Product monograph
TENOXICAM
TenoxicamTablets

20 mg

THERAPEUTIC CLASSIFICATION
Anti-inflammatory, Analgesic Agent

INFORMATION FOR THE CONSUMER

IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT TENOXICAM

• TENOXICAM is a nonsteroidal, anti-inflammatory agent. It has been prescribed by your doctor to relieve symptoms such as inflammation, swelling, fever, stiffness and joint pain, often caused by certain types of arthritis.

• TENOXICAM has been prescribed to you. It should not be given to other people or used for other problems unless specified by your doctor.

• TENOXICAM should be taken only as directed by your doctor. Do not take more of it, do not take it more often or do not take it for a longer period of time than prescribed by your doctor.

• TENOXICAM’s effect is evident in early treatment, however, in certain types of arthritis, up to two weeks may pass before the full benefit may be felt by you.
Before Using TENOXICAM:

THINGS YOU SHOULD TELL YOUR DOCTOR:

• If you have a history of stomach upset, ulcer, liver or kidney disease.

• If you are pregnant or if you intend to become pregnant.

• If you are breast-feeding.

• If you are taking any medication for other unrelated medical problems, such as anticoagulants and/or antidiabetics.

• If you have had any unusual or allergic reactions with other nonsteroidal anti-inflammatory agents or ASA (acetylsalicylic acid) related products.

• If you are presently taking medications to relieve your symptoms of arthritis.

Side Effects:

• As with other medications, some unwanted effects may occur with TENOXICAM. The most common adverse effects encountered are gastrointestinal, such as abdominal distress or discomfort, nausea and heartburn.

• Other side effects do not appear very often, however, they may require medical attention.

  Consult your doctor if the following occur:

  – tightness in chest, shortness of breath, or troubled breathing
  – bloody or black tarry stool
  – blurred vision
- hearing problems
- skin rash, itching or hives
- swelling of face, feet or lower legs
- mental confusion or depression
- indigestion, nausea, vomiting, stomach pain or diarrhea

**NOTE:** Elderly people should report adverse reactions immediately.

**How to Use TENOXICAM:**

- Take TENOXICAM as directed by your doctor.

- Take this medicine immediately after a meal or with food to lessen the chance of stomach upset.

  **NOTE:** If stomach upset (nausea, vomiting, stomach pain, diarrhea, or indigestion) occurs and persists, check with your doctor.

**REMEMBER:**

- Tell your doctor, dentist or pharmacist that you consult or see, that you are taking this medication.

- If you are drowsy, dizzy or lightheaded after taking this medication, be cautious about driving or participating in activities that require alertness.

- Call your doctor, if you have any questions or troubling symptoms.

- Keep this medicine out of the reach of children.
• Read your prescription label carefully; ask your pharmacist if you have any questions.

• Take your medication as directed by your doctor.

• Check with your doctor if you are not getting relief or if any problems develop.

**PHARMACOLOGY**

Tenoxicam has anti-inflammatory, analgesic and antipyretic properties as shown in various pharmacological models.

**Anti-Inflammatory Activity**

The anti-inflammatory activity of orally-administered tenoxicam was determined in rats. Administration of a 30 mg/kg dose of tenoxicam produced a 50% reduction of carrageenan-induced paw edema. Administration of oral doses of the drug (0.3 to 3 mg/kg) caused inhibition of the acute inflammatory response (Days 0 to 4) of adjuvant-induced arthritis in rats. At the development stage, administration of the same amount of drug inhibited the development of arthritis. In the cotton pellet-induced granuloma test, tenoxicam (ED$_{30}$ 8.2 mg/kg), piroxicam and indomethacin were approximately equipotent inhibitors of granuloma formation.

**Analgesic Activity**

The analgesic activity of tenoxicam in the phenylquinone-induced writhing test was compared to that of piroxicam, indomethacin and naproxen in rats. The analgesic potencies of tenoxicam, piroxicam and naproxen were similar (ED$_{50}$ = 1 mg/kg), while that of indomethacin was considerably less (ED$_{50}$ 17 mg/kg). Tenoxicam at doses of 1.25 to 20 mg/kg was active in the
Randall-Sellito test in which painful pressure is applied to the inflamed foot pads of rats.

Tenoxicam was inactive in the hot plate test (ED$_{50} >$300 mg/kg).

**Antipyretic Activity**

The antipyretic activity was shown in hyperetic rats. Following subcutaneous injection of a yeast suspension, the ED$_{50}$ for tenoxicam (0 to 5 hours) was 1.7 mg/kg.

Tenoxicam is a potent inhibitor of prostaglandin and thromboxane synthesis due to its inhibition of fatty acid cyclooxygenase. No difference was seen between the activity of tenoxicam and indomethacin in the inhibition of arachidonic acid-induced platelet aggregation, which is mediated by the interaction of the formed thromboxane A$_2$ and the prostaglandin E$_2$ with their specific receptors. Tenoxicam inhibits platelet aggregation with greater potency than acetylsalicylic acid, but in contrast to ASA, the inhibition is reversible. Platelet adhesion is not affected.

As a consequence of the inhibition of gastric prostaglandin synthesis, tenoxicam, like other NSAIDs, may cause gastrointestinal side effects such as ulcers and gastrointestinal bleeding.

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

As with other NSAIDs, tenoxicam inhibits to a certain extent renal excretion of water and electrolytes in the rat (but not in the dog). The perinatal and postnatal study of tenoxicam showed that it has the potential to inhibit uterine contraction, with the increased incidence of dystocia and delayed parturition, as of all cyclooxygenase inhibitors.
Further studies in mice, rats, rabbits, cats, dogs and monkeys indicate that tenoxicam is devoid of effects on the cardiovascular, respiratory, central and autonomic nervous systems at doses higher than needed for the anti-inflammatory or analgesic response. Tenoxicam does not influence weight of the thymus or the adrenal glands in rats.

**Animal Metabolism**

The pharmacokinetic profile of tenoxicam was determined in rats and dogs. The drug is completely and rapidly absorbed after oral administration to rats and dogs. In rats, radioactivity in the blood attained 70 - 90% of peak plasma concentrations within 15 minutes after oral administration. Very similar plasma-time profiles were seen in dogs after oral administration of $^{14}$C-tenoxicam. In both rats and dogs, a biphasic decline of blood concentrations of tenoxicam was observed.

A significant sex difference for the elimination of tenoxicam was observed in Sprague-Dawley rats after a single oral dose of radioactive tenoxicam. In males, the elimination half-life was 3.4 hours and 17.5 hours for the first and second phase, respectively. In females, the half-lives were 7.2 and 21.2 hours, respectively.

The distribution of the drug was extensive in both species. In rats and dogs, the drug is eliminated from the body through hepatic metabolism. After a single oral (5 mg/kg) administration of $^{14}$C-tenoxicam to male albino rats, approximately 85% of the drug was excreted in 48 hours; 50% in the feces and 35% in the urine. Similar excretion patterns of tenoxicam and its metabolites were seen in beagle dogs.
Human Metabolism

Due to the relatively rapid absorption and the long elimination half-life of tenoxicam, plasma concentration-time profiles after oral and intravenous administration were similar. The absolute bioavailability for the oral drug indicated complete absorption in the unchanged form.

The mean amounts of radioactivity in the feces and urine were 11% and 48%, respectively, 120 hours after administration of a 40 mg oral dose of tenoxicam. Urine collection up to 300 hours after dosing indicated that two-thirds of the oral dose might ultimately be excreted in the urine.

When 20 mg/day was administered orally for 18 days, only tenoxicam and 5-hydroxytenoxicam could be identified and quantified in plasma. At steady state, the concentrations of the metabolite in plasma were only 0.5 - 2% of the corresponding tenoxicam concentrations.

In the urine, 15 - 39% of the administered dose was found as the 5-hydroxy metabolite, whereas the renal excretion of unchanged tenoxicam was only 0.16 - 0.4% of the dose. A small percentage (2.6%) of the dose was excreted as the 5-hydroxytenoxicam glucuronide.

TOXICOLOGY

Acute Toxicity

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>LD$_{50}$ in mg/kg (95% confidence interval)</th>
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<tr>
<td></td>
<td></td>
<td>24 hours after administration</td>
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<tr>
<td>Mice</td>
<td>p.o</td>
<td>771 (717-829)</td>
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<tr>
<td></td>
<td>i.v.</td>
<td>340 (314-368)</td>
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<td></td>
<td>i.p</td>
<td>523 (478-571)</td>
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Toxic effects observed in animals included: yellow discolouration of urine, body weight loss, apathy, diarrhea, fecal blood loss, gastrointestinal erosions, ulceration of the mucous membranes and renal papillary necrosis.

**Chronic Toxicity**

**Rats (80 Weeks):** Tenoxicam was administered orally to rats (35/sex/group) at daily doses of 0, 1, 3 and 6 mg/kg/day. Because of continuously increasing plasma levels and associated side effects, dosing of all groups was suspended from week 39 to 44. The 1 mg/kg/day dose was well tolerated. At 3 mg/kg/day some females presented gastrointestinal mucosal erosions and renal papillary necrosis. Six mg/kg/day caused gastrointestinal erosions and papillary necrosis. The female rats of this group had to be sacrificed after 52 weeks, presenting with gastrointestinal ulceration and renal papillary necrosis.

**Baboons (12 Months):** Groups of four baboons/sex/group received tenoxicam orally at doses of 1, 4 and 20 mg/kg/day. Due to adverse effect on growth, dosing in the 20 mg/kg/day group was suspended from week 24 to 28.

One mg/kg/day was well tolerated. One baboon receiving 4 mg/kg/day was positive for occult blood. Twenty mg/kg/day produced a slightly reduced growth rate and food intake, persistent blood loss and slightly reduced red blood counts. One baboon had a repeated history of gastrointestinal infections with campylobacter and was sacrificed.
CARCINOGENICITY

The carcinogenicity of tenoxicam was studied in mice (51/sex/group) at doses of 0, 1, 3 or 5 mg/kg/day for 80 consecutive weeks, and in rats (50/sex/group) at doses of 0, 1, 3 and 6 mg/kg/day for 104 weeks. There was no evidence of carcinogenicity.

MUTAGENICITY

Investigations in three bacterial systems and four eukaryotic test systems did not reveal any mutagenic potential of tenoxicam.

FERTILITY AND GENERAL REPRODUCTIVE PERFORMANCE

Male and female rats received 0, 2, 4 or 8 mg tenoxicam daily. The males were dosed for at least 63 days prior to mating and the females from 14 days prior to mating to 7 days after mating. The drug had no effect on male fertility or female pregnancy.

At the high dose (8 mg) there was a significant decrease in the number of corpora lutea and implantations resulting in fewer numbers of live fetuses.

TERATOLOGY STUDIES

Mice: Groups of female mice were given 0, 1, 2, 4 or 8 mg/kg tenoxicam orally daily from day 6 to day 15 of gestation. There were no drug-related adverse effects on fetuses or neonates. The functional behaviour of F1 mice was not altered.
Rats: Groups of female rats were given 0, 1, 2, 4, 8 or 12 mg/kg/day tenoxicam orally. The animals were dosed from day 7 to day 17 of gestation. A higher mortality rate was observed in the dams administered 8 (27%) or 12 mg/kg/day (65%).

All dead dams had panperitonitis with gastric lesions characteristic of NSAIDs and uterine hemorrhage. In dams which delivered naturally, drug-related gastrointestinal lesions were also seen in the 8 mg/kg/day group.

Teratogenic effects were not observed and the drug had no effect on the functional behaviour of F₁ rats.

Rabbits: Groups of female rabbits were administered 0, 2, 4, 8, 16 or 32 mg/kg/day tenoxicam orally from day 6 to day 18 of gestation. The number of resorptions was significantly increased in the high dose group. Tenoxicam had no teratogenic effect at the doses tested.

Prenatal and Postnatal Study

Groups of 20 female rats were given 0, 0.25, 0.5, 1.0 or 2 mg/kg/day orally from day 18 of gestation throughout lactation. All animals had a dose-dependent significant prolongation of gestation. The neonatal viability was dose-dependently reduced at doses of 0.5 mg/kg/day or more.

Tenoxicam at doses of 2 mg/kg/day or less had no effect on the reproductive performance or functional behaviour of female rats.


