SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TILCOTIL 20 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Active ingredient:

Tenoxicam 20 mg

Excipient(s):

Lactose 90.0 mg

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Film coated tablet

Oval, cylindrical, biconvex, and grayish-yellow tablets.

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

Posology/frequency and duration of administration

Undesirable effects can be minimized by using the lowest effective dose and the shortest duration necessary for symptom control.

Unless otherwise recommended by the physician;

Standard dose: For all indications other than primary dysmenorrhea, postoperative pain, and acute gout, a single daily dose of 20 mg should be administered at the same time each day.

The recommended dose for primary dysmenorrhea is a single daily dose of 20-40 mg. The recommended dose for postoperative pain is a single daily dose of 40 mg, which can be administered for 5 days, and the recommended dose for acute gout attacks is a single daily

dose of 40 mg for 2 days, followed by 20 mg for 5 days.
When necessary, treatment can be initiated with a single daily dose administered IV or IM for 1 or 2 days, followed by oral or rectal administration.

The therapeutic efficacy of tenoxicam is evident at the start of treatment for chronic conditions, and the response increases over time. In chronic disorders, doses exceeding 20 mg daily are not recommended. In such cases, the frequency and severity of adverse reactions will increase without a significant increase in therapeutic efficacy.
In patients requiring long-term treatment, reducing the daily oral dose to 10 mg for maintenance therapy may be attempted.

Method of administration:
Tablets are taken with a glass of water. TILCOTIL tablets should preferably be taken during or immediately after a meal.

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

Hepatic impairment:
The dosage recommendations mentioned above can 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 recommendation can be made for adolescents and children. Not for use in this age group.

Geriatric population:
Older patients have a higher risk of gastrointestinal bleeding, ulceration, or perforation, which can 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 concurrently using low-dose aspirin or other drugs that increase gastrointestinal risk (see Section 4.4).

4.3 Contraindications

- 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 a history thereof (two or more distinct episodes of proven ulcer or bleeding) (see Section 4.4),
- As with other NSAIDs, in patients with severe heart failure, renal, or hepatic insufficiency,
- TILCOTIL is contraindicated during the last 3 months of pregnancy.

4.4 Special warnings and precautions for use

NSAIDs may cause undesirable effects on renal hemodynamics and salt/water balance by inhibiting renal prostaglandin synthesis. In patients with a history of kidney disease, diabetics with renal impairment, patients with hepatic cirrhosis, congestive heart failure, hypo-volaemia, or concomitant use of drugs that may increase the risk of renal impairment, such as potentially nephrotoxic drugs, diuretics, and corticosteroids, cardiac and renal functions (blood urea nitrogen (BUN), creatinine, development of oedema, weight gain, etc.) should be carefully monitored during TILCOTIL treatment. This patient group is at particular risk during the peri- and post-operative phases of major surgery due to the possibility of significant blood loss. Therefore, these patients should be closely monitored during the postoperative and recovery periods.

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 concomitant 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).

Gastrointestinal bleeding, ulceration, and perforation:

Gastrointestinal bleeding, ulceration, or perforation, which may be fatal, has been reported

with all NSAIDs, including TILCOTIL therapy, at any time during treatment, with or without warning symptoms or a prior history of serious gastrointestinal (GI) events. To date, no subgroup of patients has been identified that is at low risk of developing peptic ulcer and bleeding.

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

Skin reactions

Serious skin reactions, including 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). Patients may be at high risk for these reactions during the initial phase of treatment; reactions often begin within the first month of treatment in most cases. TILCOTIL treatment should be discontinued immediately if serious skin reactions occur.

Hematological effects

Tenoxicam inhibits platelet aggregation and may affect hemostasis. TILCOTIL has no

significant effect on blood coagulation factors, coagulation time, prothrombin time, or activated thromboplastin time.
Patients with coagulation disorders or receiving medication that affects hemostasis should be carefully monitored while using TILCOTIL.

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 and epidemiological data suggest that the use of selective 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).
Patients with uncontrolled hypertension, congestive heart failure, established ischemic heart disease, peripheral arterial 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).

Ophthalmic effects
Some undesirable eye findings have been encountered during treatment with TILCOTIL 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 signs of infection.

Laboratory tests
NSAIDs may cause undesirable effects on renal hemodynamics and salt and water balance because they inhibit renal prostaglandin synthesis. 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 should be closely monitored after surgery and during the recovery period.

Since tenoxicam binds to plasma proteins to a high degree, precautions should be taken in cases where plasma albumin levels are significantly reduced.

This medicinal product contains 90.0 mg of lactose per tablet. Patients with rare hereditary galactose intolerance, Lapp lactose deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Acetylsalicylic acid and salicylates

Salicylates displace non-steroidal anti-inflammatory drugs, including tenoxicam, from their protein-binding sites, thereby increasing their clearance and distribution volume. Due to the risk of adverse reactions, concomitant use with salicylates and other NSAIDs 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).

Methotrexate

The concomitant use of certain NSAIDs and methotrexate has been reported to cause a decrease in renal tubular secretion of methotrexate, high plasma methotrexate concentrations, and severe methotrexate toxicity. Therefore, caution should be exercised when TILCOTIL is used concomitantly with methotrexate.

Zidovudine

When zidovudine, used in the treatment of AIDS, is used concomitantly with NSAIDs, increased erythrocyte toxicity via reticulocytes 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

Since TILCOTIL reduces the renal clearance of lithium, their combined use may lead to increased plasma lithium levels and lithium toxicity. Plasma lithium levels should be monitored regularly.

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 other NSAIDs, TILCOTIL should not be used with potassium-sparing diuretics. There is a drug interaction between these two drug classes that may cause hyperkalemia and renal failure.

No clinically significant interaction has been reported between TILCOTIL and furosemide, but TILCOTIL is known to weaken the hypotensive effect of hydrochlorothiazide. As with other NSAIDs, TILCOTIL may reduce the antihypertensive effect of alpha-adrenergic blockers, ACE inhibitors, and ARBs.

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

No clinically significant interaction has been observed between TILCOTIL and atenolol. In clinical studies, no interaction has been reported in patients using digitalis preparations with tenoxicam. Therefore, it is considered that the concomitant use of TILCOTIL and digitalis preparations does not pose a significant risk.

Antacids and H2-Receptor Antagonists:

No clinically significant interactions have been observed when antacids and cimetidine are

administered together at recommended doses.

Probenecid:
Co-administration of probenecid and tenoxicam may increase the plasma concentration of tenoxicam. The clinical significance of this observation has not been determined.

Anticoagulants:
No clinically significant interactions have been observed when administered concomitantly at recommended doses with warfarin, phenprocoumon, and low molecular weight heparin. However, as with other NSAIDs, patients should be monitored carefully when administered concomitantly with anticoagulants.

Oral Antidiabetics:
The clinical effect of TILCOTIL with oral antidiabetic drugs, glibenclamide, glibornuride, and tolbutamide has not changed in a similar manner. However, as with other NSAID drugs, patients should be carefully monitored when administered with oral antidiabetics.

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

4.6 Pregnancy and lactation

General recommendation

Pregnancy category: C/D (third 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.
TILCOTIL is contraindicated during the third trimester of pregnancy.

Pregnancy

There are no clinical data available on exposure to tenoxicam during pregnancy (see Section 5.3). Studies in animals have not shown any direct or indirect harmful effects on pregnancy/embryonic/fetal development/birth or postnatal development.

TILCOTIL should be used with caution in pregnant women.

NSAIDs have an inhibitory effect on prostaglandin synthesis, and this effect may cause closure of the fetal ductus arteriosus and delay parturition by prolonging labor when the drug is administered during the late stages of pregnancy. Treatment should be avoided during the third trimester of pregnancy.

Lactation

Results from single-dose studies indicate that very low amounts of tenoxicam (average value less than 0.3% of the dose) pass into breast milk (see Section 5.2). To date, no adverse effects have been reported in infants of breastfeeding mothers using TILCOTIL, but in cases of concern, either the infant should be weaned or the medication discontinued.

Reproductive ability/Fertility

Like other drugs known to inhibit cyclooxygenase/prostaglandin synthesis, tenoxicam use may impair fertility and is not recommended for women trying to conceive. Discontinuation of tenoxicam treatment should be considered in women with difficulty conceiving or undergoing infertility investigations.

4.7 Effects on driving and operating machinery

Patients experiencing side effects such as dizziness, lightheadedness, and visual disturbances that may affect driving or operating machinery should avoid driving or operating machinery.

4.8 Undesirable effects

According to clinical studies involving a large number of patients, TILCOTIL 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 the parenteral administration of TILCOTIL 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: Dyspnea, asthma, anaphylaxis, angioedema, and other hypersensitivity reactions

Metabolism and nutrition disorders

Uncommon: Loss of appetite

Psychiatric disorders

Uncommon: Sleep disorders

Nervous system disorders

Common: Dizziness, headache

Eye disorders

Unknown: Visual disturbances

Ear and inner ear disorders

Uncommon: Vertigo

Cardiac disorders

Uncommon: Palpitations

Unknown: Heart failure

Vascular disorders

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, burning sensation, gastrointestinal perforation

Uncommon: Gastrointestinal bleeding, including hematemesis and melena, ulcer, constipation, diarrhea, stomatitis, gastritis, vomiting, dry mouth

Unknown: Flare-ups of colitis and 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, edema

Investigations

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

Post-marketing observed side effects:

The safety profile obtained from experience after the product was placed on the market is consistent with the experience obtained from 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 in accordance with local requirements.

4.9 Overdose

Symptoms and Signs:

Although no cases of acute overdose with TILCOTIL have been reported, the symptoms and signs listed in the "Undesirable Effects" section may be more pronounced. Gastrointestinal bleeding may occur. Hypertension, acute renal failure, respiratory depression, and coma may rarely occur following NSAID administration.

Anaphylactoid reactions have been reported with therapeutic use of NSAIDs and may also occur following overdose.

Treatment:

Patients with NSAID overdose should receive symptomatic and supportive treatment. There is no specific antidote. In cases of overdose, approaches that reduce absorption (e.g., gastric lavage or activated charcoal) and accelerate excretion (e.g., cholestyramine) should be

attempted.

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 agents (Oxicams)

ATC code: M01AC02

The active ingredient of TILCOTIL, tenoxicam, 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.

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

5.2 Pharmacokinetic properties

General characteristics

Absorption:

Oral absorption of tenoxicam is rapid and complete (bioavailability 100%). Peak plasma concentrations are reached within 2 hours after oral or rectal administration in fasting subjects. Absorption is the same when taken with food, but the time to peak concentration is delayed.

With the recommended dosage regimen of 20 mg once daily, steady-state conditions are reached within ten to fifteen days without unexpected accumulation. When tenoxicam is administered at oral doses of 20 mg once daily, the steady-state average concentration is 11 mg/L, and this remains unchanged even during treatment lasting up to four years.

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

Distribution:

Over 99% of the drug in the blood is bound to albumin. Tenoxicam penetrates synovial fluid very well, but reaches peak concentration later than in plasma.

Results from single-dose administration indicate that very low amounts of tenoxicam (average value less than 0.3% of the dose) pass into breast milk (see Section 4.6).

Biotransformation:

Tenoxicam is excreted from the body after being converted into pharmacologically inactive metabolites.

Elimination:

Two-thirds of the oral dose is excreted in the urine (generally as inactive 5'-hydroxy tenoxicam), while the remainder is excreted via the bile (a significant portion as glucuronide compounds). Less than 1% of the administered dose is recovered in the urine as the parent drug. The average elimination half-life of tenoxicam is 72 hours (59-74 hours). Total plasma clearance is 2 mL/minute.

Linearity/non-linearity:

The pharmacokinetics of tenoxicam have shown linear properties in studies with doses ranging from 10 to 100 mg.

Characteristic features in patients

Renal Insufficiency:

Studies in patients with renal impairment have reported that no dose adjustment is necessary to achieve plasma concentrations comparable to those in healthy individuals.

Hepatic Impairment:

Studies in patients with hepatic insufficiency have reported that no dose adjustment is necessary to achieve plasma concentrations comparable to those achieved in healthy individuals.

Geriatric population:

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

Other:

A similar kinetic profile to that observed in healthy individuals is seen in patients with rheumatoid arthritis.

Due to the high plasma protein binding of tenoxicam, caution should be exercised with TILCOTIL in cases of significant decrease in plasma albumin levels (see Section 4.4).

5.3 Preclinical safety data

Carcinogenicity:

Tenoxicam has not shown 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 with difficulty conceiving or undergoing infertility investigations.

Teratogenicity:

Tenoxicam has not shown teratogenic effects in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet:

Lactose

Maize starch

Talc

Magnesium stearate

Film coating:

Hydroxypropyl methylcellulose

Talc

Titanium dioxide

Yellow iron oxide

6.2 Incompatibilities

TILCOTIL injection powder should not be used with infusions.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at room temperature below 30°C. Protect from moisture and store the product in its original packaging.

6.5 Nature and contents of container

TILCOTIL film coated tablets, 10 and 30 tablets, in blister packs

6.6 Special precautions for disposal and other handling

Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORISATION HOLDER

DEVA HOLDİNG A.Ş.

Halkalı Merkez Mah. Basın Ekspres Cad. No:1 34303
Küçükçekmece-ISTANBUL/TÜRKİYE

8. MARKETING AUTHORISATION NUMBER(S)

220/95

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 25/09/2009

Date of renewal of authorization:

10. DATE OF REVISION OF THE TEXT