

PRODUCT MONOGRAPH

^{Pr}TEVA-TIAPROFENIC ACID

(Tiaprofenic acid)

200 mg and 300 mg Tablets

Teva Standard

Anti-inflammatory/Analgesic Agent

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(Tiaprofenic acid)

200 mg and 300 mg Tablets

THERAPEUTIC CLASSIFICATION

Anti–inflammatory/Analgesic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

TEVA–TIAPROFENIC ACID (tiaprofenic acid) is a nonsteroidal, anti–inflammatory agent with analgesic and antipyretic properties. It is a propionic acid derivative. The exact mechanism of action, responsible for the anti–inflammatory, analgesic action is unknown. Tiaprofenic acid inhibits the enzyme prostaglandin synthetase which may be responsible for the reduction in inflammation and pain. The therapeutic effect of tiaprofenic acid does not result from pituitary–adrenal stimulation.

Tiaprofenic acid did not depress the biosynthesis of proteoglycans nor alter the differentiation of proteoglycans secreted in different experimental models with cartilage and cultures of human chondrocytes. The degradation of proteoglycan aggregates was also inhibited. These in vitro results suggest a positive effect of tiaprofenic acid on the joint cartilage. The clinical significance of these findings has to be further investigated.

Pharmacokinetics:

Tiaprofenic acid is rapidly absorbed at the gastric and duodenal levels after oral administration. Peak serum levels are obtained in 30–90 minutes. Food delays the absorption and the time to reach peak plasma concentrations by 10%. Tiaprofenic acid is approximately 98% protein bound. The plasma half–life is approximately 2 hours, following a single dose of 200 mg tiaprofenic acid.

Tiaprofenic acid is primarily eliminated in the urine, 50% as unchanged tiaprofenic acid and two metabolites (II & III) accounting for less than 10%. The metabolites are inactive.

Chronic administration at a dosage of 200 mg tid demonstrated rapid elimination and absence of accumulation. Steady state was attained after one day's treatment and plasma levels approached zero within 24 hours of the last dose.

The times to reach mean peak serum levels were tested in two groups of arthritic patients treated with 200 mg tid and 300 mg bid for 7 days or more. The times were found to be 78 and 50 minutes, respectively. In synovial fluid, the mean time to peak levels was approximately 4 hours for both dosages. Following a 200 mg dose, peak serum and synovial fluid levels reached 26 $\mu\text{g/mL}$ and 5 $\mu\text{g/mL}$, respectively, and 50 $\mu\text{g/mL}$ and 7.7 $\mu\text{g/mL}$ after a 300 mg dose. At 8 hours serum blood levels were lower than those of synovial fluids but by 11 hours these levels were approximately the same.

In another study, rheumatoid arthritis patients were given tiaprofenic acid 200 mg tid for 7 days. After the first dose, a fall in the synovial PGE₂ level occurred inversely to a rise in drug level. The level of PGE₂ remained low after one week's continuous medication. These results indicate that tiaprofenic acid reaches its target organ and is retained within the joint. It also suggests that reduction in PGE₂ production is one of the ways in which tiaprofenic acid acts. The clinical significance of the relative serum and synovial fluid levels has, however, not been elucidated.

A pharmacokinetic study conducted in elderly patients receiving tiaprofenic acid 300 mg bid for 3 months showed no significant differences for all pharmacokinetic parameters (C_{max} , T_{max} , C_9 , $\text{AUC}_{0-9\text{h}}$, $t_{1/2}$) measured at weeks 0, 4, 8 and 12, thus suggesting lack of accumulation.

Fecal blood loss at the therapeutic dose range was less than with usual clinical doses of ASA.

A comparative bioavailability study was conducted between two 300 mg tablet formulations of tiaprofenic acid, TEVA-TIAPROFENIC ACID tablets and SURGAM[®] tablets. Twelve normal, healthy male volunteers completed the study. The pharmacokinetic plasma data is tabulated below:

Pharmacokinetic Indices for Tiaprofenic Acid

	Geometric Mean Arithmetic Mean (C.V.)		Percentage of SURGAM [®]
	TEVA-TIAPROFENIC ACID (300 mg tablet)	SURGAM [®] (300 mg tablet)	
AUC _T (µg•h/mL)	81.45 83.88 (30)	75.94 77.78 (25)	107%
AUC _I (µg•h/mL)	83.1 85.69 (30)	77.48 79.25 (25)	107%
C _{max} (µg/mL)	32.14 32.90 (21)	31.5 32.16 (21)	102%
T _{max} * (h)	1.14 (0.44)	1.25 (0.55)	—
T _{1/2} * (h)	2.28 (0.61)	2.27 (0.39)	—

*For the T_{max} and T_{1/2} parameters these are the arithmetic means (standard deviation).

INDICATIONS AND CLINICAL USE

TEVA-TIAPROFENIC ACID (tiaprofenic acid) is indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis (degenerative joint disease).

CONTRAINDICATIONS

TEVA-TIAPROFENIC ACID (tiaprofenic acid) is contraindicated in the following cases:

Peptic ulcer or active inflammatory disease of the gastrointestinal system.

Known or suspected hypersensitivity to the drug. TEVA-TIAPROFENIC ACID should not be used in patients in whom acute asthmatic attacks, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal, anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals.

WARNINGS

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal, anti-inflammatory drugs (NSAID's) including tiaprofenic acid.

TEVA-TIAPROFENIC ACID (tiaprofenic acid) should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment.

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal, anti-inflammatory drugs (NSAID's). For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision. (See PRECAUTIONS for further advice).

Pregnancy and Lactation:

The safe use of tiaprofenic acid in pregnancy and lactation has not been established. Although no teratogenic effects were seen in animal studies, parturition was delayed and prolonged, and there was an increase in the number of stillbirths. Tiaprofenic acid has been found to cross the placental barrier, but it is not known if it is secreted in breast milk. Hence, this drug is not recommended during pregnancy and lactation.

Use in Children:

TEVA-TIAPROFENIC ACID is not recommended for use in children since its safety and efficacy has not been established in this age group.

PRECAUTIONS

Gastrointestinal System:

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs, TEVA-TIAPROFENIC ACID (tiaprofenic acid) should be discontinued, and appropriate treatment instituted and the patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H₂ receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of tiaprofenic acid therapy when and if these adverse reactions appear.

Renal Function:

As with other NSAID's, long term administration of tiaprofenic acid to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally, nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal, anti-

inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics, and the elderly. Discontinuation of nonsteroidal, anti-inflammatory therapy is usually followed by recovery to the pretreatment state.

Tiaprofenic acid and its metabolites are eliminated primarily by the kidneys, therefore, the drug should be used with great caution in patients with impaired renal function. In these cases lower doses of TEVA-TIAPROFENIC ACID should be administered and patients carefully monitored.

During long-term therapy kidney function should be monitored periodically.

Genitourinary Tract:

In rare cases, symptoms of vesical irritation consisting of bladder pain, dysuria, urinary frequency, hematuria or cystitis have been reported. If such symptoms develop, the drug should be discontinued.

Hepatic Function:

As with other nonsteroidal, anti-inflammatory drugs, borderline increases in one or more liver tests may occur. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with this drug. Severe hepatic reactions including jaundice and cases of fatal hepatitis have been reported with this drug as with other nonsteroidal, anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If this drug is to be used in the presence of impaired liver function, it must be done under strict observation.

Fluid and Electrolyte Balance:

Fluid retention and edema have been observed in patients treated with tiaprofenic acid. Therefore, as with many other nonsteroidal, anti-inflammatory drugs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Hence, TEVA-TIAPROFENIC ACID should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients at risk.

With NSAID treatment, there is a potential risk of hyperkalemia particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; and patients receiving concomitant therapy with beta-adrenergic blockers, angiotensin-converting-enzyme inhibitors or some diuretics.

Hematology:

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when TEVA-TIAPROFENIC ACID is administered.

Blood dyscrasias associated with the use of nonsteroidal, anti-inflammatory drugs are rare, but could be with severe consequences.

Infection:

In common with other anti-inflammatory drugs, TEVA-TIAPROFENIC ACID may mask the usual signs of infection.

Ophthalmology:

Blurred and/or diminished vision has been reported with the use of tiaprofenic acid and other NSAID's. If such symptoms develop TEVA-TIAPROFENIC ACID should be discontinued and an

ophthalmologic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Use in Elderly:

TEVA-TIAPROFENIC ACID should be used with caution in the elderly, and the dosage adjusted individually.

Drug Interactions:

TEVA-TIAPROFENIC ACID is highly bound to serum albumin (98%). This may lead to interaction with anticoagulants, sulfonylurea, hypoglycemic agents, sulfonamides, phenytoin, lithium and certain chemotherapeutic agents such as methotrexate. Therefore, caution should be used when these drugs are used concurrently.

Diuretics: TEVA-TIAPROFENIC ACID may cause water retention and, therefore, could interfere with diuretics in the treatment of hypertension.

Non-steroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers as well as other antihypertensive agents.

Acetylsalicylic Acid: concomitant administration of acetylsalicylic acid results in decreased peak serum concentrations of TEVA-TIAPROFENIC ACID and slight increases in both clearance and apparent half-life.

Steroids: to avoid the possible complications of sudden steroid withdrawal, any reduction in steroid dosage should be gradual in patients receiving concomitant steroid therapy.

ADVERSE REACTIONS

The most common adverse reactions encountered with nonsteroidal, anti-inflammatory drugs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion, particularly in the elderly.

The following side effects were encountered in clinical trials with tiaprofenic acid in 1,361 patients.

	Percentage Incidence	
	Short Term (up to 8 weeks)	Long Term (3–36 months)
<u>GASTROINTESTINAL (16%)</u>		
Indigestion	3.1	13.5
Nausea	5.8	8.2
Heartburn	3.3	6.0
Epigastric pain	2.5	5.3
Vomiting	1.1	4.1
Abdominal pain	2.4	3.1
Constipation	2.9	2.7
Flatulence	1.5	2.2
Diarrhea	2.9	2.2

Less than 1%

Enterocolitis	0.4	0.2
Melena	0.4	0.0

Rare incidents of gastric or duodenal ulceration have been reported although not seen in this series of patients.

CENTRAL NERVOUS SYSTEM (6.2%)

Dizziness	2.4	3.9
Drowsiness	0.4	3.1
Headache	2.9	3.4
Depression	0.8	1.9

Less than 1% (range 0.2 – 0.7%)

Disorientation, tinnitus, insomnia, anxiety, tiredness/weakness.

CUTANEOUS (2.1%)

Rash, erythema, pruritus	1.7	7.2
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Less than 1% (range 0.2 – 0.8%)

Dry skin, onycholysis

CARDIOVASCULAR (1.1%)

Hot flushes	1.0	1.4
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Less than 1% (range 0.3–0.5%)
Chest pain, angina, bruising

RENAL (1.1%)

Edema	1.2	1.9
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Less than 1% (range 0.1–0.5%)
Incontinence, polyuria, oliguria

HEPATIC (Less than 1%)

(See LABORATORY AND BIOCHEMICAL TOLERANCE)

MISCELLANEOUS (2.2%)

Dry mouth/tongue, stomatitis	1.1	2.4
Nosebleeds	0.1	1.4

Less than 1% (range 0.1 –0.5%).

Eye itching/conjunctivitis/red eyes, minor eye ulcers, blurred vision, anorexia, weight gain, cramps, dyspnea, intermenstrual bleeding/vaginal spotting, paresthesia of fingers, sneezing, sweating.

In clinical use of this drug the following additional side effects have been reported: palpebral edema, palpitations, vertigo, tremor, cystalgia, dysuria, pollakiuria, hematuria and cystitis.

Laboratory and Biochemical Tolerance

Combined decrease of hematocrit and hemoglobin: 2.8% of patients. Decrease of hemoglobin: 2.8% of patients. Increased white blood cell count 0.6%; decreased count 0.3%.

Increased gammaglutamic transferase and AST(SGOT): less than 1%. Increased alkaline phosphatase from previously normal levels: less than 1%. In patients with initially high alkaline phosphatase the levels remained high or increased.

Increase in blood urea nitrogen (BUN): 2.5% of total patients (11.8% in the elderly). Increase in BUN and creatinine: 0.4% of patients.

Hyperkalemia: 2.4% of patients.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reports of overdosage with tiaprofenic acid. No specific antidote is known, therefore, the patient should be observed carefully and given symptomatic and supportive treatment.

DOSAGE AND ADMINISTRATION

TEVA-TIAPROFENIC ACID (tiaprofenic acid) 200mg and 300mg Tablets

Rheumatoid Arthritis: The usual initial and maintenance dose is 600 mg daily in 3 divided doses. Some patients may do well on 300 mg twice daily. The maximum daily dose is 600 mg.

Osteoarthritis: The usual initial and maintenance dose is 600 mg daily in 2 or 3 divided doses. In rare cases patients may be maintained on 300 mg daily in divided doses. The maximum maintenance daily dose is 600 mg.

PATIENT INFORMATION LEAFLET

PrTEVA-TIAPROFENIC ACID

Brand of Tiaprofenic acid Tablets

200 mg or 300 mg

Tiaprofenic acid, which has been prescribed to you by your doctor, is one of a large group of nonsteroidal, anti-inflammatory drugs (NSAID's) and is used to treat the symptoms of certain types of arthritis (rheumatism). It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and thus helping to control inflammation and other body reactions.

You should take tiaprofenic acid only as directed by your doctor. Do not take more of it, do not take it more often and do not take it for a longer period of time than your doctor ordered.

If you are taking TEVA-TIAPROFENIC ACID TABLETS:

The usual dose of TEVA-TIAPROFENIC ACID tablets is 600 mg daily taken as 1 tablet of 300 mg morning and night or 1 tablet of 200 mg three times daily. If you miss a dose of TEVA-TIAPROFENIC ACID tablets, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular schedule.

Be sure to take tiaprofenic acid regularly as prescribed. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

This medicine is available only with your doctor's prescription. Remember:

- This medicine has been prescribed for your current medical problem only. It must not be given to other people or used for other problems unless you are otherwise directed by your doctor.

PROPER USE OF THIS MEDICINE

Do not take ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of arthritis while taking tiaprofenic acid unless directed to do so by your physician.

If you are prescribed this medication for use over a long period of time, your doctor will check your health during regular visits to assess your progress and to ensure that this medication is not causing unwanted effects.

SIDE EFFECTS OF THIS MEDICINE

Along with its beneficial effects, tiaprofenic acid, like other NSAID's, may cause some undesirable reactions. Elderly frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur they may require medical attention. Check with your doctor immediately if any of the following are noted:

- Bloody or black tarry stools
- Shortness of breath, wheezing, any trouble in breathing or tightness in the chest
- Skin rash, swelling, hives or itching
- Indigestion, nausea, vomiting, stomach pain or diarrhea
- Yellow discolouration of the skin or eyes, with or without fatigue
- Any changes in the amount or colour of your urine (such as dark; red or brown)
- Swelling of the feet or lower legs
- Blurred vision or any visual disturbance

- Mental confusion, depression, dizziness, lightheadedness
- Hearing problems

ALWAYS REMEMBER

Before taking this medication tell your doctor and pharmacists if you:

- are allergic to tiaprofenic acid or other related medicines of the NSAID group such as acetylsalicylic acid, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, piroxicam, sulindac, diclofenac or tolmetin
- have history of stomach upset, ulcers, or liver or kidney diseases
- are pregnant or intend to become pregnant while taking this medication
- are breast feeding
- are taking any other medication (either prescription or nonprescription)
- have any other medical problem(s)

While taking this medication:

- Tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication.
- Be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication. Tranquilizers, sleeping pills and certain anti-histamines (anti-allergic) may increase the frequency and/or severity of these side-effects.
- Check with your doctor if you are not getting any relief or if any problems develop.
- Report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications.
- Your regular medical checkups are essential.
- If you want more information about this medicine, ask your doctor or pharmacist.

Revised: April 26, 2011

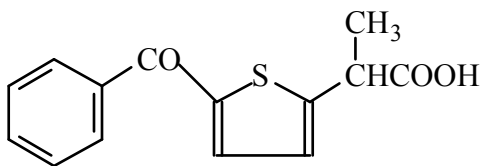
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE:

Proper Name: Tiaprofenic acid

Chemical Name: 5-benzoyl- α -methyl-2-thiophene acetic acid.

Structural Formula:



Molecular Formula: C₁₄H₁₂O₃S

Molecular Weight: 260.31

Description: Tiaprofenic acid is a white microcrystalline powder with a melting point of about 95°C. It is readily soluble in alcohol, chloroform, and acetone but is practically insoluble in water. The pka is approximately 3.0.

STABILITY AND STORAGE RECOMMENDATIONS: Store between 15°-30°C. Unit dose strips should be stored between 15°-25°C and protected from high humidity.

AVAILABILITY OF DOSAGE FORMS

TEVA-TIAPROFENIC ACID (tiaprofenic acid) tablets are available as:

200 mg – Off-white, round, biconvex compressed tablets engraved NOVO and plain on the
200

reverse, containing 200 mg tiaprofenic acid supplied in bottles of 100, 500, 1000
and unit dose boxes of 100.

300 mg – Off-white, round, deep biconvex compressed tablets engraved NOVO and plain on
300

reverse, containing 300 mg tiaprofenic acid supplied in bottles of 100, 500, 1000 and
unit dose boxes of 100.

PHARMACOLOGY

Tiaprofenic acid is a propionic acid derivative which has demonstrated to possess analgesic, anti-inflammatory and antipyretic properties in various pharmacological tests.

Anti-inflammatory activity:

1. Beta naphthoyl-heparamine-induced edema (rats),
2. Carageenin-induced edema in rat paws,
3. Traumatic edema (rats),
4. Ultraviolet induced edema (guinea pigs),
5. Acute adjuvant-induced arthritis (rats),
6. Chronic adjuvant-induced arthritis (rats).

Analgesic activity:

1. Acetic acid induced writhing (rats-mice)
2. Phenylquinone-induced writhing (rats-mice)

Antipyretic effect:

1. Febrile guinea pigs treated with oral doses of tiaprofenic acid at 20 mg/kg.

Gastrointestinal Tolerance:

The ulcerogenic effects of tiaprofenic acid were examined in starved and fed rats. Gastric ulcers were evaluated in 8–16 female rats weighing 130 g, starved for 24 hours before treatment and sacrificed 7 hours afterwards. Intestinal ulcers were evaluated in groups of 8–16 male rats weighing 150 g, 24 hours after treatment.

TABLE 1

Doses in mg/kg p.o.

		Tiaprofenic Acid	Indomethacin	Diclofenac	Ibuprofen
Gastric ulcer	D100	47	9	10	170
Intestinal ulcer	D0	25	1	5	100
	D100	200	15	50	500

D100 = The minimum dose which produced at least one ulcer in all animals.

D0 = The maximum dose which did not cause any lesion in any of the animals.

Tiaprofenic acid has no significant effects on cardiovascular, respiratory and central nervous system in dog, nor on central nervous system in mouse and rat.

TOXICOLOGY

Acute Toxicity LD₅₀ (95% confidence limits) mg/kg

TABLE II

Species	Sex	Route of Administration			
		Oral	Subcutaneous	Intraperitoneal	Intravenous
Mouse	Male	780 (684–889)	640 (595–688)	680 (523–884)	600 (567–633)
Mouse	Female	600 (512–702)	640 (592–691)	670 (587–764)	640 (581–704)
Rat	Male	253 (195–322)	230 (170–310)	253 (204–314)	370 (235–573)
Rat	Female	190 (148–244)	240 (169–312)	220 (166–280)	350 (218–560)
Rabbit	Male	380 (287–501)			340 (279–415)

Signs of toxicity observed in mice, rats and rabbits included respiratory distress, bradypnea, cyanosis, convulsions, excitability, depression, tremors, motor incoordination, writhing, prostration, ptosis and weight loss. Necropsies showed ascites, peritonitis, hypertrophy and congestion of the mesenteric ganglia.

Long-Term Toxicity:

Tiaprofenic acid was administered orally to rats (35 animals/group/sex) at doses of 0, 10, 20 and 30 mg/kg/day, 6 days a week for 24 consecutive weeks. Signs of toxicity observed were dose and sex-related; the 10 mg/kg/day dose was well tolerated. At 20 mg/kg/day jejunoileal ulcerations with perforations and peritonitis were identified and a few cases of hepatic abscesses and

pancreatitis were observed. At a dose of 30 mg/kg/day, anemia and splenic myeloid metaplasia were also observed. A higher death rate from anemia in females was evident.

In a six month study conducted in 32 beagle dogs (4 animals/group/sex) at daily oral doses of 0, 10, 20 and 40 mg/kg. Four animals treated with 10 and 20 mg/kg showed a slight to moderate erosion of the gastric mucosa. At 4 weeks, at a dose of 20 mg/kg, a transient reduction in red blood cell count in females was observed. The following toxic signs in animals receiving 40 mg/kg were observed. Weight loss, anemia, reticulocytosis, transient leucocytosis, reactive polycythaemia, fecal occult blood, jejunum and gastric ulceration, increased megakaryocyte and erythrocyte count and splenic myeloid metaplasia. These effects had been observed after 2–1/2 months.

In another study conducted in baboons (3 animals/group/sex), tiaprofenic acid was orally administered at 0, 10, 30 and 90 mg/kg/day for 6 months. No histological changes occurred in the gastrointestinal tract in the 0, 10 and 30 mg/kg/day groups. At 90 mg/kg/day there was: increased BUN, diarrhea, fecal occult blood, vomiting, weight loss, anemia, leucocytosis, decreased LAP, transient increased SGPT, gastric and ileum lesions. Slight degeneration of the renal tissue and hyalin areas in cortical tubuli were also observed. One female was sacrificed after 8 weeks of treatment due to a general deteriorating condition of unknown cause.

In a one year study, baboons (5 animals/group/sex) were given tiaprofenic acid orally at doses of 0, 10, 25, 50 and 75 mg/kg/day. At the highest dose of 75 mg/kg/day there were microscopic changes in the gastrointestinal tract, especially in the stomach, indicating minor erosions of the mucosa. Similar lesions, confined to the intestines, were noted, in 3 animals at 50 mg/kg/day and 2 female baboons at 25 mg/kg/day. There was no evidence of such lesions in animals killed after a recovery period of 16 weeks.

Carcinogenicity

No evidence of carcinogenicity of tiaprofenic acid was found in mice (60 male and 60 female/group) and in rats (50 male and 50 female/main group; 35 male and 35 female/supplementary group) at oral doses of 0 (control), 10, 20 and 30 mg/kg/day for 80 weeks and 104 weeks, respectively.

Mutagenicity

No evidence of mutagenicity of tiaprofenic acid was observed in the diffusion method, the Ames Test in bacterial strains, or in the mouse using the micronucleus test.

Reproduction and Teratology

Mice (24 animals/group) were treated with doses of 0, 25, 50 and 100 mg/kg/day from days 0 to 17 of pregnancy. No treatment-related effects on pregnancy were observed except for a small increase in the rate of fetal loss at the 100 mg/kg dose.

Rats (24 animals/group) were administered tiaprofenic acid at 0, 5, 10 and 25 mg/kg/day from days 0 to 20 of gestation. At the 10 mg/kg and 25 mg/kg, a slight increase in fetal loss was observed. Rabbits (20 animals/group) received doses of 0, 25, 50 and 75 mg/kg/day from days 0 to 27 of pregnancy. At the 75 mg/kg/day dose, the number of implantation sites were reduced. The rate of fetal loss was also increased at this dose.

Rats (20 males and 24 females per group) were given daily oral doses of 0, 5, 10 and 20 mg/kg, prior to pairing and during the mating period. Mated females were treated throughout gestation (21 days) except for the last 3 days before parturition. A second group was treated during the lactation period (21 days). There was no effect observed on the fertility and the reproductive performance of rats at all doses; however, at the 20 mg/kg/day, the pre and post implantation losses were slightly increased. There was no effect or influence on development and reproduction of the two subsequent generations (F₁ and F₂ off-spring).

In another study in rats (24 animals/group), tiaprofenic acid was administered orally at daily doses of 0, 8, 16 and 24 mg/kg, from day 15 of gestation until day 21 post partum. At doses of 16 and 24 mg/kg, 9 females in each group showed a delayed or lengthened parturition. Means of the length of gestation were $22.42 \pm .16$ and 22.73 ± 0.18 days on 16 and 24 mg/kg, respectively, versus 21.62 ± 0.16 for the control group. Another group of pregnant rats (12 animals) received 16 mg/kg orally from day 0 to 18 of gestation and from parturition until day 21 post partum. There were no adverse effects observed during gestation, parturition or lactation on mothers or pups.

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