SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Surgam Tablets 300mg.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 300 mg Tiaprofenic Acid.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, low back pain, musculo-skeletal disorders such as fibrositis, capsulitis, epicondylitis and other soft-tissue inflammatory conditions, sprains and strains, post-operative inflammation and pain and other soft tissue injuries.

4.2 Posology and method of administration

Posology

Adults

600 mg daily in divided doses:

- 300mg twice a day.
- Alternatively, 200mg three times a day.

Elderly

As for adults (see section 4.4). NSAIDs should be used with particular caution in older patients who are at increased risk of the serious consequences of adverse reactions.

In cases of renal, cardiac or hepatic impairment, the dosage should be kept as low as possible. It is suggested that in such cases, the dosage be reduced to 200 mg twice daily.

If an NSAID is considered necessary, elderly patients should receive the lowest effective dose for the shortest possible duration and be monitored regularly for gastrointestinal bleeding for following initiation of NSAID therapy.

Paediatric population

There are insufficient data to recommend use of Surgam in children.

Method of administration

- For oral administration.
- To be swallowed whole.
- To be taken preferably with or after food.

4.3 Contraindications

- Active or history of recurrent peptic ulcer/hemorrage (two or more distinct episodes of proven ulceration or bleeding).

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

- Active bladder or prostatic disease or symptoms.

- History of recurrent urinary tract disorders.

- Hypersensitivity to tiaprofenic acid or to any of the excipients.

- NSAIDs are contraindicated in patients who have previously shown hypersensitivity reactions (e.g. asthma, rhinitis, angioedema or urticaria) in response to ibuprofen, aspirin, or other non-steroidal anti-inflammatory drugs.

- During the last trimester of pregnancy (see Section 4.6)

- Severe heart failure, hepatic failure and renal failure (see section 4.4).

4.4 Special warnings and precautions for use

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see GI and cardiovascular risks below). Patients treated with NSAIDs long-term should undergo regular medical supervision to monitor for adverse events.

The use of Surgam with concomitant NSAIDs including cyclooxygenase-2 selective inhibitors should be avoided (see section 4.5).

Tiaprofenic acid should be used with caution in:

- patients with chronic renal insufficiency (particularly careful monitoring of renal function is required).
- patients with arterial hypertension and/or heart failure.
- elderly subjects as they have an increased frequency of adverse reactions to NSAIDs, particularly gastrointestinal bleeding and perforation, which may be fatal (see section 4.2).
- patients with a history of hepatic insufficiency.

Respiratory disorders

Caution is required if administered to patients suffering from, or with a previous history of, bronchial asthma since NSAIDs have been reported to precipitate bronchospasm in such patients.

Sodium and water retention

Tiaprofenic acid 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 a history of hypertension, cardiac insufficiency, liver cirrhosis, or nephrotic syndrome, and in patients on diuretics.

Urinary symptoms and cystitis

Urinary symptoms and cystitis have been reported with tiaprofenic acid and other NSAIDs. Tiaprofenic acid appears to have a greater propensity than other NSAIDs to generate reports of cystitis. Tiaprofenic acid can cause cystitis which may become severe if the treatment is continued after the onset of urinary symptoms. Non-recognition has led to extensive investigations and even surgical intervention, in some patients. If urinary symptoms such as frequency, urgency, dysuria, nocturia or haematuria occur, tiaprofenic acid should be stopped immediately and urinalysis and urine culture performed, and complete recovery is the rule.

Before starting treatment with tiaprofenic acid, the patient should be asked to inform his/her physician of any urinary symptom, even if the physician is familiar with these symptoms from the patient's medical history (see Adverse Reactions). Patients should

be warned about the onset of urinary symptoms which may suggest cystitis and are advised to stop taking the drug and seek medical advice if these occur.

Gastrointestinal bleeding, ulceration and perforation

GI bleeding, ulceration or perforation, which can be fatal, has been reported with all NSAIDs at any time during treatment, with or without warning symptoms or a previous history of serious GI events.

The risk of GI bleeding, ulceration or perforation is higher with increasing NSAID doses, in patients with a history of ulcer, particularly if complicated with haemorrhage or perforation (see section 4.3), and in the elderly. These patients should commence treatment on the lowest dose available. Combination therapy with protective agents (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other drugs likely to increase gastrointestinal risk (see below and section 4.5).

Patients with a history of GI toxicity, particularly when elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly in the initial stages of treatment.

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, anti-platelet agents such as aspirin, or nicorandil (see section 4.5).

When GI bleeding or ulceration occurs in patients receiving Surgam, the treatment should be withdrawn.

NSAIDs should be given with care to patients with a history of gastrointestinal disease (ulcerative colitis, Crohn’s disease) as their condition may be exacerbated (see section 4.8).

Dermatological

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDSs. Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Surgam should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Impaired female fertility

The use of Surgam 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 Surgam should be considered.

Cross-sensitivity reactions

There is a risk of cross-sensitivity among aspirin and NSAIDs, including the group to which tiaprofenic acid belongs. These pseudo-allergic reactions may include rash, urticaria and angioedema or more potentially severe manifestations (e.g. laryngeal oedema, bronchoconstriction and 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 a history of asthma.

Blood disorders

As NSAIDs can interfere with platelet function, they should be used with caution in patients with intracranial haemorrhage and bleeding diathesis.

Cardiovascular, renal and hepatic impairment

The administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics and the elderly. Renal function should be monitored in these patients (see also section 4.3).

Cases of acute renal failure after initiation of high dose or multiple non-steroidal anti-inflammatory drugs (NSAIDs) have been reported in patients treated with tenofovir disoproxil fumarate and with risk factors for renal dysfunction. If tenofovir disoproxil fumarate is co-administered with an NSAID, renal function should be monitored adequately.

Cardiovascular and cerebrovascular effects

Appropriate monitoring and advice are required for patients with a history of hypertension and/or mild to moderate congestive heart failure as fluid retention and oedema have been reported in association with NSAID therapy.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with a small increased risk of arterial thrombotic events (for example myocardial infarction or stroke). There are insufficient data to exclude such a risk for tiaprofenic acid.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with tiaprofenic acid after careful consideration. Similar consideration should be made before initiating longer-term treatment of patients with risk factors for cardiovascular disease (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

An increased risk for arterial thrombotic events has been reported in patients treated with non-aspirin NSAIDS (e.g. parecoxib and valdecoxib) for perioperative pain in

the setting of coronary artery bypass surgery (CABG). This effect has not been observed with tiaprofenic acid

SLE and mixed connective tissue disease

In patients with systemic lupus erythematosus (SLE) and mixed connective tissue disorders there may be an increased risk of aseptic meningitis (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Heparin, hypoglycaemic agents and diuretics: Since Surgam is highly protein-bound, it is not recommended for co-administration with other highly protein-bound drugs such as heparin. Modification of the dosage may be necessary with hypoglycaemic agents, phenytoin and diuretics. With oral hypoglycaemic agents, an inhibition of metabolism of sulphonylurea drugs, prolonged half-life and increased risk of hypoglycaemia has been reported.

Anticoagulants and antiplatelet agents: It is considered unsafe to take NSAIDs in combination with anticoagulants due to increased risk of bleeding.

- Heparin
- Vitamin K antagonists (such as warfarin)
- Platelet aggregation inhibitors (such as ticlopidine, clopidogrel)
- Thrombin inhibitors (such as dabigatran)
- Direct factor Xa inhibitors (such as apixaban, rivaroxaban, edoxaban)

If co-administration is unavoidable, patient should be closely monitored.

Other analgesics including cyclooxygenase-2 selective inhibitors: Concomitant use of Surgam with other NSAIDs (including cyclooxygenase-2 selective inhibitors) and high-dose salicylates should be avoided due to an increased risk of adverse effects, particularly upper gastrointestinal disorders.

Corticosteroids: Caution must be exercised when Surgam is administered with corticosteroids due to increased risk of gastrointestinal ulceration or bleeding.

Nicorandil: In patients concomitantly receiving nicorandil and NSAIDs, there is an increased risk for severe complications such as gastrointestinal ulceration, perforation and hemorrhage (see section 4.4).

Cardiac glycosides and sulphonamides: Caution should be exercised when Surgam is administered with cardiac glycosides and sulphonamides. With cardiac glycosides, NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma cardiac glycoside levels.

Methotrexate: Concomitant use of Surgam with methotrexate causes a decreased elimination of methotrexate. Concomitant use with high dose methotrexate should be avoided. Use with caution with low dose methotrexate.

Tenofovir: Concomitant administration of tenofovir disoproxil fumarate and NSAIDs may increase the risk of renal failure.

Lithium: Decreased elimination of lithium. NSAIDs have been reported to increase steady state plasma levels of lithium and it is, therefore, recommended that these levels are monitored in patients receiving Surgam therapy.

Mifepristone: Aspirin and other NSAIDs should not be used for at least 8-12 days after mifepristone administration as NSAIDs can reduce the effect of mifepristone.

Diuretics: Caution must be exercised when Surgam is administered with diuretics: it reduces both the diuretic and antihypertensive effect of diuretics and increase risk of renal impairment and/or hyperkalemia. Diuretics can increase the risk of nephrotoxicity of NSAIDs.

Tacrolimus: Possible increased risk of nephrotoxicity when NSAIDs are given with tacrolimus.

Zidovudine: Increased risk of haematological toxicity when NSAIDs are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Caution must be exercised when Surgam is administered with ACE inhibitors and Angiotensin II Receptor Antagonists: Further deterioration of renal function, including possible acute renal failure, in patients with compromised renal function (e.g. dehydrated patients or elderly patients).

The possibility of interaction must be taken into account with:

- *Thrombolytics:* Increased risk of haemorrhage.
- *Anti-hypertensives agents (diuretics, beta-blockers, ACE-inhibitors, Angiotensin II Receptor Antagonists):* Reduced activity of these drugs. This should be borne in mind in patients with incipient or actual congestive heart failure and/or hypertension.

Selective serotonin reuptake inhibitors (SSRIs): The possibility of interaction must be taken into account with selective serotonin reuptake inhibitors (SSRIs): increased risk of gastrointestinal bleeding.

Pentoxifylline: increased risk of bleeding

Ciclosporin: The risk of nephrotoxicity may be increased if NSAIDs are given with ciclosporins.

Quinolone antibiotics: Animal data indicate that NSAIDs can increase the risk of convulsions associated with quinolone antibiotics. Patients taking NSAIDs and quinolones may have an increased risk of developing convulsions.

Aminoglycosides or probenecid: Care should also be taken if Surgam is concomitantly administered with aminoglycosides or probenecid. Aminoglycosides may interact with NSAIDs to cause a reduction in renal function in susceptible individuals, decreased elimination of aminoglycoside and increased plasma concentrations. A reduction in metabolism and elimination of NSAID and metabolites has been observed with probenecid.

4.6 Fertility, pregnancy and lactation

Pregnancy

Congenital abnormalities have been reported in association with NSAID administration in man; however, these are low in frequency and do not appear to follow any discernible pattern. Tiaprofenic acid crosses the placental barrier. Although animal studies have not revealed evidence of teratogenicity, safety in human pregnancy and lactation cannot be assumed and, in common with other NSAIDs, Surgam should not be used during the first two trimesters of pregnancy or labour unless the potential benefit to the patient outweighs the potential risk to the fetus.

From the 20th week of pregnancy onward, Surgam use may cause oligohydramnios resulting
from fetal renal dysfunction. This may occur shortly after treatment initiation and is usually
reversible upon discontinuation. In addition, there have been reports of ductus arteriosus
constriction following treatment in the second trimester, most of which resolved after treatment cessation. Therefore, during the first and second trimester of pregnancy, Surgam should not be given unless clearly necessary. If Surgam is used by a woman attempting to conceive, or during the first and second trimester of pregnancy, the dose should be kept as low and duration of treatment as short as possible. Antenatal monitoring for oligohydramnios and ductus arteriosus constriction should be considered after exposure to Surgam for several days from gestational week 20 onward. Surgam should be discontinued if oligohydramnios or ductus arteriosus constriction are found.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors may expose the foetus to:

- cardiopulmonary toxicity (premature constriction/closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction (see above);

the mother and the neonate, at the end of pregnancy, to:

- possible prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses;
- inhibition of uterine contractions resulting in delayed or prolonged labour.

Consequently, Surgam is contraindicated during the third trimester of pregnancy (see section 4.3).

Breast-feeding
The level of Surgam in mother's milk has been studied and the total daily exposure is very small; approximately 0.2% of the administered dose and is unlikely to be of pharmacological significance. Breast-feeding or treatment of the mother should be stopped as necessary.

Fertility
See section 4.4 regarding female fertility.

4.7 Effects on ability to drive and use machines

Undesirable effects such as dizziness, drowsiness, fatigue and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Undesirable effects

The following adverse reactions are classified by system organ class and ranked under heading of frequency using the following convention: *very common (≥10%), common (≥ 1% and < 10%); uncommon (≥ 0.1% and < 1%); rare (≥ 0.01% and < 0.1%), very rare (< 0.01%), not known (cannot be estimated from the available data).*

Gastrointestinal disorders:

- *Very common:* abdominal pain upper
- *Common:* nausea, vomiting, dyspepsia, diarrhoea
- *Not known:* melaena, haematemesis, anorexia, indigestion, heartburn, flatulence, constipation, gastritis, ulcerative stomatitis, pancreatitis, colitis and Crohn's disease (see section 4.4).

Peptic ulcers, gastrointestinal haemorrhage and perforation have occasionally been reported, particularly in the elderly, and in exceptional case may have been associated with fatalities.

Skin and subcutaneous disorders:

- *Not known:* Rash, pruritis, urticaria, purpura, alopecia and erythema and dermatitis bullous (Stevens-Johnson Syndrome or toxic epidermal necrolysis), photosensitivity reaction, angioedema

Immune system disorders:

- *Common:* Non-specific allergic reactions, bronchospasm, dyspnea
- *Not known:* Hypersensitivity reactions have been reported following treatment with NSAIDs, anaphylactic shock, asthma, especially in subjects allergic to aspirin and other NSAIDs

Blood and lymphatic system disorders:

- *Not known:* Thrombocytopenia, anaemia due to bleeding may occur.

Ear and labyrinth disorders:

- *Not known:* Vertigo, tinnitus and drowsiness.

Nervous system disorders:

- *Common:* dizziness
- *Not known:* Headaches

Renal and urinary disorders:

- *Not known:* bladder pain, dysuria, and pollakiuria, hematuria may occur
- After continuous, prolonged treatment with tiaprofenic acid in presence of urinary symptoms, urinary tract inflammation, have been observed.
- NSAIDs have been reported to cause nephrotoxicity in various forms. As with other NSAIDs, isolated cases of tubulo-interstitial nephritis, nephrotic syndrome and renal failure have also been reported with tiaprofenic acid.

Metabolism and nutrition disorders:

- *Not known:* sodium and fluid retention (see section 4.4).

Hepatobiliary disorders:

- *Not known:* Hepatitis, jaundice.

Infections and infestations:

- *Common:* cystitis

Investigations:

- *Not known:* bleeding time prolonged, abnormal liver function test

Other side-effects that have been reported with NSAIDS but not specifically with Surgam are:

- *Nervous system disorders:* optic neuritis
- *Eye disorders:* visual disturbances
- *Musculoskeletal and connective tissue disorders:* paraesthesia
- *Psychiatric disorders:* depression, confusion, hallucinations
- *General disorders and administration site conditions:* fatigue, malaise
- *Blood and lymphatic system disorders:* neutropenia, agranulocytosis, aplastic anaemia, haemolytic anaemia.
- *Nervous disorders:* reports of aseptic meningitis (especially in patients with existing auto-immune disorders, such as systemic lupus erythematosus, mixed connective tissue disease), with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4)
- *Vascular and cardiac disorders:* oedema, hypertension, and cardiac failure, have been reported in association with NSAID treatment.

Clinical trial and epidemiological data suggest that use of some NSAIDs (particularly at high doses and in long term treatment) may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke) (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of overdosage with Surgam, supportive and symptomatic therapy is indicated.

a) Symptoms

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions. In cases of significant poisoning acute renal failure and liver damage are possible.

b) Therapeutic measure

Patients should be treated symptomatically as required.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Alternatively, in adults, gastric lavage should be considered within one hour of ingestion of a potentially life-threatening overdose.

Good urine output should be ensured.

Renal and liver function should be closely monitored.

Patients should be observed for at least four hours after ingestion of potentially toxic amounts.

Frequent or prolonged convulsions should be treated with intravenous diazepam.

Other measures may be indicated by the patient's clinical condition.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Non-steroidal anti-inflammatory drug.

ATC code: M01AE11

Further Information:

The effects of tiaprofenic acid on articular cartilage have been investigated in in-vitro experiments and in ex-vivo studies using different animal models of arthritis. Ex-vivo experiments on human chondrocyte cultures have also been conducted. In these experiments, tiaprofenic acid, in concentrations equivalent to the therapeutic dose, did not depress the biosynthesis of proteoglycans and did not alter the differentiation of proteoglycans secreted. The degradation of proteoglycan aggregates was inhibited. These results suggest a neutral or possibly beneficial effect of tiaprofenic acid on joint cartilage under experimental conditions. The clinical significance of these findings has been studied in a long term double-blind controlled study, in which tiaprofenic acid did not significantly increase the rate of radiological deterioration of joint space in patients with osteoarthritis of the knee.

5.2 Pharmacokinetic properties

Single dose studies: Following oral administration (max at 90 mins). Plasma level zero at 24 hours. t½ = 1.5 to 2 hours.

Repeat dose studies: Surgam is rapidly eliminated and there is no accumulation after repeated doses of 600mg/day in divided doses. Steady state after first day. No impairment of absorption in patients with RA undergoing long term therapy. There is no evidence of different pharmacokinetics in the elderly.

Protein binding = 97 - 98%

Plasma clearance = 6 litres/hour

Elimination = 60% in urine remainder in bile

Metabolites = there are two main metabolites which account for about 10% of urinary excretion and have low pharmacological activity. The parent compound is excreted mostly in the form of acylglucuronide.

5.3 Preclinical safety data

Not applicable.

6.1 List of excipients

Maize starch, poloxamer, magnesium stearate and talc.

6.2 Incompatibilities

None stated.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C. Protect from light.

6.5 Nature and contents of container

Blister packs sealed with aluminium foil in a cardboard carton in packs of 10, 12, 14, 20, 28, 30, 56 or 60.

6.6 Special precautions for disposal

N/A.

7 MARKETING AUTHORISATION HOLDER

Fidia Pharma UK Limited
170 Edmund Street, Ground Floor
Birmingham B3 2HB
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 56485/0001

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