

Data Sheet

Surgam[®]

NAME OF MEDICINE

Non-proprietary Name

Tiaprofenic acid

DESCRIPTION

SURGAM is tiaprofenic acid which is the INN for 2-(5 benzoyl-2-thienyl) propionic acid. It is a white, or practically white, microcrystalline powder. The molecular weight is 260.3 and the MP about 97°C. Tiaprofenic acid is sparingly soluble in water and dilute HCl (<0.5%), but soluble in alcohol, acetone and other organic solvents.

PHARMACOLOGY

Class

Tiaprofenic acid is a non-steroidal, anti-inflammatory, analgesic compound, developed by Roussel Uclaf, and belongs to the propionic acid class.

Site and Mode of Action

Tiaprofenic acid displays analgesic, anti-inflammatory and anti-pyretic activity.

Classical pharmacological studies in animals both in vitro and in vivo have shown that tiaprofenic acid inhibits the biosynthesis of prostaglandins, and is a non-selective antagonist of bradykinin, prostaglandin E₂, serotonin, histamine and acetyl-choline.

Further animal experiments have shown that these actions produce analgesic, anti-inflammatory and antipyretic effects. Tiaprofenic acid exhibits its anti-inflammatory effect even on adrenalectomised animals, indicating that its action is not mediated through the pituitary adrenal axis.

Results of most in vitro studies in animal models, using articular cartilage explants and chondrocyte cultures, indicate that tiaprofenic acid does not depress biosynthesis of proteoglycans. In vitro studies with animal and human tissue provide evidence of inhibition of proteoglycan degradation by tiaprofenic acid. These results suggest that a positive effect on the joint cartilage may be expected, but in vivo effects and the clinical significance of the findings are yet to be clarified.

Pharmacokinetics

Absorption

Studies in man have shown that tiaprofenic acid is rapidly and completely absorbed after oral administration, the most likely site of absorption being the duodenum. Administration of doses from 100mg to 600mg p.o. produced corresponding peak plasma levels of 7, 18 and 54 mcg/mL, at one half to one hour after administration.

Although food delays time to T_{max}, it does not significantly affect other pharmacokinetic parameters. Plasma pharmacokinetics studied during 13 days administration at 200mg t.d.s. showed that steady state concentrations are achieved after one day's administration.

Distribution

Tiaprofenic acid is not widely distributed in the body: the volume of distribution in 40 healthy volunteers after a single oral dose of 200mg was 6.7L and after a single dose of 300mg was 5.4L. Tiaprofenic acid is highly protein bound to plasma proteins (98%), which could account for the small volume of distribution figures.

However, appreciable levels of tiaprofenic acid are achieved in synovial fluid (C_{max} = 6.9 microgram/mL) and remains fairly constant over an 8 hour period. These levels are independent of plasma levels and demonstrate that the compound penetrates the synovial membrane and is retained in synovial fluid.

This mechanism helps explain the clinical finding that 200mg t.d.s. and 300mg b.d. are equally effective. The short half-life of elimination would suggest that, theoretically, this should not occur.

Metabolism

Human metabolism of tiaprofenic acid is confined to two structurally confirmed compounds. The first occurs as a result of reduction of the ketone function to an alcohol, and the second as a result of hydroxylation of the benzene ring in the para position to the ketone structure. Analysis of urine following oral administration of 100mg tiaprofenic acid reveals that less than 5% of total recovery is due to metabolites.

Excretion

The acute toxicity of both metabolites have been shown in mice to be considerably less than the parent compound. Tiaprofenic acid is excreted 50% in urine, but may rise to 80% depending on the degree of enterohepatic recycling. Approximately 10% of total excretion is in the form of the metabolites. The systemic half-life is two to three hours.

Plasma clearance is virtually complete 24 hours after administration with a particularly rapid decline after four hours.

Chronic administration studies over 13 days showed that the AUCs after the first dose and last dose of the study were not significantly different, indicating that no accumulation of tiaprofenic acid is likely to occur.

At steady state, a dose of two SURGAM SA 300mg capsules produces a C_{max} of 28.1 mg/L which is not significantly different from the C_{max} produced by a dose of one conventional SURGAM 300mg tablet (37.3 mg/L). The plasma concentration remains above 10 mg/L for 6-8 hours following a dose of two SURGAM SA capsules, compared to 2-3 hours following one 300mg tablet.

Despite these differences in profile, there is no significant difference in the amount of tiaprofenic acid absorbed as measured by areas under the plasma concentration curve (for a 24 hour period, with twice daily administration of the conventional tablet and once daily administration of the sustained-release capsule) and quantities eliminated in the urine.

INDICATIONS

Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, low back pain, musculoskeletal disorders such as fibrositis, capsulitis, epicondylitis and other soft-tissue inflammatory conditions; sprains and strains, dysmenorrhoea, post-operative inflammation and pain including that associated with dental procedures and other soft-tissue injuries.

CONTRAINDICATIONS

Severe heart failure.

SURGAM is contraindicated in patients who are hypersensitive to tiaprofenic acid or any other compound which inhibits prostaglandin synthesis or in whom aspirin or other non-steroidal anti-inflammatory agents induce rhinitis or urticaria.

Active or history of peptic ulcer/haemorrhage.

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

History of gastrointestinal bleeding or perforation, related to previous NSAIDs therapy.

Severe renal or hepatic impairment.

Pregnancy (see Use in Pregnancy)

Children (see Paediatric Use).

WARNINGS

Undesirable effects may be minimised by using the minimum effective dose for the shortest duration necessary to control symptoms.

Caution should be advised in patients receiving concomitant medications which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin-reuptake inhibitors or anti-platelet agents such as aspirin.

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti-inflammatory compounds, including SURGAM (tiaprofenic acid). These may occur at anytime during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events.

SURGAM should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulitis 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 NSAIDs, including this compound, 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.

SURGAM is not recommended for patients with active bladder or prostatic disease or symptoms, or those with a history of recurrent urinary tract disorders, as the symptoms of an adverse reaction to tiaprofenic acid may not be attributed to it.

Before starting treatment with tiaprofenic acid, patients should be asked to inform the prescriber about any urinary symptoms which develop during treatment (see Precautions - Genito-urinary Tract).

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory compounds. 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.

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, angioedema or more potentially severe manifestations (eg. laryngeal oedema, bronchoconstriction, shock). The risk of pseudo-allergic reactions is greater in patients with recurrent rhinosinusitis, nasal polyposis or chronic urticaria. Asthmatic patients are particularly at risk of dangerous reactions. Therefore, tiaprofenic acid must not be administered to patients with a history of asthma.

As with all NSAIDs, if tiaprofenic acid is to be used against inflammation resulting from infectious disorders, it must be accompanied by effective anti-infective therapy.

PRECAUTIONS

Cardiovascular Thrombotic Events:

Observational studies have shown that non-selective NSAIDs may be associated with an increased risk of serious CV events including myocardial infarction, stroke and heart failure, which may increase with dose or duration of use and patients with CV disease or risk factors for CV disease may be at greater risk. , To minimise the potential risk of an adverse CV event, especially in patients with CV risk factors, the lowest effective dose should be used for the shortest possible duration. There is no consistent evidence to suggest that concurrent use of aspirin mitigates the increased risk of serious CV events associated with NSAID use.

Hypertension:

NSAIDs can lead to onset of new hypertension or worsening of pre-existing hypertension. Patients taking antihypertensives along with NSAIDs may have an impaired antihypertensive response and hence NSAIDs should be administered with caution in patients with hypertension. Furthermore, when given to patients with hypertension, blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart Failure:

Fluid retention and oedema have been observed in some patients taking NSAIDs and NSAIDs should be used with caution in patients with fluid retention or heart failure.

Gastrointestinal Events:

All NSAIDs can cause GI discomfort and serious, potentially fatal GI effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3-6 months and in about 2-4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However even short term therapy is not without risk.

Caution is advised in patients with risk factors for GI events who may be at greater risk of developing serious GI events, eg. the elderly (increased frequency of GI bleeding and perforation, which may be fatal), those with a history of serious GI events, smoking and alcoholism. NSAIDs should be given with care to patients with a history of GI disease (ulcerative colitis, Crohn's disease) as their condition may be exacerbated. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious GI toxicity.

The concurrent use of NSAIDs and aspirin does increase the risk of serious GI events.

There is no definite 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.

Serious Cutaneous Reactions:

NSAIDs may very rarely cause serious cutaneous reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of skin rash or any signs of hypersensitivity.

Peripheral Oedema

Peripheral oedema with salt retention has been observed in some patients taking SURGAM. Therefore, it should be used with caution in patients with compromised cardiac function, cirrhosis of the liver or nephrotic syndrome, patients on diuretics, patients with chronic renal impairment and especially in aged patients.

Hepatic Function

As with other nonsteroidal anti-inflammatory agents, treatment with SURGAM should be given with close supervision of patients with a history of impaired hepatic function or liver disease. Abnormalities in liver function tests have been reported during treatment with NSAIDs. 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 function test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction whilst on therapy with SURGAM. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with NSAIDs. Such reactions are rare. Should abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (eg. eosinophilia, rash, etc.), this medication should be discontinued. Liver function should be monitored periodically.

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 haematuria, 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 volume, where the renal prostaglandins have a supportive role in the

maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory agent 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.

In patients with chronic renal insufficiency, SURGAM should be used with caution and careful monitoring of renal function is required. During long-term therapy kidney function should be monitored periodically.

Renal Impairment

SURGAM and its metabolites are eliminated primarily by the kidneys, therefore, the compound should be used with great caution in patients with impaired renal function.

SURGAM is contraindicated in patients with severe renal impairment

Genito-urinary Tract

Tiaprofenic acid is different from other NSAIDs in its capacity to cause urinary system disorders, particularly cystitis. Non-recognition has led to a number of cases of severe morbidity requiring extensive investigations and surgical intervention.

Other urinary symptoms reported with tiaprofenic acid include bladder pain, dysuria, haematuria, increased micturition, frequency etc. some of these reactions and, on occasion, cystitis have also been reported with other registered NSAIDs.

Should urinary symptoms occur, treatment with tiaprofenic acid must be stopped to achieve recovery.

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

Haematology

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.

The incidence of blood dyscrasias associated with the use of NSAIDs is rare: this condition would have severe consequences.

Infection

In common with other anti-inflammatory compounds, SURGAM 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 compound should be discontinued and an ophthalmological examination performed; ophthalmic examinations should be carried out at periodic intervals in any patient receiving this compound for an extended period of time.

Photosensitivity

As with some other NSAIDs, photosensitivity during treatment with SURGAM has been reported. Should any patients experience inexplicable rash or skin irritation, therapy should be ceased.

Effects on Fertility

The use of NSAIDs may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of NSAID should be considered.

Use in Pregnancy

Pregnancy Category C. The safety of SURGAM in pregnancy has not been established. SURGAM crosses the placental barrier. Although no teratogenic effects were seen in animal studies, parturition was delayed and prolonged, and there was an increase in the number of still-births. It should not be administered during known or suspected pregnancy and must not be used during the final three months of pregnancy.

Use in Lactation

A small quantity of tiaprofenic acid passes into breast milk but the effect of SURGAM on the newborn is not known, thus the use of SURGAM in lactating mothers is not recommended.

Paediatric Use

The safety and efficacy of SURGAM has not been established in children and its use in this age group, therefore, is not recommended. It must not be used in children under three years of age.

Use in the Elderly

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

Use while Operating Machinery

As with other drug products, the ability to drive or operate machinery may be impaired.

Interactions with other Medicines

SURGAM is extensively bound to serum albumin (98%). This may lead to interaction with anticoagulants, sulphonylurea hypoglycaemic agents, sulphonamides, phenytoin, lithium and certain chemotherapeutic agents such as methotrexate. Therefore, caution should be observed when these compounds are used concurrently. It is recommended that lithium levels are monitored in patients receiving lithium and SURGAM concomitantly.

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

Hypertensive patients controlled by anti-hypertensive therapy should be monitored to ensure that there is no loss of anti-hypertensive effect.

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.

Corticosteroids: Increased risk of GI ulceration or bleeding. In patients receiving concomitant steroid therapy, any reduction in steroid dosage should be gradual to avoid the possible complications of sudden steroid withdrawal.

Anticoagulants (ie. Heparin, warfarin) and platelet aggregation inhibitors (ie. ticlopidine, clopidogrel): The concurrent use of warfarin and NSAIDs has been associated with severe, sometimes fatal, haemorrhage. The exact mechanism of the interaction is unknown but may involve enhanced bleeding from NSAID-induced gastrointestinal ulceration, or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAIDs. Therefore NSAIDs should only be used in combination with warfarin if absolutely necessary, and patients taking this combination should be closely monitored.

SURGAM may increase the risk of haemorrhage in patient's receiving vitamin K antagonists such as ticlopidine and heparin.

Tiaprofenic acid may increase the risk of renal impairment and/or hyperkalemia associated with ACE inhibitor therapy.

Animal studies have shown that the anti-inflammatory effect of SURGAM is additive to that of indomethacin, dexamethasone and aspirin.

In animals, behavioural effects of ethanol have been shown to be potentiated by SURGAM.

Selective serotonin reuptake inhibitors (SSRIs): Increased risk of GI bleeding.

Combination use of ACE inhibitors or angiotensin receptor antagonists, anti-inflammatory drugs and thiazide diuretics

Concomitant use of a renin-angiotensin system inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID, including COX-2 inhibitor) and a thiazide diuretic may increase the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. The combination of these agents should be administered with caution, especially in the elderly and in patients with pre-existing renal impairment. Renal function (serum creatinine) should be monitored after initiation of concomitant therapy, and periodically thereafter.

Effect on Laboratory Tests

Combined decrease of haematocrit and haemoglobin: 2.8% of patients. Decrease of haemoglobin: 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.

Hyperkalaemia: 2.4% of patients.

Tiaprofenic acid may reduce the serum uric acid level in patients.

ADVERSE EVENTS

The most common adverse events 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 encompassing 1361 patients, the detailed break-down of adverse events was as follows:

	Percentage Short-term (up to 8 wks)	Incidence Long-term (3-36 months)
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
Diarrhoea	2.9	2.2
Less than 1%		
Enterocolitis	0.4	0.2
Melaena	0.4	0.0

Although not seen in this series, there have been rare incidents of gastric or duodenal ulceration, perforation, overt or occult gastrointestinal haemorrhage resulting in anaemia.

	Short-term (up to 8 wks)	Long-term (3-36 mths)
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
Photosensitivity	< 2	n/a

Less than 1% (range 0.2-0.8%)

Dry skin, onycholysis

Urticaria, purpura and very rarely (<0.01%) erythema multiform and bullous eruptions (Stevens-Johnson syndrome or, exceptionally, toxic epidermal necrolysis) have been reported.

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%)

Oedema	1.2	1.9
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Less than 1% (range 0.1-0.5%)

Incontinence, polyuria, oliguria

As with other NSAIDS, isolated cases (<0.01%) of acute interstitial nephritis have been reported with SURGAM.

Hepatic - less than 1% (see CLINICAL LABORATORY TESTS)

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, dyspnoea, intermenstrual bleeding/vaginal spotting, paraesthesia 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, haematuria, cystitis, aphtous, bladder pain and urinary frequency (see PRECAUTIONS).

The frequency of some adverse events may differ for SURGAM SA capsules compared to SURGAM conventional tablets. Studies with the sustained-release capsule have shown that constipation in long term usage may have a frequency of 4 to 6%, and may be severe in nature in some patients.

Hypersensitivity reactions such as asthmatic attacks have occurred. These occur especially, but not exclusively, in patients allergic to aspirin and other non-steroidal anti-inflammatory agents. Angio-oedema and anaphylactic shock have been reported.

Thrombocytopenia or prolongation of bleeding time has been observed.

Aseptic meningitis has been reported as a rare potential adverse effect from the administration of several anti-inflammatory medications, including selective and non-selective COX inhibitors.

DOSAGE AND ADMINISTRATION

SURGAM tablets should be taken with plenty of fluids and may be taken with or without food.

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

SURGAM Tablets

The recommended maximum dose for SURGAM is 600mg daily, in divided doses: 300mg twice daily.

Dosage has been commenced at 300mg daily (conventional tablets) and found to have some effect; therefore, dosage adjustment between 300mg and 600mg daily may be desirable.

Children

SURGAM is not recommended for use in children as the safety and efficacy in this age group has not been established.

Elderly/Impaired Renal Function

Elderly patients are more prone to adverse effects. Caution must be taken with dosing in the elderly and in renal impairment.

OVERDOSAGE

After an overdose, the principal aim should be to prevent absorption of the active compound. This may be achieved by administration of 50g to 100g of activated charcoal as a slurry, if given within two hours of overdose.

The principal features of poisoning by overdose of NSAIDs are hypotension/cardiovascular collapse, renal failure, respiratory depression, convulsions, hypoprothrombinaemia and gastrointestinal ulceration/haemorrhage. These should be treated by appropriate supportive therapy.

Contact the Poisons Information Centre for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

SURGAM 300mg Tablets

White, biconvex, 11 mm in diameter (marked "SURGAM 300 mg" on one side and logo on reverse). Each tablet contains 300 mg tiaprofenic acid.

SURGAM 300mg tablets are available in blister packs of 60 tablets. This pack should be stored below 25°C.

MEDICINE CLASSIFICATION

Prescription Medicine.

NAME AND ADDRESS

sanofi-aventis new zealand limited
Level 8, James & Wells Tower
56 Cawley St
Ellerslie
Auckland

DATE OF PREPARATION

21 September 2007