PRODUCT MONOGRAPH

PrSURGAM®

(Tiaprofenic Acid Tablets, 200 mg and 300 mg)

PrSURGAM® SR

(Tiaprofenic Acid Sustained Release Capsules, 300 mg)

Anti-inflammatory, analgesic agent

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NAME OF DRUG

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PHARMACOLOGICAL CLASSIFICATION Anti-inflammatory, analgesic agent

ACTIONS AND CLINICAL PHARMACOLOGY

SURGAM (tiaprofenic acid), a propionic acid derivative, is a nonsteroidal anti-inflammatory agent with analgesic and antipyretic properties. Its mechanism of action, as with other nonsteroidal anti-inflammatory agents, is not yet completely known. Tiaprofenic acid is an inhibitor of prostaglandin synthetase enzymes which are known to be associated with inflammation and pain. The therapeutic effect of SURGAM does not result from pituitary-adrenal stimulation.

In vitro and ex vivo studies in different experimental models with cartilage and cultures of human chondrocytes obtained from biopsy specimens have shown that exposure to tiaprofenic acid did not depress the biosynthesis of proteoglycans nor alter the differentiation of proteoglycans secreted. The degradation of proteoglycan aggregates was inhibited. In vivo data in osteoarthritis patients showed a significant reduction in stromelysin (proteoglycanase) activity further to pre-treatment with tiaprofenic acid. These results support tiaprofenic acid as an effective inhibitor of stromelysin and also suggest a positive effect on the joint cartilage under experimental conditions in patients receiving therapeutic doses. The clinical significance of these findings is under further investigation.

Pharmacokinetics

SURGAM (tiaprofenic acid) given orally is rapidly absorbed at the gastric and duodenal levels. Peak serum levels are achieved in 30-90 minutes. It is extensively plasma protein bound (98%). Following a single dose of 200 mg the plasma half-life is approximately 1.7 hours. Food delays the absorption and the time to reach peak plasma concentrations by 10%.

SURGAM is largely eliminated in the urine as unaltered tiaprofenic acid with its two metabolites (II & III) accounting for less than 10%; these metabolites having almost no activity.

Chronic administration of SURGAM at the dosage of 200 mg t.i.d. confirmed rapid elimination and absence of accumulation. Steady state was reached after one day's treatment and plasma levels approached zero within 24 hours of the last dose.

In two groups of arthritic patients treated with SURGAM 200 mg t.i.d. and 300 mg b.i.d. receiving the drug for 7 days or more, the times to reach mean peak serum levels were respectively 78 and 50 minutes; 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 mcg/mL and 5.3 mcg/mL respectively and 50 mcg/mL and 7.7 mcg/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 SURGAM 200 mg t.i.d. for 7 days. After the first dose, a fall in the synovial PGE_2 level occurred inversely to a rise in drug level. The level of PGE_2 remained low after one week's continuous medication. These results indicate that SURGAM reaches its target organ and is retained within the joint. It also suggests that reduction in PGE_2 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.

The results of a 3-month study in elderly osteoarthritis patients receiving SURGAM 300 mg b.i.d. showed no significant differences for all pharmacokinetic parameters (C_{max}, T_{max}, C_9, $AUC_{0\text{-}9h}$, $t_{1\backslash 2}$) measured at weeks 0, 4, 8 and 12, thus suggesting a lack of accumulation.

Feacal blood loss at usual clinical dose was less than with usual clinical doses of ASA.

Following repeated administration of 2 capsules of SURGAM SR 300 mg once daily, C_{max} was reached 4 to 8 hours later, with a significantly higher concentration at 6 hours than that obtained with the regular SURGAM tablets. Steady state was reached 12 hours after the first dose. There were no significant differences in C_{max}, C_{min} and AUC_{0-24h} between the regular and the sustained release formulations.

In patients with rheumatoid arthritis treated with repeated doses of SURGAM SR 600 mg once daily, the time to synovial fluid C_{max} was 8 hours and the synovial fluid AUC_{0-24h} was approximately 36% of the plasma AUC_{0-24h}. Twenty-four hours after the last dose, the tiaprofenic acid concentration was higher in the synovial fluid than in the plasma. The elimination half-life from synovial fluid (median: 8.6 h) was at least twice that from plasma (median: 4.2 h).

In a pharmacokinetics study in elderly patients, no accumulation of tiaprofenic acid was found following repeated once daily administration of SURGAM SR capsules. The mean half-life was 4.4 hours.

The effect of food on the bioavailability of SURGAM SR capsules is not known as no studies have been carried out.

INDICATIONS AND CLINICAL USE

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

CONTRAINDICATIONS

Peptic ulcer or active inflammatory disease of the gastrointestinal system.

Known or suspected hypersensitivity to the drug. SURGAM (tiaprofenic acid) should not be used in patients in whom urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. SURGAM is contraindicated in patients with a history of asthma, whether or not induced by aspirin or non-steroidal ant-inflammatory drugs. 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 (NSAIDs) including SURGAM (tiaprofenic acid).

SURGAM 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 (NSAIDs). 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. The use of this drug is not, therefore, recommended during pregnancy and lactation.

Use in children

The safety and efficacy of SURGAM (tiaprofenic acid) has not been established in children and its use in this age group is therefore not recommended.

PRECAUTIONS

Gastrointestinal system

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

There is no definitive evidence that the concomitant administration of histamine H_2-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 NSAIDs, long-term administration of SURGAM 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 pre-treatment state.

SURGAM (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 SURGAM should be anticipated and patients carefully monitored.

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

Genitourinary tract

Urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis may occur. The onset of these symptoms may occur at any time after the initiation of therapy with tiaprofenic acid. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with tiaprofenic acid **must be stopped** to obtain recovery.

Hepatic function

As with other NSAIDs, borderline elevations of 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 NSAIDs. 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 oedema have been observed in patients treated with SURGAM. Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be born in mind. SURGAM 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 SURGAM is administered.

Blood dyscrasias associated with the use of NSAIDs are rare, but could be with severe consequences.

Infection

In common with other anti-inflammatory drugs, SURGAM (tiaprofenic acid) may mask the usual signs of infection.

Ophthalmology

Blurred and/or diminished vision has been reported with the use of SURGAM and other NSAIDs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmologic examination should be carried out at periodic intervals in any patient receiving this drug for an extended period of time.

Use in elderly

SURGAM should be used with caution in the elderly, and the dosage adjusted individually.

Drug interactions

SURGAM is extensively 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 observed when these drugs are used concurrently.

SURGAM may cause water retention and therefore could interfere with diuretics in the treatment of hypertension.

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

Concomitant administration of acetylsalicylic acid results in decreased peak serum concentrations of SURGAM and slight increases in both clearance and apparent half-life. The clinical significance of these changes is unknown.

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

ADVERSE REACTIONS

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

In clinical trials with SURGAM (tiaprofenic acid) encompassing 1361 patients, the detailed break-down of side effects was as follows:

CLINICAL TOLERANCE

	Percentage of Incidence	
	Short term (up to 8 wks)	Long Term (3-36 mths)
• ***GASTROINTESTINAL (16%)***		
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

Although not seen in this series there have been rare incidents of gastric or duodenal ulceration.

• ***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

Less than 1% (range 0.2 - 0.8%)
Dry skin, onycholysis.

• ***CARDIOVASCULAR (1.1%)***		
Hot flushes	1.0	1.4

Less than 1% (range 0.3 - 0.5%)
Chest pain, angina, bruising.

• ***RENAL (1.1%)***		
Oedema	1.2	1.9

Less than 1% (range 0.1 - 0.5%)
Incontinence, polyuria, oliguria.

• ***HEPATIC*** - Less than 1% (see LABORATORY & 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.

Although not seen in this series, the following additional side effects have been reported in clinical use of this drug: palpebral oedema, palpitations, vertigo, tremor, cystalgia, dysuria, pollakiuria, hematuria and cystitis (SEE PRECAUTIONS).

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 ASAT: 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. No specific antidote is known, therefore treatment should be symptomatic and supportive.

DOSAGE AND ADMINISTRATION

SURGAM 200 and 300 mg 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 instances patients may be maintained on 300 mg daily in divided doses. The maximum maintenance daily dose is 600 mg.

SURGAM SR 300 mg SUSTAINED RELEASE CAPSULES

Rheumatoid arthritis or osteoarthritis

The initial and maintenance dose is two (2) sustained release capsules of 300 mg once daily. SURGAM SR capsules should be swallowed whole.

PHARMACEUTICAL INFORMATION

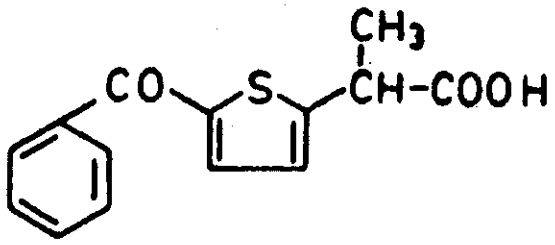
DRUG SUBSTANCE

Proper name: Tiaprofenic acid

Chemical name: Alpha-(5-benzoyl-2-thienyl) propionic acid or 5-benzoyl-alpha-methyl-2 thiophene acetic acid.

Molecular formula: $C_{14}H_{12}O_3S$

Structural formula:



Molecular weight: 260.3

Physical form: White, microcrystalline powder

Solubility: Readily soluble in alcohol, chloroform and acetone; sparingly soluble in water

pK_a: About 3.0

Melting point: About 95°C

COMPOSITION

SURGAM 200 mg, 300 mg tablets
Maize starch, Pluronic F68, magnesium stearate, talc.

SURGAM SR 300 mg capsules
Glyceryl monostearate, microcrystalline cellulose, talc.

Capsule shell:	Gelatin
Cap:	Indigo carmine, erythrosine, titanium dioxide
Body:	Indigo carmine, erythrosine

STABILITY AND STORAGE RECOMMENDATIONS

SURGAM 200 mg, 300 mg tablets, SURGAM SR 300 mg capsules
Store between 15° and 30°C. Protect from excessive heat, light and humidity.

AVAILABILITY OF DOSAGE FORM

SURGAM (tiaprofenic acid) is available as 200 mg and 300 mg white biconvex tablets marked with the Roussel logo on one side; the reverse side is scored with a break-line, one half embossed "SURGAM" and the other half either "200" or "300" as applicable. SURGAM tablets are available in amber glass bottles of 100 (200 mg and 300 mg) and 500 tablets (300 mg).

SURGAM SR (tiaprofenic acid) is available as 300 mg hard gelatin capsules with a transparent pink body and opaque maroon cap printed with "SURGAM SR" on one side and the Roussel logo on the other, each containing off-white spheroidal pellets. SURGAM SR is available in white opaque polyethylene bottles of 60 and 500.

INFORMATION FOR THE PATIENT

HOW TO MAKE SURGAM/SURGAM SR WORK BEST FOR YOU?

Your doctor has decided that SURGAM/SURGAM SR (tiaprofenic acid) is the best treatment for you. As you take SURGAM tablets or SURGAM SR capsules, remember that your chances of controlling your symptoms are greater if you cooperate fully with your doctor and try to become well informed about your condition.

This leaflet is meant to supplement what your doctor or pharmacist have told you. Your doctor knows and understands your personal condition; be sure to follow your doctor's instructions carefully and read any materials he or she gives you. If you have any questions after reading this information leaflet, be sure to ask your doctor or pharmacist.

WHAT IS SURGAM/SURGAM SR AND HOW DOES IT WORK?

SURGAM/SURGAM SR is the product name for tiaprofenic acid, a medicine used to relieve the pain and inflammation associated with certain types of arthritis. It belongs to a family of medicine known as nonsteroidal anti-inflammatory drugs (NSAIDs).

Conditions like yours are usually associated with three (3) symptoms: pain, inflammation and stiffness. By reducing the production of certain substances (prostaglandins) and thus helping to control inflammation and other body reactions, SURGAM/SURGAM SR helps to relieve these symptoms.

WHAT DOES SURGAM/SURGAM SR LOOK LIKE?

SURGAM is available as white round tablets. SURGAM SR is available as a sustained release pink and maroon capsule containing off-white pellets. The tablets and capsules are clearly marked with the Roussel logo and the product name.

HOW SHOULD YOU TAKE SURGAM/SURGAM SR TO MAKE IT WORK BEST FOR YOU?

Your doctor has chosen the strength (dose) that he or she thinks will be most effective in relieving your condition, based on experience with similar medical problems.

If you are taking SURGAM:

The usual dose of SURGAM tablets is 600 mg daily taken as 1 tablet of 300 mg morning and night or 1 tablet of 200 mg three (3) times daily.

If you are taking SURGAM SR:

SURGAM SR capsules have been designed to provide a sustained release of the medicine and thus allow for a convenient once-a-day dosing.

The usual dose of SURGAM SR capsules is two (2) capsules taken once daily. The off-white pellets contained in SURGAM SR capsules must be swallowed whole (not crushed or chewed) for optimal results. For the most relief, take your SURGAM SR at the same time each day.

To help reduce the possibility of stomach upset, take SURGAM/SURGAM SR immediately after a meal or with food or milk.

You should take SURGAM/SURGAM SR only as directed by your doctor. Do not take more or less of it, do not take it more often and do not take it for a longer period of time than your doctor ordered.

It is important to keep taking SURGAM/SURGAM SR even after you start to feel better. This helps to keep your pain, tenderness and stiffness under control. In some types of arthritis, up to two weeks may pass before you feel the full effects of this medicine. However, some people are able to feel improvement in their symptoms right away. If you are not getting adequate relief from your medicine, speak to your doctor before you stop taking it. During treatment, your doctor may decide to adjust the dosage according to your response to the medication.

WHAT TO DO IF YOU MISS A DOSE?

If you miss a dose of SURGAM 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.

If you miss a dose of SURGAM SR capsules once-a-day and remember within 8 hours, take it right away and then resume your regular dosing schedule.

NEVER DOUBLE DOSES.

COMBINING SURGAM/SURGAM SR WITH OTHER MEDICATIONS?

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

DOES SURGAM/SURGAM SR HAVE SIDE EFFECTS?

Along with its beneficial effects, SURGAM/SURGAM SR like all other NSAID drugs, may sometimes cause undesirable effects. Relatively common unwanted side effects of NSAIDs are heartburn, stomach pain, indigestion, nausea, vomiting or diarrhea. If these side effects occur and continue, contact your doctor.

Elderly, frail or debilitated people often seem to experience more frequent or more severe side effects. Although not all of the following 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 or lower abdominal pain or diarrhea (particularly if you have a history of stomach upset or ulcers);
- yellow discoloration of the skin or eyes, with or without fatigue;
- any changes in the amount, frequency 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;
- any pain experienced while urinating.

If you are prescribed this medicine 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.

WHAT SHOULD YOU ALWAYS REMEMBER?

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

- are allergic to SURGAM/SURGAM SR (tiaprofenic acid) or other related medicines of the NSAID group such as acetylsalicylic acid (Aspirin®), diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, piroxicam, sulindac, or tolmetin;
- have a history of liver or kidney diseases;
- have a history of stomach upset or ulcers, since all nonsteroidal anti-inflammatory drugs may aggravate your problem and sometimes even cause bleeding or ulcers in your stomach or intestines;
- are pregnant or intend to become pregnant while taking this medication;
- are breast feeding;
- are taking any other medication (either prescription or non-prescription). This is important because some medicines can interact with each other and cause some unwanted effects.
- 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;
- 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.

Do not share your medication with other members of your family or friends since it may not be appropriate for them.

Keep your medication out of children's reach and protect it from excessive light or humidity.

If you require more information on this drug, consult your doctor or pharmacist.

PHARMACOLOGY

The anti-inflammatory activity of tiaprofenic acid has been demonstrated in the following standard animal models:

1. Beta naphthoyl-heparamine-induced oedema (rats);
2. carageenin-induced oedema in rat paws;
3. traumatic oedema (rats);
4. ultraviolet induced oedema (guinea pigs);
5. acute adjuvant-induced arthritis (rats);
6. chronic adjuvant-induced arthritis (rats).

The analgesic activity of tiaprofenic acid was demonstrated in the following tests:

- acetic acid induced writhing (rats - mice)
- phenylquinone-induced writhing (rats - mice)

The antipyretic effect was observed in 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.

TABLE I

(Doses in mg/kg p.o.)				
	Tiaprofenic Acid	**Indomethacin**	**Diclofenac**	**Ibuprofen**
Gastric ulcer D_{100}*	47	9	10	170
Intestinal ulcer D_0**	25	1	5	100
D_{100}	200	15	50	500
Gastric ulcers were evaluated in groups of 8-16 female rats weighing 130g, starved for 24h before treatment and sacrificed 7h afterwards. Intestinal ulcers were evaluated in groups of 8-16 male rats weighing 150g, 24h after treatment.				

* D_{100} = The minimum dose which produced at least one ulcer in all animals.

** D_0 = 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: LD_{50} (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)
	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)
	Female	190 (148-244)	240 (169-312)	220 (166-280)	350 (218-560)
Rabbit	Male	380 (287-501)	--	--	340 (279-415)

Toxic effects 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.

Chronic 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 being 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 30 mg/kg/day, anemia and splenic myeloid metaplasia were also observed. There was a higher death rate from anemia in females.

A six-month study was 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 slight to moderate erosions of the gastric mucosa. At 4 weeks there was a transient reduction in red blood cell count in females at 20 mg/kg. Animals receiving 40 mg/kg showed the following toxic signs: weight loss, anemia, reticulocytosis, transient leucocytosis, reactive polycythaemia, faecal 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.

Baboons (3 animals/group/sex) were orally administered tiaprofenic acid 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, faecal 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 another study, baboons (5 animals/group/sex) were given tiaprofenic acid orally at doses of 0, 10, 25, 50 and 75 mg/kg/day for 1 year. At 75 mg/kg/day there were microscopic changes in the gastrointestinal tract, particularly 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

The carcinogenicity of tiaprofenic acid was studied in mice (60 males and 60 females/group) and in rats (50 males and 50 females/main group; 35 males and 35 females/supplementary group) at oral doses of 0 (control), 10, 20 and 30 mg/kg/day for 80 weeks and 104 weeks respectively. There was no evidence of carcinogenicity.

Mutagenicity

The possible mutagenic effects of tiaprofenic acid were investigated using the diffusion method and the Ames Test in bacterial strains. Mutagenicity was also investigated in mouse using the micronucleus test. No evidence of mutagenicity was observed.

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 with the exception of 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. A slight increase in fetal loss was observed in the groups receiving 10 mg/kg and 25 mg/kg.

Rabbits (20 animals/group) received doses of 0, 25, 50 and 75 mg/kg/day from days 0 to 27 of pregnancy. The number of implantation sites were reduced at 75 mg/kg/day. The rate of fetal loss was also increased at this dose.

In rats daily doses of 0, 5, 10 and 20 mg/kg were given orally to 20 males and 24 females per group, 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). No effect was observed on the fertility and the reproductive performance of rats at all doses; but, at 20 mg/kg/day, the pre- and the post-implantation losses were slightly increased. There was no effect or influence on development and reproduction of the two subsequent generations (F_1 and F_2 off-spring).

In a study in rats (24 animals/group) treated orally at daily doses of 0, 8, 16 and 24 mg/kg from day 15 of gestation until day 21 post partum, at 16 and 24 mg/kg, 9 females in each of these groups showed a delayed or lengthened parturition. Means of the length of gestation were 22.42 ± 0.16 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. No adverse effects were observed during gestation, parturition or lactation on mothers or pups.

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