Composition

Active ingredients: tenoxicam.
Tenoxicam is a thienothiazine derivative belonging to the chemical class of oxicams.
Tablets 20 mg
Suppositories 20 mg.
Vials containing 20 mg (lyophilisate).
Excipients: Ampoules: antioxidant (0.4 mg ascorbic acid, E300), disodium EDTA, mannitol (E421), tris (hydroxymethyl) aminomethane, water for injection.

Properties
Tenoxicam has anti-inflammatory, analgesic, antipyretic properties and also inhibits platelet aggregation. Tenoxicam is a potent inhibitor of prostaglandin biosynthesis, both in vitro (sheep seminal vesicles) and in vivo (protection of arachidonic acid-induced toxicity in mice). In vitro tests of leukocyte peroxidase suggest that tenoxicam may act as a scavenger for active oxygen at the site of inflammation. These pharmacological effects explain, at least in part, the successful use of Tilcotil in the treatment of painful inflammatory and degenerative disorders of the musculoskeletal system. Tenoxicam showed no mutagenic, carcinogenic or teratogenic effects in animals.
As with other prostaglandin inhibitors, renal and gastrointestinal effects, increased incidence of dystocia and delayed parturition were observed in animal safety studies.

Pharmacokinetics
Absorption
On extravascular administration tenoxicam is absorbed in unchanged form: on oral administration it is absorbed completely, whereas absorption after rectal administration is approximately 80%. Peak plasma concentrations following oral or rectal administration are reached within two hours in fasting subjects. If tenoxicam is taken orally with a meal, it is absorbed to the same extent but at a somewhat slower rate.

Distribution
Following I.V. administration of 20 mg tenoxicam, plasma levels of the drug decline rapidly during the first two hours mainly due to distribution processes. After this short period, no difference in plasma concentrations between I.V. and oral dosing is seen. Following I.M., injection levels at or above 90% of the maximally achieved concentrations are reached as early as 15 minutes after a dose, i.e. earlier than after oral dosing. However, again the differences in blood levels between the two routes of administration are restricted to the first two hours after a dose. The bioavailability after an I.M. dose is complete and indistinguishable from that determined after oral dosing.
In the blood over 99% of the drug is bound to albumin. Tenoxicam penetrates well into the synovial fluid, but peak concentrations are reached later than in plasma.
At the recommended dosage of 20 mg once daily (given orally, rectally or parenterally) steady-state conditions are reached within 10-15 days without unexpected accumulation. Maximum steady-state concentrations in the plasma amount to 10-15 µg/ml (29.7-44.5 µmol/l) and did not change even on treatment for up to two years.

Metabolism
The major part of tenoxicam is converted to the inactive metabolite 5-hydroxy-pyridyl. Other metabolites occur in the form of glucuronidated compounds.

Elimination
Tenoxicam is eliminated with an average half-life of 72 hours (range: 42-98 hours). Up to two thirds of an oral dose is excreted in the urine (mainly as the inactive 5-hydroxy-pyridyl metabolite) and the rest via the bile (a significant portion in the form of glucuronidated compounds).

Pharmacokinetics in Special Situations
Studies in elderly and in patients with renal insufficiency or liver cirrhosis suggest than no dose adjust-
ment is necessary to achieve plasma concentrations similar to those in healthy subjects. Because of the high plasma protein binding of tenoxicam, caution is required when plasma albumin levels are markedly reduced (e.g. in nephrotic syndrome).

**Indications**

Tilcotil is indicated for the symptomatic treatment of the following painful inflammatory and degenerative disorders of the musculoskeletal system, the parenteral formulation being particularly suited for initial treatment:
- rheumatoid arthritis;
- osteoarthritis; arthritis;
- ankylosing spondylitis;
- extraarticular disorders, e.g. tendinitis, bursitis, periarthritis of shoulders (shoulder-hand syndrome) or hips, strains and sprains;
- acute gout (oral and rectal formulations only).

**Contraindications**

Tilcotil should not be administered to patients known to be hypersensitive to the drug. Patients in whom salicylates or other nonsteroidal anti-inflammatory drugs (NSAIDs) induce symptoms of asthma, rhinitis or urticaria should also be excluded. This also applies to patients who are suffering or have suffered from severe diseases of the upper gastrointestinal tract, including gastritis, gastric and duodenal ulcer. Before anesthesia or surgery, Tilcotil, like other NSAIDs, should not be given to elderly patients, to patients at risk of kidney failure, or to patients with increased risk of bleeding, because of an increased risk of acute renal failure and possibly of impaired hemostasis.

Concurrent treatment with salicylates or other NSAIDs should be avoided because of the increased risk of gastrointestinal adverse reactions.

**Side Effects**

During clinical trials lasting from two weeks to one year, Tilcotil proved to be generally well tolerated in the recommended daily dose of 20 mg: The local tolerance was good. In patients given Tilcotil parenterally, undesirable clinical effects or deviations from normal laboratory values were usually mild and transient. These effects subsequently disappeared, even when treatment was continued with the oral form. During clinical trials lasting from two weeks to one year, Tilcotil proved to be generally well tolerated in the recommended daily dose of 20 mg. The proportion of patients with undesirable clinical or laboratory effects was found to be around 12.5%. Usually these effects were mild and transient, and resolved even when treatment was continued. Only in about 1% of all patients did these effects necessitate interruption of treatment with Tilcotil at a dosage of 20 mg daily. Based on these trials, the following incidences of side effects can be estimated:

In treatment lasting several weeks to three months:
11%: gastrointestinal tract (gastralgia, heartburn, nausea, diarrhea, constipation; rarely: hemorrhage, ulcers, perforation);
3%: central nervous system (dizziness and headache);
1-2%: skin (itching—also in the anal region after rectal administration—rash, erythema, urticaria). As with other NSAIDs, in rare instances severe skin reactions such as Stevens-Johnson syndrome and Lyell syndrome may occur;
1-2%: urinary tract and kidneys (increase in BUN or creatinine);
1-2%: liver and biliary tract (increase in SGOT, SGPT, gamma-GT, bilirubin).

Rare miscellaneous effects include decreased hemoglobin, granulocytopenia, thrombocytopenia, slight edema and photodermatosis.

Long-term studies (12-48 months) have not revealed any increase in the frequency of side effects.

Hypersensitivity reactions such as dyspnea, asthma and angioedema may occur.

Elevated blood pressure may also occur in isolated cases, particularly in patients receiving cardioactive medications.

Isolated cases of vasculitis and hepatitis have been reported.
Precautions
As with other NSAIDs simultaneous treatment with anticoagulants and/or oral antidiabetics should be avoided unless the patient can be closely monitored. Prostaglandin synthetase inhibition may have an adverse effect on renal function. As with other NSAIDs, therefore, with Tilcotil it is necessary to adequately monitor renal function (BUN, creatinine, development of edema, weight gain, etc.), when giving a NSAID to the elderly or to patients with conditions that could increase their risk of developing renal failure, such as:
- preexisting renal disease;
- impaired renal function in diabetics;
- hepatic cirrhosis;
- congestive heart failure;
- volume depletion;
- concomitant treatment with diuretics;
- concomitant treatment with drugs of known nephrotoxic potential.

Pregnancy and Lactation
1st and 2nd trimesters: No teratogenic effects were seen in animal studies, but no controlled trials have so far been carried out in pregnant women. The suitability of using Tilcotil during pregnancy or lactation has not, therefore, been established.
3rd trimester: Because of the possibility of premature closure of the ductus arteriosus and the possibility of inhibition of uterine contractions, Tilcotil should not be used.

Overdosage
Although there is no experience of acute overdosage with tenoxicam, it may be expected that the signs and symptoms mentioned under Side Effects would be more pronounced. In case of real or suspected overdosage the drug should be discontinued. No specific antidote is known at present. Overdosage should be countered by measures to reduce absorption and speed up elimination. Gastrointestinal disorders may be treated with antacids and H2-receptor-blocking drugs. If necessary, the elimination of tenoxicam can be accelerated significantly by the administration of three 4g doses of cholestyramine.

Stability
This medicine should not be used after the expiry date (EXP) shown on the pack.

Drug Interactions
No interaction has been found with concomitantly administered antacids, probenecid, cimetidine, warfarin and phenprocoumon at the recommended dosages. As in the case of other NSAIDs, salicylate displaces tenoxicam from protein binding sites and thus increases clearance and volume of distribution of tenoxicam (see Contraindications). Blood glucose should be monitored closely in patients concomitantly receiving Tilcotil and oral antidiabetics. No interactions have been seen with the hypoglycemic agents glibornuride and tolbutamide.

No clinically relevant interaction was found in the small number of patients receiving concomitant treatment with gold or penicillamine. No changes in blood pressure or heart rate were observed in patients being treated concomitantly with various antihypertensives.

Nevertheless, a decrease in the efficacy of antihypertensive agents cannot be excluded. During clinical trials no interaction was reported for patients treated concomitantly with digitalis products. As with NSAIDs in general Tilcotil should not be administered concomitantly with potassium sparing, dehydrating drugs (diuretics). Until further data are available, the possibility that the diuretic effect of other dehydrating drugs is reduced by Tilcotil cannot be ruled out. No clinically relevant interactions have been observed between Tilcotil and low molecular weight heparin.

Dosage and Administration
Standard Dosage
For all indications except gouty arthritis, a daily dosage of 20mg should be given (1 tablet or 1 suppository) at the same time of day. Where indicated, treatment may be initiated with 1 vial of Tilcotil (20mg) I.V. or I.M. daily for one to two days. The tablets should be taken with a glass of water.

Dissolve the lyophilisate in the diluent provided (2ml of water for injection). The reconstituted solution
should be used immediately. Although the therapeutic effect of Tilcotil is evident early in treatment, there is a progressive increase in response over the first two weeks until the steady-state plasma level is reached.

Daily doses higher than 20 mg should be avoided, since this would increase the frequency and intensity of adverse reactions without significantly increasing efficacy. For patients needing long-term treatment a reduction to a daily dose of 10 mg (½ tablet) may be tried for maintenance.

For acute attacks of gouty arthritis, the recommended dose is 40 mg (2 tablets or 2 suppositories) once daily for two days followed by 20 mg (1 tablet or 1 suppository) once daily for a further five days.

Special Dosage Instructions
In principle, the above dosage recommendations also apply to elderly patients and to patients suffering from kidney or liver disease (see Contraindications). Because of lack of clinical experience, no dosage recommendations have so far been established for patients under 18 years of age.