Summary of product characteristics

1. NAME OF THE MEDICINAL PRODUCT

LONOFLAM 8MG

2 Pharmaceutical Forms

Each film coated tablets contain,

Lornoxicam ……8mg

For full list of excipients see section 6.1

3. Pharmaceutical Form

Tablets

A Brown coloured round shape, film coated tablet bisected on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

short-term relief of acute mild to moderate pain
- Symptomatic relief of pain and inflammation in osteoarthritis
- Symptomatic relief of pain and inflammation in 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 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, but 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

4.3 Contraindications

- Hypersensitivity to lornoxicam or any of the excipients
- 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

4.4 Special warnings and 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 lornoxicamshould 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 (e.g. 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 are 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.

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, 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 drugs likely to increase gastrointestinal risk. 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 medications, which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or antiplatelet agents such as acetylsalicylic acid.
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.
The elderly have an increased frequency of adverse reactions to NSAIDs especially gastrointestinal bleeding and perforation, which may be fatal
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.
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. 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 occassional 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.
The use of lornoxicam, as with any drug known to inhibit cyclooxygenase/prostaglanding 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.

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.
- Angiotensin II receptor blocker: Decreased antihypertensive efficacy.
- Digoxin: Decreased renal clearance of digoxin.
- Corticosteroids: Increased risk of gastrointestinal ulceration or bleeding - Quinolone antibiotics: Increased risk of seizures.
- Anti-platelet agents: Increased risk of gastrointestinal bleeding - 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 - 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
- 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.

4.6 Fertility, 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

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

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 ofcolitis and Crohn's disease 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 mostfrequent adverse effects of lornoxicam include nausea, dyspepsia, indigestion, abdominal pain, vomiting, anddiarrhoea. 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 termtreatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction orstroke) (see section 4.4).

Exceptionally, occurrence of serious cutaneous and soft tissues infectious complications during varicella.

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 (1/10); Common (1/100, <1/10); Uncommon (1/1,000, <1/100); rare (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, leukopenia, 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 and anaphylaxis. Metabolism and nutritional 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: Conjuctivitis.

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 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 and angioedema, alopecia.
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 administrative 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 as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9 Overdose

At this time, there is no experience of overdose to permit definition of the consequence of an overdose, or to suggestspecific managements. However, it can be expected that after an overdose with lornoxicam, the following symptoms can be seen: Nausea, 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, lornoxicamis 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: Antiinflammatory and antirheumatic products, non-steroids, oxicams
ATC code: M01 AC05
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. 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 side 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 absolutebioavailability (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 bindingoflornoxicam 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 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 5hydroxylornoxicam. The elimination half-life of 5-hydroxylornoxicam is about 9 hours after a parenteral single or twice daily dose.
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 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 postimplantation 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: Lactose monohydrate
Cellulose
microcrystalline
Povidone K 30
Croscarmellose sodium
Magnesium stearate
Film: Macrogol
Titanium dioxide (E171)
Talc
Hypromellose

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
3 years

6.4 Special precautions for storage
Do not store above 30°C. Keep vial in the outer carton.

6.5 Nature and contents of container
10 Tablets in a ALU-ALU strip such 1 strip in one carton
6.6 Special precautions for disposal and other handling
Not applicbale
7 NAME OF THE MARKETING AUTHORIZATION HOLDER AND MANUFACTURER

KRISHNA CHEMISTS LTD

MANUFACTURED BY
DAGON PHARMACEUTICALS PVT. LTD
Baddi-Nalagarh Road, Village & Post: Manpura, Dist: Solan, Himachal Pradesh - 174 101, INDIA

8.MARKETING AUTHORIZATION NUMBER
CTD5973
9. DATE OF FIRST REGISTRATION/ RENEWAL
03/11/2021
10. DATE OF REVISION OF TEXT.

03/11/2021