

SUMMARY OF PRODUCT CHARACTERISTICS

1.) TRADE NAME OF THE MEDICINAL PRODUCT

XEFO 8 mg film-coated tablets
M01AC05 (lornoxicam)

2.) QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet 8 mg contains: lornoxicam 8 mg.

3.) PHARMACEUTICAL FORM

Film-coated severable tablets 8 mg.

4.) CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of moderate to severe pain.

Symptomatic treatment of pain and inflammation associated with inflammatory and degenerative rheumatic diseases.

4.2 Posology and method of administration

Treatment of moderate to severe pain: an initial dose of 16 mg, followed by 8 mg up to a maximum dosage of 32 mg during the first 24 hours. Subsequent dosing should not exceed 16 mg per day.

Inflammatory and rheumatic diseases: The appropriate dosing regimen should be based upon each individual patient's response to treatment. The recommended daily dose is 8-16 mg, preferably given as 8 mg twice daily.

The use of the product is only for adult patients.

During therapy the patient should be followed in order to determine the individual optimal dose regimen. If necessary the daily dose should be divided into three doses.

The duration of treatment depends on the type and course of the illness. The maximum recommended dose for patients with gastrointestinal disorders and patients with renal or hepatic dysfunction is 8 mg/day.

XEFO should be taken with a sufficient quantity of liquid well before meals.

In the elderly, the posology should be carefully established by doctor who may take into account a dosage reduction.

4.3 Contra-indications

XEFO must not be administered in the following cases:

- Hypersensitivity to lornoxicam, acetylsalicylic acid or other non steroidal anti-inflammatory drugs;
- Hypersensitivity to other components of the product;
- Patients whom ASA or NSAID have been induced bronchial asthma, rhinitis, oedema of the nasal membranes, angioedema urticaria;
- Acute gastrointestinal bleeding;
- Acute gastric or duodenal ulcer;
- Blood dyscrasia of unknown aetiology, blood coagulation disorders and hemorrhagic diathesis;
- Hypovolemia and dehydration;
- Severely impaired renal or hepatic function;
- Real or suspected pregnancy, lactation, children (see section 4.6).

4.4. Special warnings and special precautions for use

Patients who suffer from chronic respiratory infections, bronchial asthma, swelling of the nasal mucous membranes or hay fever, are more likely to develop hypersensitivity reactions.

As with other NSAIDs, XEFO inhibits platelet aggregation and may therefore prolong the bleeding time. Patients in whom absolute hemostasis is a requirement or those who receive medications which inhibit hemostasis (including low dose heparin), should be closely monitored, due to the increased risk of hemorrhage with concomitant administration of lornoxicam. As with other NSAID's peptic ulceration and gastrointestinal bleeding may also occur with lornoxicam. In patients who develop gastrointestinal bleeding, or complication due to ulcers, treatment with lornoxicam must be discontinued immediately,

with appropriate therapeutic measures being taken. Special caution is also required for patients with gastrointestinal diseases receiving their first course of treatment with lornoxicam.

Patients with impaired renal function should receive lornoxicam only after the hypovolemia has been corrected. Like other NSAIDs, lornoxicam can cause an increase in the blood urea nitrogen or creatinine concentration, as well as increased water and sodium retention, oedema, hypertension, and other early signs of nephropathy; continued treatment with XEFO in these patients may lead to the following sequelae: glomerulonephritis, interstitial nephritis, papillary necrosis, nephrotic syndrome, acute renal decompensation.

In older patients and those with hypertension or obesity treated with XEFO it is necessary to carefully monitor the blood pressure. It is especially important to monitor the renal function in elderly patients and in patients with: -hepatic diseases, -cardiac failure, -concomitant treatment with diuretics, -concomitant treatment with drugs that are suspected to or known to be able to cause kidney damage; -in patients who are to undergo major surgery. In chronic treatment with XEFO, blood, liver and renal function should be monitored.

The use of XEFO, like of any prostaglandin synthesis or cyclooxygenase inhibitor, is not recommended in women planning pregnancy. The administration should be withdrawn in women with fertility problems or undergoing investigations on fertility.

4.5 Interaction with other medicaments and other forms of interaction

Due to the possibility of interactions a particular attention must be paid to the association of XEFO with the following drugs:

- Anticoagulants or platelet aggregation inhibitors (the bleeding risk increases)
- Sulphonylureas (the hypoglycaemic effect may be increased)
- Other non steroidal anti-inflammatory drugs (increased risk of adverse reactions)
- Diuretics (decreased diuretic and anti-hypertensive effect)
- Beta-blockers and ACE-inhibitors (the antihypertensive effect may decrease)
- Lithium (the serum concentration of lithium may increase above the toxicity limits)
- metotrexate (the serum concentration of metotrexate may increase)
- Cimetidine (higher plasma concentrations of Lornoxicam. (On the other hand, no interactions of XEFO with ranitidine nor with antacids were described)
- Digoxin (decreased renal clearance of digoxin).

4.6 Pregnancy and lactation

XEFO should not be administered during pregnancy nor in nursing mothers.

4.7 Effects on ability to drive and use machines

Patients showing dizziness and / or sleepiness under treatment with lornoxicam, should abstain to drive cars or operate dangerous machines.

4.8 Undesirable effects

Abdominal pain, diarrhoea, dizziness, dyspepsia, headache, nausea and vomiting may occur occasionally. During clinical trials the following adverse reaction were rarely observed: constipation, dysphagia, dry mouth, eructation, flatulence, gastritis, gastrooesophageal reflux, peptic ulceration and/or gastrointestinal bleeding, stomatitis, hemorrhoidal or rectal bleeding, oesophagitis, liver function abnormalities; alopecia, dermatitis, pruritus; increased sweating; micturition disorders; oedema; leg cramps, paraesthesia, tremor, migraine; conjunctivitis, vision disorder; tinnitus; taste perversion; allergic reactions; flushing, dyspnoea, rash; anaemia; thrombocytopenia, increased bleeding time, ecchymoses; symptoms of upper respiratory tract infection; blood pressure changes; palpitations, tachycardia; agitation; depression, insomnia, somnolence, alteration in appetite, inappetence; weight loss, weight gain, myalgia, malaise, weakness.

4.9 Overdose

In the case of a real or suspected overdose, the medication should be withdrawn. The measures to reduce the absorption of lornoxicam should be considered (e.g. the administration of active charcoal or cholestyramine). The usual emergency measures should include also gastric lavage. Due to its short half-

life, lornoxicam is rapidly excreted. Lornoxicam is not dialyzable. Gastrointestinal disorders can for example be treated with a prostaglandin analogue or ranitidine.

5.) PHARMACEUTICAL PROPERTIES

5.1) Pharmacodynamic properties

Lornoxicam is a non steroidal anti-inflammatory drug with marked analgesic properties and belongs to the class of oxicams. Lornoxicam mode of action is at least in part based on inhibition of the prostaglandin synthesis (inhibition of the cyclooxygenase enzyme). The inhibition of cyclooxygenase does not result in an increase in leukotriene formation. In addition, lornoxicam inhibits the release of oxygen radicals from active leukocytes.

The analgesic action of lornoxicam is not due to any narcotic effect. XEFO possesses no opiate-like central nervous system effect and, therefore, does not exhibit any respiratory-depressant, antipropulsive or miotic effects.

5.2) Pharmacokinetic properties

Lornoxicam is absorbed rapidly and almost completely from the gastrointestinal tract. Maximum plasma concentrations are achieved after approx. 1-2 hours. The absolute bioavailability (calculated on AUC) of XEFO tablets is 90-100%. No first-pass effect was observed. The mean elimination half-life is 3 to 4 hours; the plasma half-life is nearly unchanged in elderly patients or in patients with renal or hepatic -insufficiency. Lornoxicam is found in the plasma in unchanged form and to a minor extent as its hydroxylated metabolite. The hydroxylate metabolite exhibits no pharmacological activity. The plasma protein binding of lornoxicam -mainly to the albumine fraction- is 99% and not concentration dependent. Lornoxicam is metabolised completely, with approximately 1/3 eliminated via the kidneys and approximately 2/3 via the liver. When tested in animal models, XEFO did not induced liver enzymes. From clinical trial data there is no evidence of an accumulation of lornoxicam after repeated administrations, when given according to recommended dosage.

Concomitant intake of Lornoxicam with meals reduced C_{max} by approx. 30%, T_{max} was increased up to 2-3 hours, and the absorption of lornoxicam (calculate on AUC) is reduced up to 20%. Concomitant intake with antiacids has no effect on the pharmacokinetics of lornoxicam.

There is no significant change in the kinetic profile of XEFO in elderly patients as well in patients with renal or hepatic failure.

5.3) Preclinical safety data

Changes in the gastrointestinal tract and kidneys were observed in the repeated dose toxicity studies, as for all non steroidal anti-inflammatory drugs. Results from studies in primates demonstrated that doses like those utilised in humans therapy, are well tolerated even if administered for one year.

Studies on reproduction and development have been performed in both the rat and rabbit. Although no indication of a teratogenic potential has been found in reproductive studies performed with lornoxicam, due to the lack of clinical experience in humans lornoxicam is contraindicated in pregnancy.

6.) PHARMACEUTICAL PARTICULARS

6.1) List of excipients

Film-coated tablets 8 mg:
magnesium stearate, povidone K25, Carboxy-Methyl-Cellulose, microcrystalline cellulose, lactose, polyethylene glycol 6000, titanium dioxide (E171), talc, hydroxypropyl methylcellulose 2910.

6.2) Incompatibilities

None known.

6.3) Shelf life

5 years.

6.4) Special precautions for use

Protect from moisture.

6.5) Nature and contents of container

Blister PVC/PVDC/ aluminium

Package sizes: 30 film-coated tablets 8 mg

6.6) Instruction for use/handling

XEFO tablets have a breaking line on one side, which allows a simple subdivision into two parts by gently pressure on the side with the breaking line.

7. MARKETING AUTHORIZATION HOLDER

Dott. FORMENTI S.p.A.

License: NYCOMED Austria GmbH – Linz (Austria)

8.) MARKETING AUTHORIZATION NUMBER

Film-coated tablets: 30 severable 8 mg tablets -AIC: 029313032

9.) DATE OF FIRST AUTHORISATION

29.01.1997

10) DATE OF REVISION OF THE TEXT

4.01.2003