PRODUCT MONOGRAPH

[Pr]SURGAM®

(Tiaprofenic Acid Tablets, 300 mg)

[Pr]SURGAM® SR

(Tiaprofenic Acid Sustained Release Capsules, 300 mg)

Anti-inflammatory, analgesic agent

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NAME OF DRUG

PrSURGAM®
(Tiaprofenic Acid Tablets, 300 mg)

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PHARMACOLOGICAL/THERAPEUTIC 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 have 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 $AUC_{0\text{-}24h}$ 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

The following are contraindicated to the use of SURGAM (tiaprofenic acid):

1. Active peptic ulcer, a history of recurrent ulceration or active inflammatory disease of the gastrointestinal system.

2. Known or suspected hypersensitivity to the drug or other non-steroidal anti-inflammatory drugs (NSAIDs). The potential for cross-reactivity between different NSAIDs must be kept in mind.

3. SURGAM is contraindicated in patients with a history of asthma, whether or not induced by aspirin or non-steroidal anti-inflammatory drugs.

4. SURGAM should not be used in patients with the complete or partial syndrome of nasal polyps, or in whom asthma, anaphylaxis, urticaria, rhinitis or other allergic manifestations are precipitated by ASA or other nonsteroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals. As well, individuals with the above medical

problems are at risk of a severe reaction even if they have taken NSAIDs in the past without any adverse effects.

5. Significant hepatic impairment or active liver disease.

6. Severely impaired or deteriorating renal function (creatinine clearance <30 mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.

7. SURGAM is not recommended for use with other NSAIDs because of the absence of any evidence demonstrating synergistic benefits and the potential for additive side effects.

8. Pregnancy (See Warnings).

WARNINGS

- Gastrointestinal system (GI)

- Serious GI toxicity, such as peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal can occur at any time, with or without symptoms in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs) including SURGAM (tiaprofenic acid).

  Minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy. Physicians should remain alert for ulceration and bleeding in patients treated with non-steroidal anti-inflammatory drugs, even in the absence of previous GI tract symptoms.

  In patients observed in clinical trials of such agents, symptomatic upper GI ulcers, gross bleeding, or perforation appear to occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. The risk continues beyond one year and possibly increases.

  The incidence of these complications increases with increasing dose.

- 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 such as ulcerative colitis and Crohn's

disease. In these cases the physician must weigh the benefits of treatment against the possible hazards.

- Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and instruct them to contact a physician immediately if they experience persistent dyspepsia or other symptoms or signs suggestive of gastrointestinal ulceration or bleeding.

- Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients by checking their hemoglobin periodically and by being vigilant for the signs and symptoms of ulceration and bleeding and should inform the patients of the importance of this follow-up.

- If ulceration is suspected or confirmed, or if GI bleeding occurs, SURGAM should be discontinued immediately, appropriate treatment instituted and the patient monitored closely.

- No studies, to date, have identified any group of patients <u>not</u> at risk of developing ulceration and bleeding. A prior history of serious GI events and other factors such as excess alcohol intake, smoking, age, female gender and concomitant oral steroid and anti-coagulant use have been associated with increased risk.

- Studies to date show that all NSAIDs can cause GI tract adverse events. Although existing data does not clearly identify differences in risk between various NSAIDs, this may be shown in the future.

- <u>Genitourinary tract</u>

  Some NSAIDS are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with a NSAID. Some cases have become severe on continued treatment. Tiaprofenic acid appears to have a greater propensity than other NSAIDS to generate reports of cystitis. Although the reaction is generally reversible, non-recognition has led to extensive investigations and even surgical intervention, in some patients. Should urinary symptoms occur, treatment with SURGAM **<u>must be stopped immediately</u>** to obtain recovery. This should be done before any urological investigations or treatments are carried out. Before starting treatment with SURGAM, the patient should be asked to inform his/her physician of any urinary symptoms, even if the patient is familiar with these symptoms from the patient's medical history.

- Use in the Elderly

  Patients older than 65 years and frail or debilitated patients are most susceptible to a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAIDs): the incidence of these adverse reactions increases with dose and duration of treatment. In addition, these patients are less tolerant to ulceration and bleeding. Most reports of fatal GI events are in this population. Older patients are also at risk of lower esophageal ulceration and bleeding.

  For such patients, consideration should be given to a starting dose lower than the one usually recommended, with individual adjustment when necessary and under close supervision. See "Precautions" for further advice.

- Cross-sensitivity

  Patients sensitive to any of the non-steriodal anti-inflammatory drugs may be sensitive to any one of the other NSAIDs also. There is a risk of cross-sensitivity among aspirin and non-steroidal anti-inflammatory drugs, including the group to which tiaprofenic acid belongs. These pseudo-allergic reactions may include symptoms such as rash, urticaria, angiodema or more potentially severe manifestations (e.g. laryngeal oedema, bronchoconstriction, shock). The risk of pseudo-allergic reactions is greater in patients with recurrent rhino sinusitis, nasal polyposis or chronic urticaria. Asthmatic patients are particularly at risk of dangerous reactions. Therefore, tiaprofenic acid must not be administered to patients with asthma.

- Aseptic Meningitis

  In occasional cases, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissues diseases, etc.) seem to be pre-disposed. Therefore, in such patients, the physician must be vigilant to the development of this complication.

- Use in 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. There is also the possible risk of premature closure of the ductus arteriosus, and development of a bleeding tendency

or renal risk in the neonate. Tiaprofenic acid crosses the placental barrier and 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.

- Infection

In common with other anti-inflammatory drugs, tiaprofenic acid may mask the usual signs of infection. If SURGAM is used against symptoms of inflammation accompanying infectious disorders, effective anti-infective therapy is mandatory.

- Fluid Balance

SURGAM may cause sodium and water retention with oedema. At the start of therapy, urine volume and renal function should be carefully monitored in patients with cardiac insufficiency, liver cirrhosis, or nephrotic syndrome and in patients on diuretics (See also Precautions).

PRECAUTIONS

- Gastrointestinal system

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 the continuation of SURGAM (tiaprofenic acid) therapy when and if these adverse reactions appear.

- Renal function

Long term administration of nonsteroidal anti-inflammatory drugs 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 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 utilization of lower doses of SURGAM should be considered and patients carefully monitored.

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

- Hepatic function

As with other NSAIDs, borderline elevations of one or more liver function tests may occur. Though these have been seen in up to 15% of patients treated with other NSAIDS, they have been reported in less than 1% of patients treated with SURGAM during clinical trials (See Adverse Reactions). 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 there is a need to prescribe this drug 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 borne in mind. SURGAM should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With NSAID treatment, there is a potential risk of hyperkalemia particularly in patients with conditions such as diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with beta-adrenergic blockers, angiotensin-converting-enzyme inhibitors or some diuretics. Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients who are at risk.

- Hematology

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to varying degrees; therefore, patients who may be adversely affected by such an action should be carefully observed when SURGAM is administered.

Blood dyscrasias (such as neutropenia, leukopenia, thrombocytopenia, aplastic anemia and agranulocytosis) associated with the use of NSAIDs are rare, but could occur with severe consequences.

- 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.

- Central nervous system:

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of SURGAM. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

- Use in elderly

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

- Drug interactions

Acetylsalicylic acid (ASA) or other NSAIDs:

The use of SURGAM in addition to any other NSAID, including those over the counter ones (such as ASA and Ibuprofen) is not recommended due to the possibility of additive side effects.

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.

Drugs Affecting Blood Formation and Coagulation:

Numerous studies have shown that the concomitant use of NSAIDs and anticoagulants increases the risk of GI adverse events such as ulceration and bleeding.

SURGAM is not recommended for co-administration with vitamin K antagonists, ticlopidine, and heparin due to increased risk of hemorrhage. The possibility of interaction with thrombolytics must be taken into account.

Diuretics

SURGAM can reduce the activity of diuretics (i.e. both their diuretic and antihypertensive effects).

Anti-hypertensives

Nonsteroidal anti-inflammatory drugs can reduce the antihypertensive effect of propranolol and other beta-blockers as well as other antihypertensive agents. Co-administration of NSAIDs and ACE-inhibitors can promote impairment of renal function and/or hyperkalemia.

Glucocorticoids:

Numerous studies have shown that the concomitant use of NSAIDs and oral glucocorticoids increases the risk of GI side effects such as ulceration and bleeding. This is especially the case in older (>65 years of age) individuals.

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

Lithium

SURGAM can reduce the renal excretion of lithium.

Methothrexate

SURGAM can interfere with the plasma protein binding and renal clearance of methothrexate.

Other Drug Interactions

SURGAM is extensively bound to serum albumin (98%). This may lead to interaction with sulfonylurea, hypoglycemic agents, sulfonamides, phenytoin, Therefore caution should be observed when these drugs are used concurrently.

- Laboratory and Diagnostic Tests

No interference known.

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, 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.

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.

In addition, the following side effects have been reported in clinical and postmarket use of tiaprofenic acid:

Gastrointestinal: Disorders of intestinal transit, ulcer, perforation, overt or occult gastrointestinal haemorrhage resulting in anaemia.

Muco-cutaneous: Purpura, urticaria, very rarely erythema multiforme and bulbous eruptions (Stevens-Johnson syndrome or exceptionally toxic epidermal necrolysis); very rarely photosensitivity reactions.

Hypersensitivity Reactions: Asthmatic attacks, especially in subjects allergic to aspirin and other non-steroidal anti-inflammatory agents, angio-oedema, anaphylactic shock.

Haematological: thrombocytopenia, prolongation of bleeding time.

Urinary System: Urinary symptoms (bladder pain, dysuria, and frequency), haematuria or cystitis may occur. When treatment with tiaprofenic acid has been continued for months after onset of the urinary symptoms, inflammatory changes to the urinary tract, sometimes severe, have been observed and a few patients have undergone surgical procedures. Therefore, should any urinary symptom occur, treatment with tiaprofenic acid must be discontinued immediately, Complete recovery after discontinuation is the rule (See Warnings).

Nervous System: Vertigo, tinnitus, tremor.

Renal: Sodium and water retention (see Warnings). As with other NSAIDS, isolated cases of acute interstitial nephritis have been reported with tiaprofenic acid.

Hepatic: Liver test abnormalities.

Other: Palpebral oedema, palpitations.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There have been no reports of overdosage. No specific antidote is known, therefore treatment should be symptomatic and supportive. Early gastric lavage is indicated.

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

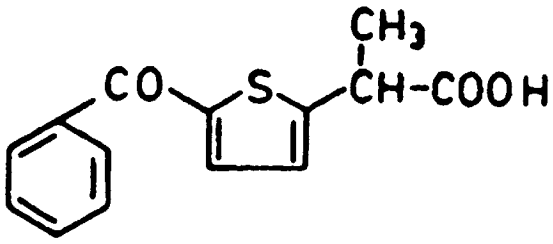
Proper name: Tiaprofenic acid

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 300 mg tablets
Non-medicinal ingredients: Maize starch, Pluronic F68, magnesium stearate, talc.

SURGAM SR 300 mg capsules
Non-medicinal ingredients: Glyceryl monostearate, microcrystalline cellulose, talc.

Capsule shell: Gelatin

Cap: FD&C Blue No.2, FD&C Red No. 3, titanium dioxide

Body: FD&C Blue No.2, FD&C Red No. 3

STABILITY AND STORAGE RECOMMENDATIONS

SURGAM 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 300 mg white to creamy-white biconvex tablets, embossed with the Roussel logo on one side; the reverse side is scored with a break-line, one half embossed "SURGAM" and the other half "300".

SURGAM tablets are available in amber white opaque polyethylene bottles of 100 tablets.

SURGAM SR (tiaprofenic acid) is available as 300 mg hard gelatin capsules with a transparent pink body and opaque maroon cap printed in black 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 capsules.

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). It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and by helping to control inflammation. NSAIDs do not cure arthritis, but they promote suppression of the inflammation and the tissue damaging effects resulting from this inflammation. This medicine will help you only as long as you continue to take it.

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.

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.

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. Taking too much of any of these medicines may increase the chance of unwanted effects, especially if you are an elderly patient.

Be sure to take SURGAM/SURGAM SR as prescribed. 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.

STOMACH UPSET IS ONE OF THE COMMON PROBLEMS WITH NSAIDs:

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. Also, you should remain standing or sitting upright (i.e. do not lie down) for about 15-30 minutes after taking the medicine. This helps to prevent irritation that may lead to trouble swallowing. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your doctor.

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 DOSE.

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 especially when used for a long time or in large doses. 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;
- persistent 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;
- malaise, fatigue, or loss of appetite
- blurred vision or any visual disturbance;
- mental confusion, depression, dizziness, lightheadedness;
- hearing problems;
- any pain or difficulty experienced while urinating.

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

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?

THE RISKS OF TAKING THIS MEDICATION MUST BE WEIGHED AGAINST THE BENEFITS IT WILL HAVE.

BEFORE TAKING THIS MEDICATION TELL YOUR DOCTOR AND PHARMACISTS IF YOU:

- or a family member are allergic to or have had a reaction 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, tolmetin, nabumetone or tenoxicam) manifesting itself by increased sinusitis, hives, the initiating or worsening of asthma or anaphylaxis (sudden collapse);

- or a family member has had asthma, nasal polyps, chronic sinusitis or chronic urticaria (hives);

- 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;

- have blood or urine abnormalities;

- have high blood pressure;

- have diabetes;

- are on any special diet, such as a low-sodium or low-sugar diet.

- are pregnant or intend to become pregnant while taking this medication;

- are breast feeding or intend to breast feed while taking this medication;

- are taking any other medication (either prescription or non-prescription) such as other NSAIDs, high blood pressure medication, blood thinners, corticosteroids, methotrexate, cyclosporin, lithium, phenytoin. This is important because some medicines can interact with each other and cause some unwanted effects.

- have any other medical problem(s) such as alcohol abuse, bleeding problems, etc.

WHILE TAKING THIS MEDICATION:

- tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication;

- some NSAIDs may cause drowsiness or fatigue in some people taking them. 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.

- stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore, do not drink alcoholic beverages while taking this medication;

- check with your doctor immediately if you experience unexpected weakness while taking this medication, or if you vomit any blood or have dark or bloody stools;

- some people may become more sensitive to sunlight than they are normally. Exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, blisters on the skin, skin rash, redness, itching or discoloration; or vision changes. If you have a reaction from the sun, check with your doctor;

- check with your doctor immediately if chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur shortly before, or together with, a skin rash. Very rarely, these effects may be the first signs of a serious reaction to this medication;

- YOUR REGULAR MEDICAL CHECKUPS ARE ESSENTIAL.

HOW SHOULD YOU STORE SURGAM/SURGAM SR?

Store SURGAM/SURGAM SR between 15˚ and 30˚C. Protect from excessive heat, light and humidity.

THE SAFETY AND EFFICACY OF SURGAM HAS NOT BEEN ESTABLISHED IN CHILDREN AND ITS USE IN THIS AGE GROUP IS THEREFORE NOT RECOMMENDED.

DO NOT KEEP OUTDATED MEDICINE OR MEDICINE NO LONGER NEEDED.

THIS MEDICATION HAS BEEN PRESCRIBED FOR YOUR MEDICAL PROBLEM.
DO NOT GIVE IT TO ANYONE ELSE.

KEEP YOUR MEDICATION OUT OF CHILDREN'S REACH.

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	Intra-peritoneal	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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