PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1 NAME OF THE MEDICINE

XEFO® RAPID 8 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 8 mg lornoxicam

For full list of excipients, see section 6.1

Sugar Free

3 PHARMACEUTICAL FORM

Film-coated tablets

White to slightly yellowish, round, biconvex film-coated tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Short term treatment of mild to moderate pain, where intra-muscular use is inappropriate (not exceeding 72 hours)

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.

Treatment of pain

XEFO® RAPID should be given in doses of 8 mg, and the daily dose should

in general not exceed 16 mg. In some patients a further 8 mg given within the first 24 hours could be needed. Use the lowest effective dose for the shortest possible duration of treatment.

Special populations

Elderly patients

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

Patients with renal or hepatic impairment

For patients with renal or hepatic impairment the dose frequency of **XEFO® RAPID** must be reduced to once daily. For details see section 4.4.

Paediatric population

XEFO® RAPID is not recommended for use in children under 18 years.

Method of administration

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

4.3 Contraindications

- Hypersensitivity to lornoxicam or to any of the excipients (see section 6.1)
- Hypersensitivity reactions (bronchospasm, rhinitis, angioedema or urticaria) to other non-steroidal anti-inflammatory medicines, including, acetylic salicylic acid
- History of gastro-intestinal bleeding or perforation related to previous NSAID use
- Hypovolaemia or dehydration
- Confirmed or suspected cerebrovascular bleeding
- Bleeding and coagulation disorders
- Active peptic ulcer or history of recurrent peptic ulceration/ haemorrhage/ perforations

- Severe liver impairment
- Severe renal impairment (serum creatinine > 700 µmol/l or creatinine clearance < 30 mL/min)
- Thrombocytopenia
- Heart failure
- The elderly (> 65 years)
- Body weight less than 50 kg
- 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
- Patients under 18 years of age

4.4 Special warnings and precautions for use

In patients with the following disorders, **XEFO® RAPID** should only be administered after careful risk-benefit assessment**.**

XEFO® RAPID 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; systemic lupus erythematosus; 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® RAPID** therapy.

Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as **XEFO® RAPID**. 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® RAPID** and evaluate the patient immediately.

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

Renal impairment

Caution is advised in patients with mild to moderate renal impairment. Reduction of dose of **XEFO® RAPID** to once daily in patients with mild to moderate renal impairment.

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® RAPID** must discontinue medicine administration with appropriate therapeutic actions being taken.

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 are recommended (e.g., liver enzymes).

Elderly patients (65 years or above)

The elderly has 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® RAPID** in patients with a history of ulcers, and the elderly. When gastrointestinal bleeding or ulceration occurs in patients receiving **XEFO® RAPID** , treatment with **XEFO® RAPID** should be stopped.

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.

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.

4.5 Interaction with other medicines and other forms of interaction

- Concomitant administration of **XEFO® RAPID** 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 medicines; NSAIDs counteract the diuretic effect of furosemide.
- ACE inhibitors and ARBs: 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 (see section 4.3).
- Cimetidine: higher plasma concentrations of lornoxicam. (No interaction between **XEFO® RAPID** and ranitidine, or **XEFO® RAPID** and antacids has been demonstrated).
- Digoxin: decreased renal clearance of digoxin.
- Ciclosporin: increased renal toxicity.
- Corticosteroids: increased risk of gastrointestinal ulceration or bleeding
- Anti-coagulants: **XEFO® RAPID** may enhance the effects of anti-coagulants such as Warfarin.
- Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.
- **XEFO® RAPID** has interactions with known inducers and inhibitors of CYP2C9 isoenzymes such as phenytoin, amiodarone, miconazole, tranylcypromine and rifampicin (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of **XEFO® RAPID** is contraindicated during pregnancy.

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

The use of **XEFO® RAPID** is contraindicated during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the safety profile

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.

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® RAPID**, can cause Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.4).

b. Tabulated summary of adverse reactions

Adverse reactions identified are listed, according to MedDRA System Organ Class and frequency categories. Frequencies are based on all grades and defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1000) very rare (< 1/10 000)

including spontaneous cases; not known.

System organ class	**Frequency**	**Adverse reactions**
Infections and infestations	Rare	Pharyngitis
Blood and lymphatic system disorders	Rare	Anaemia, thrombocytopenia, leucopenia, prolonged bleeding time
	Very rare	Ecchymosis
Immune system disorders	Rare	Hypersensitivity, anaphylactoid reaction 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 systemic lupus erythematosus and mixed connective tissue disorder
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, esophagitis,

		gastroesophageal reflux, dysphagia, aphthous stomatitis, glossitis, perforated peptic ulcer, gastrointestinal haemorrhage.
Hepatobiliary disorders	Uncommon	Increase in liver function tests, ALT or AST
	Rare	Hepatic function abnormal
	Very rare	Hepatocellular damage, hepatotoxicity resulting in e.g. hepatic failure, hepatitis, jaundice and cholestasis.
Skin and subcutaneous tissue disorders	Uncommon	Rash, pruritus, hyperhidrosis, rash erythematous, urticaria, alopecia, angioedema
	Rare	Dermatitis, 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 and creatinine levels.
	Very rare	Acute renal failure in patients with pre-existing renal impairment, who are dependent on renal prostaglandins for maintenance of renal blood flow. Nephrotoxicity in various forms including

		nephritis and nephrotic syndrome.
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 "6.04 Adverse Drug Reactions & Quality Problem Reporting Form", found online under SAHPRA's publications: https://sahpra.org.za/wp-content/uploads/2020/01/6.04_ARF1_v5.1_27Jan2020.pdf

4.9 Overdose

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 3.1 Antirheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, oxicams, ATC code: M01AC05

Lornoxicam is a non-steroidal anti-inflammatory drug (NSAID) 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.

5.2 Pharmacokinetic properties

Absorption

Lornoxicam is absorbed rapidly and almost completely from the gastro-intestinal tract.
Maximum plasma concentrations are achieved after approximately 30 minutes. The absolute bioavailability (calculated on AUC) of lornoxicam tablets 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 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.

Distribution

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.

Biotransformation and Elimination

Lornoxicam is metabolised completely, and approximately ⅔ is eliminated via the liver and ⅓ via the kidneys as inactive substance. Lornoxicam is metabolised by cytochrome P450 2C9.
Due to genetic polymorphism slow and rapid metabolisers exist for this medicine, which could result in markedly increased plasma levels of lornoxicam in slow metabolisers.
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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Calcium hydrogen phosphate anhydrous

Calcium stearate

Hydroxypropylcellulose

Low substituted hydroxypropylcellulose

Microcrystalline cellulose

Sodium hydrogen carbonate

Film coating

Hypromellose

Propylene glycol (E1520)

Talc

Titanium dioxide, (E 171/CI 77891)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 ºC.

6.5 Nature and contents of container

Alu/Alu blister pack. Each blister strip contains 10 film-coated tablets. The blister strips are packed in an outer cardboard box with 10, 20 or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Litha Pharma (Pty) Ltd

106 16th Road

Midrand

1686

8 REGISTRATION NUMBER

44/3.1/0331

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

01 December 2021

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