders, lornoxicam should only be administered after careful risk-benefit assessment.

Renal impairment: Lornoxicam should be administered with precaution in patients with mild (serum creatinine 150-300 µmol/l) to moderate (serum creatinine 300 – 700 µmol/l) renal impairment due to dependency on renal prostaglandins for maintenance of renal blood flow. Treatment with lornoxicam should be discontinued if renal function deteriorates during treatment.

- Renal functions should be monitored in patients who undergo major surgery, with cardiac failure, receiving treatment with diuretics, receiving concomitant treatment with drugs that are suspected to or known to be able to cause kidney damage.
- Patients with blood coagulation disorders Careful clinical monitoring and laboratory assessment is recommended. (eg. APTT).
- 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 12-16 mg. Apart from that, hepatic impairment does not seem to affect pharmacokinetic parameters of lornoxicam as compared to healthy subjects.
- Long term treatment (longer than 3 months)
Regular laboratory assessments of haematology (haemoglobin), renal functions (creatinine) and liver enzymes is recommended.
- Elderly patients above 65 years: Monitoring of renal and hepatic function is recommended. Precaution is advised in elderly postoperative patients.

The use of lornoxicam 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 GI and cardiovascular risks below).

Gastrointestinal bleeding, ulceration and perforation: GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at anytime 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. Combination therapy with protective 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 active substances 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 when elderly, should 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 lornoxicam, the treatment should be withdrawn.

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

The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation which may be fatal (see section 4.3).

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 NSAID therapy.

Appropriate monitoring and advice are required for patients with a history of 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 a small 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).

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, 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 the reaction occurring in the majority of cases within the first month of treatment. Lornoxicam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis.

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

Concomitant treatment of NSAIDs 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.

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 lornoxicam should be stopped and appropriate investigations prescribed.

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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.

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 lornoxicam and

- Cimetidine: Increased plasma concentrations of lornoxicam. (No interaction between lornoxicam and ranitidine, or lornoxicam and antacids has been demonstrated).
- Anti-coagulants: NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4). Careful monitoring of INR should be undertaken
- 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.
- ACE inhibitors: The antihypertensive effect of the ACE inhibitor may decrease.
- Diuretics: Decreased diuretic and antihypertensive effect of loop diuretics, thiazide diuretics and potassium sparing diuretics
- Beta-adrenergic blockers: Decreased antihypertensive efficacy.
- Digoxin: Decreased renal clearance of digoxin.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Quinolone antibiotics: Increased risk of seizures.
- Anti-platelet agents: Increased risk of gastrointestinal bleeding (see section 4.4).
- Other NSAIDs: Increased risk of gastrointestinal bleeding.
- Methotrexate: Increased serum concentration of methotrexate. Increased toxicity may result. When concomitant therapy has to be used careful monitoring should be undertaken.
- Selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

- 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.
- 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.
- Sulphonylureas: Increased risk of hypoglycaemia.
- 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).
- Tacrolimus: Increase the risk of nephrotoxicity owing to reduced synthesis of prostacyclin in the kidney. During combined treatment renal function should be monitored.
- 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}.

4.6 Pregnancy and lactation

Pregnancy

Lornoxicam is contraindicated on 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 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 embryo-foetal lethality. During the first and second trimester of pregnancy, prostaglandin synthesis inhibitors should not be given unless clearly necessary.

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 lornoxicam is contraindicated during the third trimester of pregnancy (see section 4.3).

Lactation

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. Therefore lornoxicam should not be used in breastfeeding women.

4.7 Effects on ability to drive and use machines

Patients showing dizziness and/or sleepiness under treatment with lornoxicam should refrain from driving or operation 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 diarrhea. 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).

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 ($\geq 1/10$); Common ($\geq 1/100$, $< 1/10$); Uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10.000$, $< 1/1.000$); Very rare ($< 1/10.000$), not known (cannot be estimated from the available data)

Infections and infestations

Rare: Pharyngitis.

Blood and the lymphatic system disorders

Rare: Anaemia, thrombocytopenia, leucopenia, prolonged bleeding time

Very rare: Ecchymosis. NSAIDs have been reported to cause potentially severe hematological disorders like neutropenia, agranulocytosis, aplastic anaemia, and hemolytic anaemia as class effects..

Immune system disorders

Rare: Hypersensitivity, anaphylactoid reaction, anaphylaxis

Metabolism and nutrition disorders

Uncommon: Anorexia, weight changes.

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 4.4).

Eye 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.

Gastrointestinal disorders

Common: Nausea, abdominal pain, dyspepsia, diarrhoea, vomiting.

Uncommon: Constipation, flatulence, eructation, dry mouth, gastritis, gastric ulcer, abdominal pain upper, duodenal ulcer, mouth ulceration.

Rare: Melaena, haematemesis, stomatitis, oesophagitis, gastrooesophageal reflux, dysphagia, aphthous stomatitis, glossitis, perforated peptic ulcer, gastrointestinal hemorrhage.

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 and alopecia, dermatitis, ecchymoses.

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 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.

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 managements. However, it can be expected that after an overdose with Lornoxicam, the following symptoms can be seen, nausea and vomiting, cerebral symptoms (dizziness, , disturbances in vision). Severe symptoms are ataxia ascending to coma and cramps, liver and kidney damages and maybe coagulation disorders.

In the case of a real or suspected overdose, the medication 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 including gastric lavage 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: antiinflammatory and antirheumatic products, non-steroids, oxicams

ATC code: M 01 AC 05

Lornoxicam is a non steroidal anti-inflammatory drug with analgesic properties and belongs to the class of oxicams. Lornoxicam's mode of action is mainly related to the inhibition of the prostaglandin synthesis (inhibition of the cyclooxygenase 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.

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

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 gastrointestinal tract. Maximum plasma concentrations are achieved after approx. 1-2 hours. The absolute bioavailability of lornoxicam is 90-100%. No first-pass effect was observed. The mean elimination half-life is 3 to 4 hours.

Simultaneous intake of lornoxicam with meals reduced C_{max} by approx. 30%. T_{max} was increased from 1.5 to 2.3 hours. The absorption of lornoxicam (calculated on AUC) can be reduced 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.

Biotransformation

Lornoxicam is extensively metabolised in the liver, primarily to the inactive 5-hydroxylornoxicam by hydroxylation. CYP2C9 is involved in this 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 metabolized 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 1 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 about 9 hours after a parenteral single or twice daily dose.

In elderly patients above 65, the clearance is reduced with 30-40 %. 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.

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

Core: Magnesium stearate, povidone, croscarmellose sodium, microcrystalline cellulose, lactose monohydrate, Film: macrogol 6000, titanium dioxide, talc, hypromellose.

6.2 Incompatibilities

None known.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C, in the outer pack.

7. Manufacturer:

Takeda Pharma A/S Denmark
Dybendal Alle 10
DK-2630 Taastrup
Denmark

8. License Holder/Importer

CTS Ltd.
4 Haharash street, Hod Hasharon
ISRAEL