SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tenoxicam 20mg Lyophilisate for Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 20mg tenoxicam as lyophilised sterile powder for reconstitution.

Tenoxicam is 4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno-[2, 3e]-1,2-thiazine-3-carboxamide-1, 1-dioxide, a non steroidal anti-inflammatory agent.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Vials for IV or IM administration.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Tenoxicam Lyophilisate is indicated for the relief of pain and inflammation in osteoarthritis and rheumatoid arthritis. It is also indicated for the short term management of acute musculoskeletal disorders including strains, sprains and other soft-tissue injuries. IV, IM tenoxicam can be used for these indications in those patients considered unable to take oral tenoxicam.

4.2 Posology and method of administration

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

Adults

Tenoxicam Lyophilisate should be given IV or IM. A single daily dose of 20mg for one to two days initially to be continued with the oral form, with administration at the same time each day. The lyophilisate should be dissolved in 2ml of sterile water for injections and the reconstituted solution should be used immediately.

Higher doses should be avoided as they do not usually achieve significantly greater therapeutic effect but may be associated with a higher risk of adverse events.

In acute musculoskeletal disorders treatment should not normally be required for more than 7 days, but in severe cases it may be continued up to a maximum of 14 days.

Elderly

As with other non-steroidal anti-inflammatory drugs, Tenoxicam Lyophilisate should be used with special caution in elderly patients. The elderly are at increased risk of the serious consequences of adverse reactions. They are also more likely to be receiving concomitant medication or to have impaired hepatic, renal or cardiovascular function. If an NSAID is considered necessary, the lowest effective dose should be used and for the shortest possible duration. The patient should be monitored regularly for GI bleeding during NSAID therapy.

Children

There are insufficient data to make a recommendation for administration of Tenoxicam Lyophilisate to children.

Use in renal and hepatic insufficiency

Creatinine clearance	**Dosage regimen**
Greater than 25ml/min	Usual dosage but monitor patients carefully (see *Special warnings and special precautions for use*)
Less than 25ml/min	Insufficient data to make dosage recommendations

Because of the high plasma protein-binding of tenoxicam, caution is required when plasma albumin concentrations are markedly reduced (e.g. in nephrotic syndrome) or when bilirubin concentrations are high.

There is insufficient information to make dosage recommendations for Tenoxicam Lyophilisate in patients with pre-existing hepatic impairment.

4.3 Contraindications

1. Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding), ulcerative colitis, Crohn's disease, severe gastritis, or history of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.
2. Hypersensitivity to tenoxicam or to any of the excipients. Tenoxicam Lyophilisate is also contraindicated in patients who have previously shown hypersensitivity reactions (symptoms of asthma, rhinitis, angioedema or urticaria) to other non-steroidal anti-inflammatory drugs, including ibuprofen and aspirin, as the potential exists for cross-sensitivity to tenoxicam.

3. Severe heart failure, hepatic failure and renal failure (see section 4.4).
4. Last trimester of pregnancy (see section 4.6).

4.4 Special warnings and precautions for use

The use of Tenoxicam Lyophilisate with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2, and GI and cardiovascular risks below).

Cardiovascular and cerebrovascular effects

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 tenoxicam.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with tenoxicam 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).

Cardiovascular, renal and hepatic impairment:

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at a greater risk of this reaction are those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

Occasional elevations of serum transaminases or other indicators of liver function have been reported. In most cases these have been small and transient increases above the normal range. If the abnormality is significant or persistent, Tenoxicam Lyophilisate should be stopped and follow-up tests carried out. Particular care is required in patients with pre-existing hepatic disease.

In rare cases, non-steroidal anti-inflammatory drugs may cause interstitial nephritis, glomerulonephritis, papillary necrosis and the nephrotic syndrome. Such agents inhibit the synthesis of renal prostaglandin which plays a supportive role in the maintenance of renal perfusion in patients whose renal blood flow and blood volume are decreased. In these patients, administration of a non-steroidal anti-inflammatory drug may precipitate overt renal decompensation, which returns to the pre treatment state upon withdrawal of the drug. Patients at greatest risk of such a reaction are those with pre-existing

renal disease (including diabetics with impaired renal function), nephrotic syndrome, volume depletion, hepatic disease, cardiac impairment and those patients receiving concomitant therapy with diuretics or potentially nephrotoxic drugs. Such patients should have their renal, hepatic and cardiac functions carefully monitored. The dose should be kept as low as possible in these patients. NSAIDs should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with ibuprofen administration.

Dermatological:

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 for 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. Tenoxicam Lyophilisate should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

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). Particular care should be taken to regularly monitor elderly patients to detect possible interactions with concomitant therapy and to review renal, hepatic and cardiovascular function which may be potentially influenced by non-steroidal anti-inflammatory drugs.

Impaired female fertility:

The use of Tenoxicam Lyophilisate may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of fertility, withdrawal of Tenoxicam Lyophilisate should be considered.

Gastrointestinal bleeding, ulceration and perforation:

NSAIDs should only be given with care to patients with a history of gastrointestinal disease. GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time 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 aspirin, or other drugs likely to increase gastrointestinal risk (see section 4.5).

Patients with a history of GI toxicity, particularly the 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 medication 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 aspirin (see section 4.5).

Any patient being treated with Tenoxicam Lyophilisate who presents with symptoms of gastrointestinal disease should be closely monitored. If peptic ulceration or gastro-intestinal bleeding occurs, Tenoxicam Lyophilisate should be withdrawn immediately.

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

Haematological effect:

Tenoxicam reduces platelet aggregation and may prolong bleeding time. This should be borne in mind for patients who undergo major surgery (e.g. joint replacement) and when bleeding time needs to be determined.

Opthalmic effect:

Adverse eye findings have been reported with non-steroidal anti-inflammatory drugs, therefore it is recommended that patients who develop visual disturbances during treatment with Tenoxicam Lyophilisate have ophthalmic evaluation.

Respiratory disorders:

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

SLE and mixed connective tissue disease:

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Anticoagulants: In healthy subjects no clinically relevant interaction between Tenoxicam Lyophilisate and low molecular weight heparin has been observed. Tenoxicam is highly bound to serum albumin, and can, as with all NSAIDs, enhance the anticoagulant effect of warfarin and other anticoagulants (see section 4.4). Close monitoring of the effects of anticoagulants and oral glycaemic agents is advised, especially during the initial stages of treatment with Tenoxicam Lyophilisate.

Antiplatelet agents and selective serotonin reuptake inhibitors (SSRIs): Increased risk of gastrointestinal bleeding (see section 4.4).

Antihypertensives: Tenoxicam and other NSAIDs can reduce the effects of anti-hypertensive drugs.

Cardiac glycosides: NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels when co-administered with cardiac glycosides.

Ciclosporin: As with all NSAIDs caution is advised when ciclosporin is co-administered because of the increased risk of nephrotoxicity.

Cimetidine: No interaction has been found with concomitantly administered cimetidine.

Corticosteroids: As with all NSAIDs, caution should be taken when co-administering corticosteroids because of the increased risk of GI ulceration or bleeding (see section 4.4).

Diuretics: Reduced diuretic effect. Non-steroidal anti-inflammatory drugs may cause sodium, potassium and fluid retention and may interfere with the natriuretic action of diuretic agents, which can increase the risk of nephrotoxicity of NSAIDs. These properties should be kept in mind when treating patients with compromised cardiac function or hypertension since they may be responsible for a worsening of those conditions.

Lithium: Non-steroidal anti-inflammatory drugs have been reported to decrease elimination of lithium. If tenoxicam is prescribed for a patient receiving lithium therapy, the frequency of lithium monitoring should be increased, the patient warned to maintain fluid intake and to be aware of symptoms of lithium intoxication.

Methotrexate: Caution is advised where methotrexate is given concurrently because of possible enhancement of its toxicity, since NSAIDs have been reported to decrease elimination of methotrexate.

Mifepristone: NSAIDs should not be used for 8 – 12 days after mifepristone administration as NSAIDs can reduce the effects of mifepristone.

NSAIDs, Cyclooxygenase-2 Selective Inhibitors, Salicylates: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of edverse effects (see section 4.4).

Salicylates can displace tenoxicam from protein-binding sites and so increase the clearance and volume of distribution of Tenoxicam Lyophilisate. Concurrent treatment with salicylates or other non-steroidal anti-inflammatory drugs should therefore be avoided because of the increased risk of adverse reactions (particularly gastro-intestinal).

Penicillamine and parenteral gold: No clinically relevant interaction was found in small numbers of patients receiving treatment with penicillamine or parenteral gold.

Quinolones: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and

haematoma in HIV positive haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

4.6 Fertility, pregnancy and lactation

Pregnancy:

The safety of Tenoxicam Lyophilisate during pregnancy and lactation has not been fully established and the drug should therefore not be given in these conditions.

Congenital abnormalities have been reported in association with NSAID administration in men; however, these are low in frequency and do not appear to follow any discernible pattern.

From the 20th week of pregnancy onward, Tenoxicam Lyophilisate use may cause oligohydramnios resulting from foetal renal dysfunction. This may occur shortly after treatment initiation and is usually reversible upon discontinuation. In addition, there have been reports of ductus arteriosus constriction following treatment in the second trimester, most of which resolved after treatment cessation. **Therefore, during the first and second trimester of pregnancy, Tenoxicam Lyophilisate should not be given.** If Tenoxicam Lyophilisate is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Tenoxicam Lyophilisate for several days from gestational week 20 onward. Tenoxicam Lyophilisate should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:
- Cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- Renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:
- Possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- Inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Tenoxicam Lyophilisate is contraindicated during the third trimester of pregnancy (see sections 4.3 and 5.3).

Lactation:

In the limited studies available so far, NSAIDs can appear in the breast milk in very low concentrations. NSAIDs should, if possible, be avoided when breastfeeding.

No information is available on penetration of Tenoxicam Lyophilisate into milk in humans; animal studies indicate that significant levels may be achieved.

Fertility:

See section 4.4 Special warnings and precautions for use, regarding female fertility.

4.7 Effects on ability to drive and use machines

Patients experiencing adverse events that may affect driving or using machines, such as vertigo, dizziness, drowsiness, fatigue or visual disturbances should refrain from driving or using machines.

4.8 Possible side effects

For most patients, any side-effects are transient and resolve without discontinuation of treatment. The most commonly observed adverse events are gastrointestinal in nature.

Cardiovascular and cerebrovascular: Oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment. Palpitations and dyspnoea have been reported rarely.

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).

Dermatological: Photosensitivity and bullous reactions including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (very rare) have been reported.

Eye disorders: Visual disturbances (such as visual impairment and blurred vision) have been reported with frequency unknown.

Gastrointestinal disorders: The most common side-effects relate to the gastro-intestinal tract. They include dyspepsia, nausea, vomiting, abdominal pain and discomfort, constipation, diarrhoea, flatulence, indigestion, epigastric distress, melaena, haematemesis, ulcerative stomatitis, anorexia, exacerbation of colitis and Crohn's disease (see section 4.4).

As with other non-steroidal anti-inflammatory drugs, there is a risk of peptic ulceration, perforation or gastro-intestinal bleeding, which may be fatal, particularly in the elderly (see section 4.4).

Less frequently, gastritis has been observed.

Pancreatitis has been reported very rare.

Haematological: Decreases in haemoglobin, unrelated to gastro-intestinal bleeding, have occurred. Anaemia, aplastic anaemia, haemolytic anaemia, thrombocytopenia and non-thrombocytopenic purpura, leucopenia, neutropenia and eosinophilia have been reported. Epistaxis has been reported infrequently. Rare cases of agranulocytosis have been reported.

Hepatic: Abnormal liver function. As with most other non-steroidal anti-inflammatory drugs, changes in various liver function parameters have been observed. Some patients may develop raised serum transaminase levels during treatment. Although such reactions are rare, if abnormal liver function tests persist or worsen, if clinical signs and symptoms consistent with liver disease

develop or if systemic manifestations occur (e.g. eosinophilia, rash), Tenoxicam Lyophilisate should be discontinued. Hepatitis and jaundice have also been reported.

Hypersensitivity: Hypersensitivity reactions have been reported following treatment with NSAIDs, these include:

a) Non specific allergic reactions and anaphylaxis

b) Respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea or

c) Assorted skin disorders; including rashes of various types. Angiodema, pruritus, and purpura have been reported. Nail disorders, alopecia, erythema, urticaria, and photosensitivity reactions have been reported rarely. As with other non-steroidal anti-inflammatory drugs, exfoliative and bullous dermatoses, including epidermal necrolysis, erythema multiforme and Stevens-Johnson syndrome. Vesiculo-bullous reactions and vasculitis have also been reported rarely.

Metabolism: Metabolic abnormalities, such as weight decrease or increase and hyperglycaemia, have occurred rarely.

Nervous system disorders: Malaise and tinnitus may occur.

Other less common reports include: Aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation, dizziness, malaise, fatigue and drowsiness.

Headache, insomnia, depression, nervousness, dream abnormalities, and vertigo have been reported rarely. Somnolence and paraesthesia have been reported with frequency unknown.

Psychiatric disorders: Confusional state and hallucinations have been reported with frequency unknown.

Renal: Nephrotoxicity has been reported in various forms, including interstitial nephritis, nephrotic syndrome and renal failure.

Reversible elevations of blood urea nitrogen and creatinine have been reported (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms: There is no reported experience of serious overdosage with Tenoxicam Lyophilisate. Symptoms of NSAID overdose include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

Therapeutic measure: Patients should be treated symptomatically as required. Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after a potentially toxic dose. Frequent or prolonged convulsions should be treated with intravenous diazepam. Administration of H2 antagonist drugs may be of benefit. Other measures may be indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Tenoxicam Lyophilisate is a non-steroidal anti-inflammatory drug which has marked anti-inflammatory and analgesic activity and some antipyretic activity. As with other non-steroidal anti-inflammatory drugs, the precise mode of action is unknown, though it is probably multifactorial, involving inhibition of prostaglandin biosynthesis and reduction of leucocyte accumulation at the inflammatory site.

5.2 Pharmacokinetic properties

Tenoxicam Lyophilisate is long-acting; a single daily dose is effective.

Tenoxicam penetrates well into synovial fluid to give concentrations approximately half those in plasma. The mean plasma elimination half-life is approximately 72 hours.

Following intravenous administration of 20mg tenoxicam, plasma levels of the drug decline rapidly during the first two hours mainly due to distribution processes. Following intramuscular injection levels at or above 90% of the maximally achieved concentrations are reached as early as 15 minutes after a dose.

With the recommended dosage regimen of 20mg once daily, steady-state plasma concentrations are reached within 10 – 15 days, with no unexpected accumulation.

Tenoxicam is strongly bound to plasma proteins.

Tenoxicam is cleared from the body almost exclusively by metabolism. Approximately two-thirds of the administered dose is excreted in the urine, mainly as the pharmacologically inactive 5-hydroxypyridyl metabolite, and the remainder in the bile, much of it as glucuronide conjugates of hydroxy-metabolites.

No age-specific changes in the pharmacokinetics of Tenoxicam have been found although inter-individual variation tends to be higher in elderly persons.

5.3 Preclinical Safety Data

None Stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, ascorbic acid, disodium edatate, sodium hydroxide, tromethamine and hydrochloric acid as a lyophilised powder for dissolving in solvent.

6.2 Incompatibilities

None known.

6.3 Shelf Life

3 years unopened.
24 hours after reconstitution.

6.4 Special precautions for storage

The pack should be stored at a temperature below 30ºC.

6.5 Nature and contents of container

Colourless 3 ml type I glass vial, with a bromobutyl rubber stopper and an aluminium tear-off cap.
Each vial contains 20 mg tenoxicam.
Each pack contains one vial.

6.6 Instruction for Use/Handling

Not Applicable.

7 MARKETING AUTHORISATION HOLDER

Essential Generics
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Egham, Surrey
TW20 8RN
United Kingdom

8. Marketing Authorisation Number

PL 17736/0088

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/10/2008

10 DATE OF REVISION OF THE TEXT

17/02/2026