

# **SUMMARY OF PRODUCT CHARACTERISTICS**

## **1 NAME OF THE MEDICINAL PRODUCT**

Tenoxicam 20mg Tablets

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains 20mg Tenoxicam.

Also contains lactose.

For a full list of excipients, see section 6.1.

## **3 PHARMACEUTICAL FORM**

Film-coated tablet.

Round, yellowish film-coated tablet.

## **4 CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Tenoxicam tablets are for the treatment of pain and inflammation in osteoarthritis and rheumatoid arthritis. It is also indicated for short term treatment of acute musculoskeletal disorders including strains, sprains and other soft-tissue injuries.

### **4.2 Posology and method of administration**

The tablets are for oral use and should be taken with water or other fluid, preferably with or after food.

Adults: The recommended dosage is a single daily dose of 20mg taken at the same time each day.

As there is no significantly greater therapeutic effect at higher doses, and higher doses may result in an increase of adverse events, oral doses greater than recommended should be avoided.

Tenoxicam 20 mg Tablets should only be used for up to a maximum of 2 weeks in cases of severe acute musculoskeletal disorders. Usually treatment of up to 7 days is sufficient.

Elderly: 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 for 4 weeks following initiation of NSAID therapy.

Children: Tenoxicam 20mg Tablets should not be used in children until sufficient data become available.

Use in renal and hepatic insufficiency:

<b>Creatinine clearance</b>	<b>Dosage regimen</b>
Greater than 25ml/min	Usual dosage but monitor patients carefully (see section 4.4)
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 are insufficient data to make dosage recommendations for Tenoxicam in patients with pre-existing hepatic impairment. (see 4.4 *Special warnings and special precautions for use*).

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

### **4.3 Contraindications**

Tenoxicam 20 mg Tablets are contra-indicated in:

- Severe heart failure, hepatic failure and renal failure (see section 4.4).
- Active, or history of recurrent peptic ulcer/haemorrhage (two or more distinct episodes of proven ulceration or bleeding).

- History of gastrointestinal bleeding (melaena, haematemesis) or perforation, related to previous NSAIDs therapy or severe gastritis.
- Patients with a known hypersensitivity to ibuprofen, aspirin or other non-steroidal anti-inflammatory drugs (symptoms of asthma, rhinitis, angioedema or urticaria).
- Previous known hypersensitivity to tenoxicam or any of the excipients contained in Tenoxicam 20 mg Tablets
- The last trimester of pregnancy (see section 4.6).

#### **4.4 Special warnings and precautions for use**

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).

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

Care should be taken to regularly monitor the patients to detect possible interactions with concomitant therapy and to review renal, hepatic and cardiovascular function which may be potentially influenced by NSAIDs.

##### *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). Debilitated patients seem to tolerate ulceration or bleeding less well than others. Most of the fatal gastrointestinal events associated with nonsteroidal anti-inflammatory drugs occurred in the elderly and/or debilitated patients.

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.

##### *Cardiovascular, Renal and Hepatic Impairment:*

In rare cases, NSAIDs 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. Administration of a NSAID in these patients 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, congestive cardiac failure and those patients receiving concomitant therapy with diuretics or potentially nephrotoxic drugs and the elderly. Such patients should have their renal, hepatic and cardiac functions carefully monitored (see also section 4.3), and the dose should be kept as low as possible in patients with renal, hepatic or cardiac impairment. NSAIDs should be given with care to patients with a history of heart failure or hypertension since oedema has been reported in association with NSAID administration.

*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.

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

*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).

*Gastrointestinal bleeding, ulceration and perforation:*

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 below and section 4.5).

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 anti-platelet agents such as aspirin (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Tenoxicam, the treatment should be withdrawn.

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

*SLE and mixed connective tissue disease:*

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

*Dermatological:*

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 should be advised of the signs and symptoms and monitored closely for skin reactions. 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 should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

If the patient has developed SJS or TEN with the use of tenoxicam, tenoxicam must not be re-started in this patient at any time.

*Impaired female fertility:*

The use of Tenoxicam 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 infertility, withdrawal of Tenoxicam should be considered.

*Platelet aggregation:*

Tenoxicam reduces platelet aggregation and may prolong bleeding time. Care is therefore required in patients undergoing major surgery (e.g. joint replacement) and in patients whose bleeding time needs to be determined.

*Ophthalmological Impairment:*

Minor and serious ocular effects have been reported rarely in patients taking NSAIDs; ophthalmic evaluation is recommended for patients who develop visual disturbances during treatment with Tenoxicam.

*Antipyretic effects*

As known for other anti-inflammatory drugs, Tenoxicam may mask the usual signs of infection.

*Renal impairment*

NSAIDs inhibit renal prostaglandin synthesis and consequently may have an undesirable effect on renal haemodynamics and on salt and water balance. It is necessary to adequately monitor the patient with a special emphasis on cardiac and renal function (BUN, creatinine, development of edema, weight gain, etc.) when giving Tenoxicam to patients with conditions that could increase their risk of developing renal failure, such as pre-existing renal disease, impaired renal function in diabetics, hepatic cirrhosis, congestive heart failure, volume depletion or concomitant treatment with potentially nephrotoxic drugs, diuretics and corticosteroids. This group of patients is at special risk in peri and post-operative phases of major surgery due to possibility of serious blood loss. They therefore require close monitoring in the post-operative and recovery periods.

Because of the high plasma protein binding of tenoxicam, caution is required when plasma albumin levels are markedly reduced.

*Tenoxicam tablets contain lactose*

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

#### ***Haematological effects***

Tenoxicam inhibits platelet aggregation and may affect haemostasis. Tenoxicam has no significant influence on blood coagulation factors, coagulation time, prothrombin time or activated thromboplastin time.

Patients having coagulation disorders or receiving drug therapy that interferes with haemostasis should, however, be carefully observed when Tenoxicam is administered.

### **4.5 Interaction with other medicinal products and other forms of interaction**

#### ***Antacids and H<sub>2</sub>-receptor antagonists***

Antacids may reduce the rate, but not the extent, of absorption of tenoxicam. The differences are not likely to be of clinical significance.

No interaction has been found with concomitantly administered cimetidine.

No clinically relevant interaction between tenoxicam and low molecular weight heparin has been observed in healthy subjects.

Care should be taken in patients treated with any of the following drugs as interactions have been reported in some patients.

#### ***Anti-hypertensives***

As known from other NSAIDs, Tenoxicam might attenuate the antihypertensive effects of alpha-adrenergic blockers beta-adrenergic blockers and ACE inhibitors. There was no clinically relevant interaction when Tenoxicam was administered together with atenolol.

#### ***Cardiac glycosides:***

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma glycoside levels when co-administered with cardiac glycosides. During clinical trials no interaction was reported for patients treated concomitantly with digitalis products. Thus concurrent dosing of Tenoxicam and digoxin appears to be without major risk.

#### ***Diuretics:***

NSAIDs 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. This 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.

No clinically significant interaction between Tenoxicam and furosemide was noted, but Tenoxicam attenuates the blood pressure lowering effect of hydrochlorothiazide.

***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

***Ciclosporin:***

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

***Mifepristone:***

NSAIDs should not be used for 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

***Other analgesics including cyclooxygenase-2 selective inhibitors:***

Avoid concomitant use of two or more NSAIDs (including aspirin) due to increased risk of adverse effects (see section 4.4).

***Acetylsalicylate and Salicylates:***

Salicylates can displace tenoxicam from protein-binding sites and so increase the clearance and volume of distribution of tenoxicam. Concomitant treatment should therefore be avoided because of the increased risk of adverse reactions (particularly gastro-intestinal).

***Corticosteroids:***

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

***Anti-coagulants:***

As tenoxicam is highly bound to serum albumin it can 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. No interaction with digoxin has been observed. In healthy subjects no clinically relevant interaction between tenoxicam and low molecular weight heparin has been observed.

***Quinolone antibiotics:***

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.

***Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs):***

There is an increased risk of gastrointestinal bleeding (see section 4.4) when anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) are combined with NSAIDs.

***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 (+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

***Oral Antidiabetics:***

The clinical effect of the oral antidiabetic drugs glibornuride, glibenclamide, tolbutamide, was likewise not modified by Tenoxicam. Nevertheless, as for other NSAIDs, careful monitoring is recommended when patients concomitantly receive oral antidiabetic drugs.

***Colestyramine:***

Colestyramine may increase the clearance and reduce the half-life of tenoxicam.

***Dextromethorphan:***

The concomitant administration of tenoxicam and dextromethorphan may increase the analgesic effect compared to monotherapy.

***Food***

The extent of absorption of tenoxicam is not influenced by food, but the rate of absorption ( $C_{max}$ ) may be slower than in fasting state.

***Gold/penicillamine:***

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

*Others:*

Co-administration of probenecid and tenoxicam treatment may increase plasma concentration of tenoxicam. The clinical significance of this observation has not been established.

#### **4.6 Fertility, pregnancy and lactation**

*Fertility:*

The use of tenoxicam, 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 difficulty conceiving or are undergoing investigation of infertility, withdrawal of tenoxicam should be considered. (See section 4.4).

*Pregnancy:*

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 and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1%, up to approximately 1.5%.

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.

In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period. From the 20th week of pregnancy onward, Tenoxicam 20mg Tablets 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 should not be given unless clearly necessary. If tenoxicam 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 20mg Tablets for several days from gestational week 20 onward. Tenoxicam 20mg Tablets 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 (with premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above), which may progress to renal failure with oligo-hydramnios;

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 low doses.
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, tenoxicam is contraindicated during the third trimester of pregnancy (see section 4.3 and 5.3).

#### *Lactation:*

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

Based on findings from single dose administration, a very small amount (mean value less than 0.3% of the dose) of tenoxicam passes into breast milk (see section 5.2 Pharmacokinetic properties). There is no evidence of adverse reactions in breast-fed infants of mothers taking Tenoxicam. Nevertheless, infants should be weaned or the drug discontinued.

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

## **4.7 Effects on ability to drive and use machines**

Dizziness, vertigo, drowsiness, visual disturbances or headaches are possible undesirable effects after taking NSAIDs, if affected, patients should not drive or operate machinery.

## **4.8 Undesirable effects**

Usually, the undesirable effects reported were mild and transient. In a small proportion of patients the interruption of treatment due to undesirable effects was necessary.

The most commonly observed adverse events 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, constipation, indigestion, flatulence, dyspepsia, abdominal pain and discomfort, melaena, epigastric distress, haematemesis, stomatitis, ulcerative stomatitis, anorexia, exacerbation of colitis and Crohn's disease (see section 4.4) have been reported following administration. Less frequently, gastritis has been observed. Should any of these be reported during treatment, Tenoxicam should be stopped immediately and appropriate treatment instituted.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Not known (cannot be estimated from the available data)

#### *Blood and lymphatic disorders*

Not known: agranulocytosis, anaemia, aplastic anaemia, haemolytic anaemia, leukopenia, thrombocytopenia, non-thrombocytopenic purpura, eosinophilia. Decreases in haemoglobin, unrelated to gastro-intestinal bleeding, have occurred.

#### *Immune system disorders*

Not known: hypersensitivity reactions such as asthma, anaphylactic reactions, angioedema

#### *Metabolism and nutrition disorders*

Uncommon: Decreased appetite

Rare: Metabolic abnormalities (like: hyperglycaemia, weight increased/decreased)

#### *Psychiatric disorders*

Uncommon: sleep disorder (e.g. insomnia),

Rare: depression, nervousness, dream abnormalities, mental confusion, paraesthesia.

Not known: confusional state, hallucinations

#### *Nervous system disorders*

Common: dizziness, headache

Not known: Somnolence, paraesthesia

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 (see section 4.4), depression, nervousness, confusional state, hallucinations, dream abnormalities, insomnia, tinnitus, vertigo, dizziness, malaise, fatigue and drowsiness, have been reported

#### *Eye disorders*

Not known: visual disturbances (such as visual impairment and vision blurred), swollen eyes, eye irritation, optic neuritis.

No evidence of ocular changes has been revealed by ophthalmoscopy and slit-lamp examination.

#### *Ear and labyrinth disorders*

Uncommon: vertigo

Not known: tinnitus

#### *Cardiac disorders*

Uncommon: palpitations

Not known: cardiac failure

The possibility of precipitating congestive cardiac failure in elderly patients or those with compromised cardiac function should therefore be borne in mind.

#### *Vascular disorders*

Rare: Thrombotic events (e.g. myocardial infarction or stroke)

Not known: vasculitis, hypertension

Clinical trial and epidemiological data suggest that use of selective Cyclooxygenase 2 inhibitors (COX2 inhibitors) and 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) (see section 4.4). Although tenoxicam has not shown to increase thrombotic events such as myocardial infarction, there are insufficient data to exclude such a risk with tenoxicam.

#### *Respiratory, thoracic and mediastinal disorders*

Rare: bronchospasm, aggravated asthma, dyspnoea

Not known: epistaxis

Bronchospasm and aggravated asthma have been reported following treatment with NSAIDs.

#### *Gastrointestinal disorders*

Very common: stomatitis

Common: gastric, epigastric and abdominal pain and discomfort, dyspepsia, nausea, peptic ulcer, sometimes fatal, particularly in the elderly

Uncommon: gastrointestinal haemorrhage (including haematemesis and melaena), gastrointestinal ulcers, constipation, diarrhoea, vomiting, mouth ulceration, gastritis, dry mouth

Very rare: pancreatitis

Not known: Gastrointestinal perforation, exacerbation of colitis and Crohn's disease, flatulence

#### *Hepatobiliary disorders*

Uncommon: increased hepatic enzymes

Not known: hepatitis, jaundice

#### *Skin and subcutaneous tissue disorders*

Uncommon: pruritus, erythema, exanthema, rash, urticaria

Rare: vesiculo-bullous reactions.

Very rare: Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome, toxic epidermal necrolysis (see section 4.4)

Not known: photosensitivity reaction.

Nail disorders and, photosensitivity reaction, alopecia, erythema, purpura and more rarely exfoliative, angioedema and, less commonly, bullous dermatoses (including epidermal necrolysis and erythema multiforme) have been reported rarely following treatment with NSAIDs.

#### *Renal and urinary disorders*

Uncommon: increased blood urea or creatinine

Not known: nephrotoxicity (e.g. renal failure, interstitial nephritis, nephrotic syndrome).

#### *Reproductive system and breast disorders*

Not known: Female infertility\*

\*Isolated cases of female infertility have been reported with drugs known to inhibit cyclooxygenase/prostaglandin synthesis including tenoxicam.

#### *General disorders and administration site conditions*

Uncommon: fatigue, oedema

Not known: Malaise

### **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](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

#### **4.9 Overdose**

##### **a) Symptoms**

In general, patients with an NSAID overdose are asymptomatic. NSAID overdose causes only minor CNS or gastrointestinal disturbances. Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, dizziness, tinnitus, fainting, occasionally convulsions. There have been isolated reports of more serious toxicity after ingestion of substantial quantities; they include seizures, excitation, drowsiness, coma electrolyte imbalance and renal failure, and cardiorespiratory arrest may occur.

Hepatic dysfunction, acute renal failure, hypoprothrombinemia and metabolic acidosis are also reported. Exacerbation of asthma is a possible effect.

##### **b) Therapeutic measure**

Patients should be treated symptomatically as required. In case of overdose appropriate supportive treatment is indicated and discontinuation of the drug, antacids and proton-pump inhibitors may be indicated.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. There are no specific antidotes. Dialysis does not significantly clear NSAIDs from the blood stream. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured - maintain adequate hydration.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by patient's clinical condition.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic Properties**

Antirheumatic, anti-inflammatory and analgesic agent

ATC code: M01AC02

#### *Mechanism of action*

Tenoxicam is a non-steroidal anti-inflammatory drug. It has anti-inflammatory, analgesic, and antipyretic effects and it also inhibits platelet aggregation. Tenoxicam reduces prostaglandin biosynthesis by inhibition of cyclooxygenase 1 (COX1) and 2 (COX2), both in vitro (sheep seminal vesicles) and in vivo (protection of arachidonic acid-induced toxicity in mice).

In-vitro investigation on cyclo-oxygenase isoenzymes prepared from human COS-7 cells have shown that tenoxicam inhibits COX-1 and COX-2 isoenzymes approximately to the same extent, i.e. COX-2/COX-1 ratio equals to 1.34.

In-vitro tests of leukocyte peroxidase suggest that tenoxicam may act as a scavenger for active oxygen at the site of inflammation.

Tenoxicam is a potent in-vitro inhibitor of human metalloproteinases (stromelysin and collagenase) which induce cartilage breakdown.

A further possible mechanism of action is the reduction of nitrite levels indicating an alteration of NO pathways.

These pharmacological effects explain, at least in part, the therapeutic benefit of Tenoxicam in the treatment of painful inflammatory and degenerative disorders of the musculoskeletal system.

#### Clinical / Efficacy Studies

The clinical efficacy of tenoxicam is proven in clinical studies for:

Rheumatoid arthritis: It was shown that a dose of 20 or 40 mg once daily was effective and the effect was maintained for up to two years.

Osteoarthritis: Tenoxicam is effective in the treatment of osteoarthritis. Anti-inflammatory and analgesic effects have been maintained for up to three years.

Extra-articular disorders: Tenoxicam (20 mg once daily) was at least as effective as piroxicam (20 mg daily) and diclofenac (75 mg daily). Tenoxicam was better tolerated than diclofenac.

## **5.2 Pharmacokinetic properties**

### *Absorption*

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

Following oral administration, tenoxicam is rapidly and completely absorbed as unchanged drug from the gastrointestinal tract. Concurrent administration of food reduces the rate but not the extent of absorption of tenoxicam. Tenoxicam does not undergo any pre-systemic metabolism. The bioavailability of the drug is essentially 100%.

Tenoxicam is distributed rapidly throughout the body. It is highly bound to plasma proteins, primarily to albumin. Peak concentrations of tenoxicam in synovial fluid are approximately half those in plasma. The mean plasma elimination half-life is approximately 72 hours.

With the recommended dosage regimen of 20mg once daily, steady-state plasma concentrations are reached within 10 - 15 days, with no unexpected accumulation. The average concentration at steady state is 11 mg/L when tenoxicam is given at oral doses of 20 mg once daily and this does not change even on treatment for up to four years.

The pharmacokinetics of tenoxicam are linear in the investigated dose range of 10 to 100 mg.

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

### *Distribution*

During the first two hours following intravenous administration of tenoxicam, plasma levels of the drug decline rapidly.

After this short period, no differences in plasma concentrations between intravenous and oral dosing are seen. The mean volume of distribution at steady state is 10 to 12 L.

In the blood over 99% of the drug is bound to albumin. Tenoxicam penetrates well into the synovial fluid. Peak concentrations are reached later than in plasma.

### *Metabolism and elimination*

Tenoxicam is cleared from the body almost exclusively by metabolism. Tenoxicam is eliminated slowly from the plasma, the mean plasma elimination half-life in healthy volunteers is approximately 67 hours and 40-52 hours in rheumatic patients. Elimination is almost entirely by metabolism in the liver. The majority of an oral dose (67%) is excreted in the urine mainly as the pharmacologically inactive metabolite, 5-hydroxytenoxicam, and the

remainder in the bile much of it as glucuronide conjugates of hydroxy-metabolites. Less than 1% of the administered dose is recovered in the urine in form of the parent drug. The mean elimination half-life of tenoxicam is 72 hours (range 59 to 74 hours). The total plasma clearance is 2 mL/min.

#### *Special Populations*

Studies in the elderly and in patients with renal insufficiency or liver cirrhosis suggest that no dose adjustment is necessary to achieve plasma concentrations similar to those seen in healthy subjects.

Patients with rheumatic diseases and the elderly show the same kinetics profile as healthy volunteers.

Because of the high plasma protein binding of tenoxicam, caution is required when plasma albumin levels are markedly reduced.

### **5.3 Preclinical Safety Data**

#### *Carcinogenicity*

Tenoxicam showed no carcinogenic effects in animals.

#### *Mutagenicity*

Tenoxicam showed no mutagenic effects in animals.

#### *Impairment of fertility*

See section 4.6

#### *Teratogenicity*

Tenoxicam showed no teratogenic effects in rats.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Lactose  
Maize starch  
Pregelatinised starch  
Magnesium stearate  
Talc  
Colloidal silicon dioxide  
Hypromellose  
Titanium dioxide (E171)  
Iron oxide yellow (E172)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

60 months

**6.4 Special precautions for storage**

Do not store above 25°C.

**6.5 Nature and contents of container**

PVC/PVdC / Al/PVdC blisters in carton boxes of 28.

**6.6 Special precautions for disposal**

Not applicable.

**7. MARKETING AUTHORISATION HOLDER**

Ennogen Healthcare Ltd  
Unit G4, Riverside Industrial Estate,  
Riverside Way,  
Dartford, DA1 5BS, UK.

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 40739/0255

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