Summary of product characteristics

Xefo 8mg/2ml Injection

1. NAME OF THE MEDICINAL PRODUCT
XEFO 8 mg/2ml injection: powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One vial contains 8 mg lornoxicam.
After reconstitution in 2 ml solvent, reconstituted solution contains 4mg/ml of lornoxicam

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Powder and solvent for solution for injection.

Powder: Yellow solid substance.
Solvent: Clear, colourless liquid, practically free from particles.
The osmolarity of the reconstituted solution is about 328 mosmol/kg and pH is about 8.7

4. CLINICAL PARTICULARS

4.1.Therapeutic indications
- Short term treatment of moderate postoperative pain

4.2. Posology and method of administration
This specific application form should only be used if a quick onset of pain relief is needed or if an oral application or an application via suppository is not possible. Generally the treatment should comprise one single injection for therapy initiation only.
For all patients the appropriate dosing regimen should be based upon individual response to treatment.
Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4.).

Pain
Recommended dose: 8 mg intravenous (IV) or intramuscular (IM) injection. Daily dose should not exceed 16 mg. Some patients may need a further 8 mg given during the first 24 hours.

Special populations

Paediatric population
Lornoxicam is not recommended for use in children and adolescents below 18 years of age because of a lack of data on safety and efficacy.

Elderly
No special dosage modification is required for elderly patients above 65 years of age unless renal or hepatic function is impaired, but Lornoxicam should be administered with caution 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).
Lornoxicam is contraindicated in patients with severe renal impairment (see section 4.3).

Hepatic impairment
For patients with moderate hepatic impairment dose reduction should be considered (see section 4.4).
Lornoxicam is contraindicated in patients with severe hepatic impairment (see section 4.3).

Method of Administration

The medicinal product is for single use only.

The route of administration is IV or IM injection. 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, a sufficiently long needle for a deep intramuscular injection is necessary.

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

4.3. Contraindications

- Hypersensitivity to lornoxicam or to any of the excipients listed in section 6.1.
- Thrombocytopenia
- Hypersensitivity (symptoms like asthma, rhinitis, angioedema or urticaria) to other NSAIDs including acetylsalicylic acid
- Severe heart failure
- Gastro-intestinal bleeding, cerebrovascular bleeding or other bleeding disorders
- History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy
- Active or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding)
- Severe hepatic impairment
- Severe renal impairment (Serum creatinine > 700 µmol/L)
- The third trimester of pregnancy (see section 4.6)

4.4. Special warnings and special precautions for use

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

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

- Renal impairment: Lornoxicam 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 dependency on renal prostaglandins for maintenance of renal blood flow (see section 4.2). 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 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.
- 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).

Gastrointestinal bleeding, ulceration and perforation

Gastrointestinal (GI) 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 (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 medications 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 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 them 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.

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).

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.

Fetal Toxicity

Premature Closure of Fetal Ductus Arteriosus:
Avoid use of NSAIDs, including lornoxicam, in pregnant women at about 30 weeks gestation and later. NSAIDs, including lornoxicam, increase the risk of premature closure of the fetal ductus arteriosus at approximately this gestational age.

Oligohydramnios/Neonatal Renal Impairment:
Use of NSAIDs, including lornoxicam, at about 20 weeks gestation or later in pregnancy may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may, for example, include limb contractures and delayed lung maturation. In some postmarketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.
If NSAID treatment is necessary between about 20 weeks and 30 weeks gestation, limit lornoxicam use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if lornoxicam treatment extends beyond 48 hours. Discontinue lornoxicam if oligohydramnios occurs and follow up according to clinical practice [*see 4.6 Fertility, pregnancy and lactation*].

4.5 Interaction with other medicaments and other forms of interaction
Concomitant administration of lornoxicam and

- Cimetidine: Increased plasma concentrations of lornoxicam, which may increase the risk of adverse effects 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 haematomas when given concomitantly to heparin in the context of spinal or epidural anaesthesia (see section 4.4)
- ACE inhibitors: The antihypertensive effect of the ACE inhibitor may decrease.
- Diuretics: Decreased diuretic and antihypertensive effect of loop diuretics, thiazide diuretics, and with potassium sparing diuretics diuretics (increased risk of hyperkalaemia and nephrotoxicity)
- Beta-adrenergic blockers: Decreased antihypertensive efficacy.
- Angiotensin II receptor blocker: Decreased antihypertensive efficacy.
- Digoxin: Decreased renal clearance of digoxin, which increases risk of digoxin toxicity.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding (see section 4.4).
- Quinolone antibiotics (e.g. levofloxacin, ofloxacin): Increased risk of seizures.
- Anti-platelet agents (e.g. clopidogrel): Increased risk of bleeding (see section 4.4).
- Other NSAIDs: Increased risk of gastrointestinal bleeding or ulceration.
- 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 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 (e.g. glibenclamide): 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 (see section 4.4).
- Pemetrexed: NSAIDs may reduce renal clearance of pemetrexed resulting in increased renal and gastrointestinal toxicity, and myelosuppression.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary:
Use of NSAIDs, including lornoxicam, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of lornoxicam use between about 20 and 30 weeks of gestation, and avoid lornoxicam use at about 30 weeks of gestation and later in pregnancy (see Labor and Delivery - Clinical Considerations, Data).

Premature Closure of Fetal Ductus Arteriosus
Use of NSAIDs, including lornoxicam, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment
Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and 15-20% for pregnancy loss. Studies in animals have shown reproductive toxicity (see section 5.3). Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as lornoxicam, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

Labor and Delivery
Clinical Considerations:
Fetal/Neonatal Adverse Reactions
Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including lornoxicam, can cause premature closure of the fetal ductus arteriosus (*see Data*).

Oligohydramnios/Neonatal Renal Impairment
If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If lornoxicam treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue lornoxicam and follow up according to clinical practice (*see Data*).

Data:
Human Data
Premature Closure of Fetal Ductus Arteriosus:
Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.
Oligohydramnios/Neonatal Renal Impairment:
Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.
Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Breast-feeding
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.

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.

4.7. Effects on ability to drive and use machines

Patients showing dizziness and/or somnolence under treatment with lornoxicam should refrain from driving or 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.

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, <1/10); Uncommon (≥1/1000, <1/100); rare (≥1/10.000, <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 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 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

System organ class	Frequency	Adverse reaction(s)
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, stomatitis, oesophagitis, gastrooesophageal reflux, dysphagia, aphthous stomatitis, glossitis, perforated peptic ulcer, gastrointestinal haemorrhage
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, 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

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 may be observed: Nausea, vomiting, cerebral symptoms (dizziness, disturbances in vision). Severe symptoms are ataxia (ascending to coma and cramps), liver and kidney damages 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. 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 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.

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 8 mg powder for injection is intended for intravenous (IV) as well as intramuscular (IM) administration. After IM injection, maximum plasma concentrations are achieved after approximately 0.4 hours. The absolute bioavailability (calculated on AUC) after IM administration 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. 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 about 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 with 30-40%. Apart from 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 has caused renal toxicity and gastrointestinal ulceration in single- and repeat-dose toxicity studies in several species.

In rats, lornoxicam 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
Powder: Mannitol, trometamol, disodium edetate
Solvent: Water for injection

6.2. Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3. Shelf life
The expiry date of the product is indicated on the packaging materials.
Single use only.
Reconstituted solution: Chemical and physical in-use stability has been demonstrated for 24 hours at 21 °C (±2 °C).
From a microbiological point of view, the product should be used immediately.
If not used immediately, in-use storage times and conditions prior to use is the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage
Do not store above 25°C. Keep vial in the outer carton. Protect from light.
For storage conditions of the reconstituted medicinal product, see section 6.3

6.5. Nature and contents of container
Immediate packaging:
1 set contains:
Powder for injection: Amber glass vial with rubber stopper, sealed with aluminium snap-off closure
Water for injection: 2 ml clear glass ampoule
Pack Sizes: 1,5, 6 or 10 sets
Not all pack sizes may be marketed

6.6. Special precautions for disposal and other handling
The solution for injection is prepared by dissolving the content of one vial in water for injection from the accompanying ampoule, immediately prior to use. The appearance of the product after reconstitution is a yellow, clear liquid.

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. MANUFACTURER

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

8. LICENSE HOLDER AND IMPORTER:
CTS Ltd.
4 Haharash st., Hod Hasharon
ISRAEL

Revised in 05/2021 according to the MOHs guidelines