SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT

TILCOTIL 20 mg/2 mL vial containing lyophilized powder for IM/IV injection
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Each vial contains:

Tenoxicam ..... 20 mg

The diluted TILCOTIL injection solution contains 10 mg/mL tenoxicam.

Excipients:

Disodium edetate ..... 0.22 mg

Sodium hydroxide (10% solution) ... 3.68 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Vial containing lyophilized powder

Green-yellow colored, free from foreign particles lyophilized cake mass

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TILCOTIL is effective in the treatment of symptoms and signs of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, as well as acute gouty arthritis, acute musculoskeletal pain, postoperative pain, and dysmenorrhea.

4.2 Posology and method of administration

Dosage/administration frequency and duration:

To control symptoms, the lowest effective dose should be used for the shortest possible duration to minimize adverse effects (see Section 4.4).

For all indications except acute gout and postoperative pain, a single daily dose of 20 mg should be administered at the same time each day.

The recommended dose for postoperative pain is 40 mg daily for 5 days, and the recommended dose for acute gout attacks is 40 mg once daily for 2 days followed by 20 mg daily for the next 5 days.

In the treatment of chronic diseases, the therapeutic efficacy of TILCOTIL is evident at the start of treatment, and the response obtained increases over time. In chronic disorders, the daily dose

should not exceed 20 mg. Otherwise, the frequency and severity of adverse effects will increase without a significant increase in therapeutic efficacy.

In cases requiring long-term treatment, the daily dose may be reduced to 10 mg orally for maintenance therapy.

Method of administration:
The lyophilized powder in the vial should be dissolved with the 2 mL of sterile water for injection provided with the medicinal product. The prepared solution should be administered immediately by intramuscular (IM) or IV bolus injection.

When necessary, treatment should be started with one or two days of once-daily IV or IM administration, followed by continued administration of TILCOTIL orally or rectally.

The lyophilized powder for injection is developed for IM and IV bolus administration; its use as an infusion is not recommended due to the possibility of precipitation.

Additional information for specific populations:
Renal impairment:
The dosage recommendations above can be applied to patients with kidney disease. However, when TILCOTIL is used in patients with renal impairment, careful monitoring of kidney function is recommended. It should not be used in patients with severe renal impairment.

Liver impairment:
The dosage recommendations listed above may be applied to patients with liver disease. However, when TILCOTIL is used in patients with liver failure, careful monitoring of liver function is recommended. It should not be used in patients with severe liver failure.

Pediatric population:
Due to lack of clinical experience, no dosage recommendations can be made for adolescents and children. It should not be used in this age group.

Geriatric population:
The risk of gastrointestinal bleeding, ulceration, or perforation is higher in elderly patients and may lead to fatal outcomes. Treatment should be initiated at the lowest dose in these patients, and combination therapy with protective agents (e.g., misoprostol or proton pump inhibitors) should be considered for patients receiving concomitant low-dose salicylates or other drugs that increase gastrointestinal risk (see Section 4.4).

4.3 Contraindications

TILCOTIL is contraindicated for perioperative pain management in patients

undergoing coronary artery bypass graft (CABG) surgery (see Section 4.4).

- In patients with known hypersensitivity to tenoxicam or any of the excipients in TILCOTIL,
- Patients in whom salicylates or other non-steroidal anti-inflammatory drugs (NSAIDs) are known to cause symptoms such as asthma, rhinitis, or urticaria,
- In patients who have experienced gastrointestinal bleeding or perforation associated with previous NSAID therapy or who have these conditions (see Section 4.4),
- Patients with recurrent peptic ulcer or bleeding, or who have experienced such conditions (two or more distinct episodes of proven ulcer or bleeding) (see Section 4.4),
- In patients with severe heart failure, renal, or hepatic insufficiency, as with other NSAIDs,
- TILCOTIL is contraindicated during the last 3 months of pregnancy.

4.4 Special warnings and precautions for use

Cardiovascular risk
NSAIDs may cause potentially fatal increases in the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. This risk may increase with duration of use. This risk is highest in patients with cardiovascular disease or risk factors for cardiovascular disease.

Gastrointestinal risk
NSAIDs may cause an increase in the risk of serious gastrointestinal adverse effects, such as bleeding, ulceration, and stomach or intestinal perforation, which can be fatal. These effects can occur at any time during use, without warning symptoms. The elderly are the group at greatest risk for serious gastrointestinal effects.

Since tenoxicam binds to plasma proteins to a high degree, caution should be exercised and precautions taken when plasma albumin levels are significantly reduced.

The simultaneous use of tenoxicam with NSAIDs, including cyclooxygenase-2 (COX-2) selective inhibitors, should be avoided.

To control symptoms, the lowest effective dose should be used for the shortest duration possible to minimize adverse effects (see Section 4.2 and the information below on gastrointestinal bleeding, ulceration, and perforation).

Tenoxicam cannot replace corticosteroid therapy or treat corticosteroid deficiency. Abrupt discontinuation of corticosteroids may cause exacerbation of the disease. For patients undergoing

long-term corticosteroid therapy, if the decision is made to discontinue corticosteroid therapy, treatment should be tapered off slowly and gradually.

The anti-inflammatory and antipyretic pharmacological effects of tenoxicam may reduce the usefulness of these diagnostic signs in determining the complications of suspected non-infectious painful conditions.

Gastrointestinal bleeding, ulceration, and perforation:
At any time during treatment with all NSAID drugs, including TILCOTIL treatment, serious gastrointestinal adverse effects, including bleeding, ulceration, or perforation of the stomach, small intestine, or colon, which may be fatal, may occur with or without warning symptoms or a prior history of serious gastrointestinal events. Only one in five patients exposed to serious upper gastrointestinal side effects from NSAID use is symptomatic. Therefore, symptoms of gastrointestinal ulceration, bleeding, and perforation should be carefully monitored. Serious upper gastrointestinal ulcers, major bleeding, or perforations associated with NSAID use have been shown to occur in approximately 1% of patients treated for 3-6 months and in 2-4% of patients treated for one year. These trends continue with prolonged use, and the risk of serious gastrointestinal adverse effects increases during the course of treatment. However, there is also a risk with short-term treatment.

The incidence of adverse reactions to NSAIDs, particularly gastrointestinal bleeding and perforation, which can be fatal in the elderly, is high. Frail patients have a lower tolerance to ulceration or bleeding than other patients. Most fatal gastrointestinal events associated with NSAIDs have occurred in the elderly and/or debilitated patients. The risk of gastrointestinal bleeding, ulceration, or perforation is higher in patients using high doses of NSAIDs, particularly those with a history of ulceration complicated by hemorrhage or perforation (see Section 4.3), and in the elderly. Treatment in these patients should be initiated at the lowest dose, and concomitant use of protective agents (e.g., misoprostol or proton pump inhibitors) should be considered for patients also taking low-dose salicylates or other drugs that increase gastrointestinal risk (see below and Section 4.5).

NSAIDs should be used with caution in patients with a history of inflammatory bowel disease (ulcerative colitis, Crohn's disease) as they may exacerbate their condition. Patients with a history of gastrointestinal toxicity, especially elderly patients, should report any unusual abdominal symptoms (particularly gastrointestinal bleeding) at the start of treatment.

TILCOTIL treatment should be discontinued immediately if peptic ulcer or gastrointestinal bleeding occurs.

Caution is advised in patients taking TILCOTIL concomitantly with drugs that may increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants like warfarin, selective serotonin reuptake inhibitors, or antiplatelet drugs like salicylates (see Section 4.5).

Anaphylactoid reactions:
As with other NSAIDs, anaphylactoid reactions may occur in patients with no prior known exposure to tenoxicam. Tenoxicam should not be administered to patients who have experienced the aspirin triad. This symptom complex typically occurs in patients with asthma who develop nasal polyps or rhinitis with or without nasal polyps, or severe, potentially fatal bronchospasm following the administration of aspirin or other NSAIDs (see "Pre-existing asthma" heading). Emergency assistance should be sought if an anaphylactoid reaction occurs.

Pre-existing asthma:
Aspirin-sensitive asthma may be present in asthmatic patients. Aspirin use in patients with aspirin-sensitive asthma has been associated with severe bronchospasm, which can be fatal. Since cross-reactivity, including bronchospasm, has been reported between aspirin and other NSAIDs in these patients with aspirin sensitivity, tenoxicam should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with pre-existing asthma.

Skin reactions
Serious skin reactions, including very rare cases of exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (Lyell's syndrome), some of which may be fatal, have been reported in association with NSAIDs (see Section 4.8). During the initial phase of treatment, patients may be at high risk for these reactions; in many cases, reactions begin within the first month of treatment. If serious skin reactions (skin rash, mucosal/lesions, or any other signs of hypersensitivity) occur, TILCOTIL treatment should be discontinued immediately.

Hematologic effects
Anemia may sometimes occur in patients taking NSAIDs, including TILCOTIL. This may be due to fluid retention, occult or extensive gastrointestinal blood loss, or an ill-defined effect on erythropoiesis. In patients receiving long-term treatment with NSAIDs, including TILCOTIL, hemoglobin or hematocrit levels should be monitored if any signs or symptoms of anemia are observed.

NSAIDs inhibit platelet aggregation, and in some patients, these drugs have been shown to prolong bleeding time. Unlike aspirin, their effects on platelet function are quantitatively less, shorter in duration, and reversible. Patients receiving TILCOTIL treatment who have adverse effects from changes in platelet function (such as patients with coagulation disorders or those taking anticoagulants) should be monitored closely.

Cardiovascular and cerebrovascular effects

Appropriate monitoring is recommended in patients with a history of hypertension and/or mild-to-moderate congestive heart failure, as fluid retention and edema associated with NSAIDs have been reported.

Clinical studies of up to 3 years with many COX-2 selective and non-selective NSAIDs have shown an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. A similar risk may be present with all COX-2 selective and non-selective NSAIDs. The risk may be higher in patients with known cardiovascular disease or cardiovascular risk factors. To minimize the potential risk of adverse cardiovascular effects in patients receiving NSAID therapy, the lowest effective dose should be used for the shortest duration possible. Even if no previous cardiovascular symptoms have been observed, patients and doctors should be alert to the possibility of such events occurring. Patients should be informed about the signs and/or symptoms of serious cardiovascular events and what to do if they occur.

There is no consistent evidence that concomitant use of aspirin reduces the risk of serious cardiovascular thrombotic events associated with the use of NSAIDs. Concomitant use of aspirin and an NSAID increases the risk of serious gastrointestinal effects (see Section 4.4 - Gastrointestinal bleeding, ulceration, and perforation).

In two large, controlled clinical trials, the use of COX-2 selective NSAIDs for pain management within the first 10-14 days after coronary artery bypass surgery was associated with an increased incidence of myocardial infarction and stroke (see Section 4.3).

Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral artery disease, and/or cerebrovascular disease should only be treated with TILCOTIL after careful evaluation. Similar evaluations should be performed before initiating long-term treatment in patients with cardiovascular disease risk factors (e.g., hypertension, hyperlipidemia, diabetes mellitus, smoking).

Hypertension:
NSAIDs, including TILCOTIL, may cause hypertension or worsen pre-existing hypertension, which may lead to an increased incidence of cardiovascular events. Patients using thiazide or loop diuretics may experience impaired response to treatment when taking NSAIDs. All NSAIDs, including TILCOTIL, should be used with caution in patients with hypertension. Blood pressure should be closely monitored at the start of NSAID treatment and throughout the course of treatment.

Renal effects:
Long-term use of NSAIDs can lead to renal papillary necrosis or other renal pathologies. Renal toxicity is also observed in patients in whom renal prostaglandins play a compensatory role in maintaining renal perfusion. Administration of an NSAID to these patients may cause a dose-

dependent decrease in prostaglandin production and renal blood flow, leading to significant renal decompensation. Patients at risk include those with renal dysfunction, heart failure, liver dysfunction, those using diuretics and ACE inhibitors, and elderly patients. Discontinuation of NSAID therapy generally results in a return to the pre-treatment state.

Advanced kidney disease:
Controlled clinical studies have not provided any data on the use of tenoxicam in patients with advanced kidney disease. Therefore, treatment with tenoxicam is not recommended in patients with advanced kidney disease. If tenoxicam treatment is necessary, close monitoring of the patient's kidney function is recommended.

Hepatic effects:
Up to 15% of patients taking NSAIDs, including TILCOTIL, may experience elevations in one or more liver tests at the upper limit of normal. These laboratory abnormalities may progress, remain unchanged, or resolve spontaneously with continued treatment. In clinical trials with NSAIDs, approximately 1% of patients have reported significant increases in ALT or AST activity (approximately three times the upper limit of normal or more). In addition, rare cases of severe hepatic reactions, some fatal, such as jaundice and fatal fulminant hepatitis, liver necrosis, and liver failure, have been reported.

During TILCOTIL treatment, patients with symptoms and/or signs suggestive of liver dysfunction or abnormal liver test values should be evaluated for evidence of a more serious hepatic reaction. If clinical signs and symptoms indicate the development of liver disease or systemic symptoms appear (e.g., eosinophilia, rash), TILCOTIL treatment should be discontinued.

Ophthalmic effects
Some undesirable eye findings have been encountered during treatment with tenoxicam and other NSAID drugs. Therefore, an eye examination is recommended in patients suspected of having visual impairment.

Antipyretic effects
Like other anti-inflammatory drugs, TILCOTIL may mask general infection symptoms.

Information for patients
Like other NSAIDs, tenoxicam may cause serious cardiovascular side effects such as myocardial infarction or stroke, which can result in hospitalization and even death. Although serious cardiovascular events can occur without warning symptoms, patients should be alert to signs and symptoms such as chest pain, shortness of breath, fatigue, and speech difficulties, and seek medical help if they experience any similar signs or symptoms. The importance of this monitoring should be emphasized to patients (see Cardiovascular and Cerebrovascular Effects).

Like other drugs in this class, tenoxicam may cause serious side effects such as gastrointestinal ulceration and bleeding, which can be uncomfortable and, rarely, may require hospitalization or even be fatal. Since serious gastrointestinal ulceration and bleeding can occur without warning symptoms, doctors should warn patients undergoing chronic treatment to be alert for signs and symptoms of ulceration and bleeding and monitor them for any signs or symptoms, including epigastric pain, dyspepsia, melena, and hematemesis, and inform them of the importance of this monitoring (see Gastrointestinal bleeding, ulceration, and perforation).

Like other NSAIDs, tenoxicam can cause serious skin side effects that require hospitalization and can even be fatal, such as exfoliative dermatitis, Stevens Johnson syndrome, and toxic epidermal necrolysis. Although serious skin reactions may occur without warning, patients should be alert for other signs and symptoms of hypersensitivity, such as rash and vesicles, fever, or itching, and seek medical attention if any signs or symptoms occur. Patients should be advised to stop taking the medication immediately if any type of rash develops and to consult their doctor as soon as possible.

Patients should be advised to report unexplained weight gain or edema signs and symptoms to their doctor immediately.

Patients should be informed about the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and flu-like symptoms). If these occur, patients should be advised to stop treatment and seek medical help immediately.

Patients should also be advised to seek emergency medical help if an anaphylactoid reaction occurs (e.g., difficulty breathing, swelling of the face or throat) (see Anaphylactoid reactions).

Laboratory tests
Since NSAIDs inhibit renal prostaglandin synthesis, they may cause undesirable effects on renal hemodynamics and salt and water balance. Patients with a history of kidney disease, diabetics with renal dysfunction, patients with hepatic cirrhosis, congestive heart failure, hypovolemia, and when used in combination with diuretics, corticosteroids, and drugs known to have nephrotoxic effects, should be monitored closely, especially with regard to cardiac and renal function (BUN, creatinine, edema development, weight gain, etc.). These patients are at high risk during and after major surgical procedures due to the possibility of significant blood loss. Therefore, they must be closely monitored after surgery and during the recovery period.

Severe gastrointestinal tract ulcerations and bleeding can occur without warning symptoms; therefore, physicians should monitor patients with for signs or symptoms of gastrointestinal bleeding. Complete blood counts and biochemical profiles should be monitored periodically in patients receiving long-term NSAID therapy. If clinical signs or symptoms indicating the development of liver or kidney disease appear, systemic symptoms (e.g., eosinophilia, rash)

occur, or liver test results remain abnormal or worsen, tenoxicam treatment should be discontinued.

This medicinal product contains less than 1 mmol (23 mg) of sodium per vial; i.e., it is essentially 'sodium-free'.

4.5. "Interaction with other medicinal products and other forms of interaction"

Acetylsalicylic acid and salicylates

When tenoxicam is administered concomitantly with acetylsalicylic acid, the clearance of free tenoxicam does not change, but the protein binding rate decreases. The clinical significance of this interaction is unknown. Due to the increased risk of adverse effects, concomitant use of TILCOTIL with other NSAIDs and acetylsalicylic acid is not recommended.

Gastrointestinal interactions

The risk of gastrointestinal bleeding increases when NSAIDs are used concomitantly with antithrombotic drugs and selective serotonin reuptake inhibitors (see Section 4.4).

Corticosteroids

Caution is advised when tenoxicam is used concomitantly with oral corticosteroids.

They may increase the risk of gastrointestinal ulceration or bleeding.

Methotrexate

Concomitant use of methotrexate with some NSAIDs has been associated with decreased renal tubular secretion of methotrexate, increased plasma concentrations, and serious methotrexate toxicity. Therefore, caution should be exercised when TILCOTIL is administered concomitantly with methotrexate.

Zidovudine

When zidovudine, used in the treatment of AIDS, is used concomitantly with NSAIDs, increased erythrocyte toxicity accompanied by severe anemia is observed one week after starting treatment. Blood counts should be monitored two weeks after starting treatment with NSAIDs.

Mifepristone

NSAIDs may reduce the effect of mifepristone; therefore, TILCOTIL should not be used for 8-12 days following mifepristone administration.

Lithium

NSAIDs have caused an increase in plasma lithium levels and a decrease in renal lithium clearance. The average minimum lithium concentration increased by 15% and renal clearance decreased by approximately 20%. This effect is thought to be caused by the inhibition of renal

prostaglandin synthesis by NSAIDs. Individuals receiving concomitant TILCOTIL and lithium should be closely monitored for signs of lithium toxicity.

Cyclosporine and Tacrolimus
Due to the increased risk of nephrotoxicity, caution should be exercised when cyclosporine is used concomitantly with NSAIDs.

Quinolones
There may be an increased risk of convulsions in patients using quinolones.

Diuretics and antihypertensives
As with all NSAIDs in general, TILCOTIL should not be administered concomitantly with potassium-sparing diuretics. There is a known interaction between the two drug classes, which may lead to hyperkalemia and renal failure.

Clinical studies and post-marketing observations have shown that tenoxicam may reduce the natriuretic effects of furosemide and thiazides in some patients. This effect is thought to be due to inhibition of renal prostaglandin synthesis. During concomitant treatment with NSAIDs, the patient should be carefully monitored for signs of renal failure and diuretic efficacy.

TILCOTIL reduces the blood pressure-lowering effect of hydrochlorothiazide. As with other NSAIDs, TILCOTIL may also reduce the antihypertensive effect of alpha-adrenergic blockers, ACE inhibitors, and ARBs. This interaction should be considered in patients receiving NSAIDs and ACE inhibitors concomitantly.

No interaction has been reported between tenoxicam and centrally acting alpha agonists or calcium channel blockers.

No clinically significant interaction has been observed when tenoxicam and atenolol are used concomitantly.

No interactions have been reported in patients using digitalis products concomitantly during clinical studies. Therefore, no major risk is seen with the concomitant use of TILCOTIL and digoxin.

Antacids and H_2-receptor blockers
No clinically significant interaction has been observed with the simultaneous administration of antacids and cimetidine at recommended doses.

Probenecid
Concomitant treatment with probenecid and tenoxicam may increase the plasma concentration of tenoxicam. However, the clinical significance of this observation has not been established.

Anticoagulants
No clinically significant interaction has been observed with concomitant use of warfarin, phenprocoumon, and low molecular weight heparin at recommended doses. However, as with other NSAIDs, patients receiving concomitant anticoagulants should be monitored carefully.

Oral Antidiabetics
The clinical effects of the oral antidiabetics gliburide, glibenclamide, and tolbutamide were not altered by tenoxicam. However, as with other NSAIDs, patients receiving concomitant oral antidiabetic drugs should be monitored carefully.

Alcohol
Alcohol increases gastric mucosal damage when taken with tenoxicam.
No clinically significant interactions have been observed in the few patients who have used tenoxicam in combination with gold or penicillamine.

Additional information for specific populations:
No clinical interaction studies have been conducted in special populations.

Pediatric population:
No clinical interaction studies have been conducted in the pediatric population.

4.6 Pregnancy and lactation
General recommendation
Pregnancy Category: C/D (3rd trimester)

Women of childbearing potential/Birth control (Contraception)
There is no information available on the effects of TILCOTIL on birth control (contraception). As with other drugs known to inhibit cyclooxygenase/prostaglandin synthesis, tenoxicam use may impair fertility and is therefore not recommended for women attempting to conceive. When TILCOTIL is used by women attempting to conceive, the dose should be kept as low as possible and the duration of treatment as short as possible.

Pregnancy
There are no clinical data available on exposure to tenoxicam during pregnancy (see Section 5.3).

Animal studies have not shown any direct or indirect harmful effects on pregnancy/embryonic/fetal development/birth or postnatal development (see Section 5.3).

TILCOTIL should be used with caution in pregnant women.

NSAIDs inhibit prostaglandin synthesis, and this effect may cause closure of the fetal ductus arteriosus and delay parturition by prolonging labor when administered during the late stages of pregnancy. The use of TILCOTIL during the third trimester of pregnancy is contraindicated.

Lactation period
Results from single-dose studies indicate that very low amounts of tenoxicam (less than 0.3% of the average dose) pass into breast milk (see Section 5.2).

To date, no side effects have been reported in infants of breastfeeding mothers using tenoxicam; however, the possibility of side effects should not be overlooked, and in case of suspicion, either the infant should be weaned or the medication should be discontinued.

Reproductive ability/Fertility
As with other drugs known to inhibit cyclooxygenase/prostaglandin synthesis, tenoxicam use may impair fertility and is therefore not recommended in women attempting to conceive. Discontinuation of tenoxicam therapy should be considered in women with difficulty conceiving or undergoing infertility investigations (see Section 5.3).

4.7 Effects on the ability to drive and use machines
Patients who experience adverse effects such as vertigo, dizziness, or visual disturbances that may affect the use of vehicles and machinery should avoid driving or usining machines.

4.8 Undesirable effects
According to clinical studies involving a large number of patients, tenoxicam has been well tolerated at the recommended doses. The reported adverse effects have generally been mild and transient. Treatment had to be discontinued due to adverse effects in a small number of patients. The local tolerance of parenteral administration of tenoxicam has been found to be good.

The following terms and frequency categories have been used for adverse effects associated with the use of TILCOTIL:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Unknown: Anemia, agranulocytosis, leukopenia, thrombocytopenia

Immune system disorders
Unknown: Hypersensitivity reactions such as dyspnea, asthma, anaphylaxis, angioedema

Metabolic and nutritional disorders
Uncommon: Loss of appetite

Psychiatric disorders
Uncommon: Sleep disorders

Nervous system disorders
Common: Dizziness, headache

Eye disorders
Unknown: Vision problems

Ear and inner ear disorders
Uncommon: Vertigo

Cardiac disorders
Uncommon: Palpitations, edema, hypertension, and heart failure

Vascular diseases
Unknown: Vasculitis. Clinical studies and epidemiological data suggest that the use of selective cyclooxygenase-2 (COX-2) inhibitors and some NSAIDs (especially at high doses and during long-term treatment) may be associated with a small increased risk of arterial thrombotic events (e.g., myocardial infarction or stroke).

Although tenoxicam has not been shown to increase thrombotic events such as myocardial infarction, there is insufficient data to exclude this risk with tenoxicam.

Gastrointestinal disorders
Common: Gastric, epigastric, and abdominal discomfort, dyspepsia, nausea, heartburn, gastrointestinal perforation, flatulence
Uncommon: Hematemesis, melena, gastrointestinal bleeding, peptic ulcer, constipation, diarrhea, ulcerative stomatitis, gastritis, vomiting, dry mouth
Unknown: Colitis and exacerbation of Crohn's disease have been reported following administration.

Hepatobiliary disorders
Unknown: Hepatitis

Skin and subcutaneous tissue disorders
Uncommon: Itching (in the anal area after rectal application), erythema, exanthema, rash, urticaria

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), photosensitivity reactions

Pregnancy, puerperium conditions, and perinatal diseases
Unknown: 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

Investigations
Uncommon: Increased liver enzymes, blood urea nitrogen (BUN), or creatinine
Unknown: Increased blood pressure, especially in patients treated with cardiovascular medications

Post-marketing data
The safety profile in post-marketing experience is consistent with the experience in clinical trials.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9 Overdose and treatment
Symptoms
Although there is no experience with acute overdose with tenoxicam, the adverse effects listed in Section 4.8 may be expected to occur more prominently.

Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression, and coma may rarely occur following the administration of NSAIDs. Anaphylactic reactions have been reported with the therapeutic use of NSAIDs and may also occur following overdose.

Treatment
There is no known specific antidote for tenoxicam. However, in cases of NSAID overdose, patients should receive symptomatic treatment and supportive measures to reduce absorption (e.g., gastric lavage or activated charcoal) and accelerate excretion (e.g., cholestyramine). Dialysis does not significantly remove NSAIDs from the bloodstream.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory and anti-rheumatic products (Oxicams)
ATC code: M01AC02

Tenoxicam, the active ingredient in TILCOTIL, is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, and anti-rheumatic properties that inhibits platelet aggregation. Tenoxicam inhibits prostaglandin biosynthesis both *in vitro* and *in vivo*. *In vitro* studies conducted on cyclooxygenase (COX) isoenzymes prepared from human COS-7 cells have shown that tenoxicam inhibits COX-1 and COX-2 isoenzymes to approximately the same degree, with a COX-2/COX-1 ratio of 1.34.

In vitro leukocyte peroxidase tests suggest that tenoxicam may have an oxygen-scavenging effect in the inflammation site.

Tenoxicam exhibits a potent inhibitory effect on human metalloproteinases (stromelysin and collagenase) enzymes that stimulate cartilage destruction. These pharmacological effects explain the efficacy of tenoxicam in painful inflammatory and degenerative diseases of the musculoskeletal system.

5.2 Pharmacokinetic properties

General Characteristics

Absorption:

Following intramuscular administration, bioavailability is complete and there is no difference compared to oral administration. Following intramuscular injection, peak plasma concentrations or at least 90% of peak plasma concentrations are reached approximately 15 minutes earlier than with oral administration.

With the recommended dose of 20 mg once daily, steady-state plasma concentrations are achieved within 10-15 days without accumulation. The average steady-state plasma concentration with 20 mg once daily is 11 mg/L, and this level has remained unchanged even during treatments lasting up to 4 years.

As predicted from single-dose kinetics, steady-state plasma concentrations are 6 times higher than those achieved with a single dose.

Distribution:

Following intravenous administration, tenoxicam plasma levels decline rapidly during the first 2 hours. After this short period, there is no difference in plasma concentrations between intravenous and oral administration. The mean distribution volume at steady state is 10-12 L.
At least 99% of the drug in the blood is bound to albumin. Tenoxicam penetrates well into synovial fluid.

However, it reaches peak plasma concentration later than plasma.

Based on single-dose administration data, a very small amount of tenoxicam (less than 0.3% of the average dose) passes into breast milk (see Section 4.6).

Biotransformation:
Tenoxicam is excreted after being converted into pharmacologically inactive metabolites in the liver.

Elimination:
Two-thirds of the oral dose is excreted in urine (primarily as inactive 5'-hydroxy tenoxicam) and the remainder in bile (mostly as glucuronide compounds). At most 1% of the administered dose is excreted unchanged in urine. The elimination half-life of tenoxicam is 72 hours (59-74 hours). Total plasma clearance is 2 mL/min.

Linearity/Nonlinearity:
The pharmacokinetics of tenoxicam are linear in the 10-100 mg dose range studied.

Characteristic features in patients
Renal impairment:
Studies in patients with renal impairment indicate that no dose adjustment is necessary to achieve plasma concentrations comparable to those in healthy individuals.

Hepatic impairment:
Studies in patients with hepatic impairment indicate that no dose adjustment is necessary to achieve plasma concentrations comparable to those in healthy individuals.

Geriatric population:
Studies in elderly patients have reported that no dose adjustment is required to achieve plasma concentrations comparable to those in healthy individuals. Elderly patients exhibit a similar kinetic profile to healthy individuals.

Other:
A similar kinetic profile to that seen in healthy individuals is observed in patients with rheumatoid disorders.
Due to the high plasma protein binding of tenoxicam, caution should be exercised in cases of significant decrease in plasma albumin levels (see Section 4.4).

5.3 Preclinical safety data
Carcinogenicity:
Tenoxicam has not shown any carcinogenic effects in animals.

Mutagenicity:
Tenoxicam has not shown mutagenic effects in animals.

Fertility impairment:
As with other drugs known to inhibit cyclooxygenase/prostaglandin synthesis, tenoxicam use may impair fertility and is therefore not recommended for women attempting to conceive. Discontinuation of tenoxicam therapy should be considered in women experiencing difficulty conceiving or undergoing infertility investigations.

Teratogenicity:
Tenoxicam has not shown teratogenic effects in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Ascorbic acid
Disodium edetate
Sodium hydroxide (10% solution)
Tromethamine
Hydrochloric acid (2 N) (pH adjustment to pH=9.5)
Injection water

6.2 Incompatibilities

Do not use TILCOTIL injection solution lyophilisate with infusions due to the possibility of precipitation.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at room temperature below 30°C.

6.5 Nature and contents of container

The box contains one vial with a rubber stopper and a metal cap, containing 20 mg of lyophilized powder, and one ampoule containing 2 mL of water for injection as a solvent.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local disposal regulations.

7. MARKETING AUTHORISATION HOLDER

DEVA Holding A.S.
Halkalı Merkez Mah. Basın Ekspres Cad.
No: 1 34303 Küçükçekmece – Istanbul/TÜRKİYE
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MARKETING AUTHORISATION NUMBER 8
235/45

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first Authorization: 10/10/2011
Date of last renewal:

10. DATE OF REVISION OF THE TEXT