**Professional Information (PI) for Medicines for Human Use**
**FLAMARET (Capsules)**

**SCHEDULING STATUS:**

**S3**

## 1. NAME OF THE MEDICINE

**FLAMARET** (Capsules)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each FLAMARET capsule contains 25 mg indomethacin.

Contains Lactose monohydrate: 95,00 mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM:

Size 3 yellow gelatine capsules containing a white to off-white powder imprinted with ‘GS’.

## 4. CLINICAL PARTICULARS:

### 4.1 Clinical inidications:

FLAMARET is indicated in the active stage of:

- rheumatoid arthritis
- ankylosing spondylitis
- osteoarthritis
- acute gouty arthritis
- degenerative joint disease of the hip

FLAMARET is also indicated for:

- acute musculoskeletal disorders, such as, bursitis, tendonitis, synovitis, tenosynovitis, capsulitis of the shoulder, sprains and strains;
- low back pain (commonly referred to as lumbago);
- fever (as short-term adjunct to specific therapy);
- inflammation, pain, trismus and swelling following dental procedures;
- inflammation, pain and swelling following orthopaedic surgical procedures and nonsurgical procedures associated with reduction and immobilisation of fractures or dislocations;
- pain and associated symptoms of primary dysmenorrhoea.

**4.2 Posology and method of administration:**

**Posology**

*Adults*

The recommended dosage of FLAMARET 50 mg to 200 mg daily in divided doses. Therapy may be initiated with low doses and gradually, increasing them where necessary according to the patients' response and requirements. Use the lowest effective dose for the shortest duration.

A loading dose of FLAMARET is not necessary. In chronic rheumatic disorders, initiating therapy with low doses, increasing gradually when necessary, and continuing for an adequate period (up to one month is recommended), will produce a maximum benefit and minimise adverse reactions.

In patients with persistent night pain and/or morning stiffness, a dose of up to 100 mg at bedtime may be helpful in affording relief. A dosage of 200 mg per day should not be exceeded.

In the treatment of acute gouty arthritis, the recommended daily dosage of 150 mg to 200 mg in divided doses until symptoms and signs subside.

In primary dysmenorrhoea, the recommended dosage is 75 mg daily as a single or divided dose, starting at the onset of cramps and bleeding and continuing for as long as symptoms usually last. To minimise or reduce the possibility of gastrointestinal disturbances, it is recommended that FLAMARET capsules be taken with food, milk or an antacid (see section 4.5). In chronic conditions start the therapy with a low dosage, increasing as required.

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.4).

**Paediatric Population**

The safety and efficacy of indomethacin, as in FLAMARET**,** in children has not been established.

**4.3 Contraindications:**

FLAMARET is contraindicated in:

- persons hypersensitive to indomethacin or to aspirin or to any of the ingredients in FLAMARET (see section 6.1);
- persons operating machinery;
- ~~or~~ patients with psychiatric disorders, epilepsy or Parkinsonism;
- patients in whom acute asthmatic attacks, urticaria or rhinitis and nasal polyps are precipitated by acetylsalicylic acid (aspirin) or other nonsteroidal anti-inflammatory drugs (NSAIDs);
- FLAMARET and diflunisal should not be used concomitantly;
- patients with severe hepatic failure and renal failure;
- in patients with current and / a history of perforation, peptic ulcers or active peptic ulcers or bleeding (PUBS) related to previous NSAIDs, including FLAMARET,

gastritis, regional enteritis and ulcerative colitis, or with a recurrent history of gastrointestinal ulceration;

- in patients with a history of, or current gastrointestinal lesions;
- in patients with a history of angioedema following exposure to NSAIDs and/or aspirin;
- in the treatment of peri-operative pain relief in the setting of coronary artery surgery;
- in pregnancy and lactation (see section 4.6);
- in patients with heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease;

The safety of FLAMARET in children has not been established.

## 4.4 Special warnings and precautions for use:

| |
|---|
| FLAMARET may predispose to cardiovascular events, gastrointestinal events, or cutaneous reactions which may be fatal. |

Undesirable effects may be minimised by using the lowest effective dose for the shortest duration necessary to control symptoms (see section 4.2).

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

Indomethacin, as in FLAMARET should be used cautiously in patients with impaired renal function and bleeding disorders as FLAMARET may tend to aggravate these. FLAMARET is contraindicated in patients with severe renal failure, psychiatric disorders, epilepsy or Parkinsonism (see section 4.3).

Patients should be carefully observed to detect any unusual manifestations of medicine sensitivity.

**Cardiovascular, renal and hepatic impairment:**

In patients with renal, cardiac, hepatic impairment, hypertension, heart failure or conditions predisposing to fluid retention caution is required since the use of NSAIDs may result in deterioration of renal function (see section 4.8). The dose should be kept as low as possible and renal function should be monitored. NSAIDs may also cause fluid retention which may further aggravate these conditions.

FLAMARET is contraindicated in patients with severe renal and hepatic failure (see section 4.3).

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of FLAMARET may precipitate overt renal decompensation.

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, hepatic dysfunction, those taking diuretics, the elderly, diabetes mellitus, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotoxic medicines. FLAMARET should be given with caution and renal function should be monitored in these patients (see section 4.3). Discontinuation of NSAID therapy is usually followed by recovery to the pre-treatment state.

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.

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should only be treated with indomethacin, as in FLAMARET 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).

Because of its lack of platelet effects, FLAMARET is not a substitute for aspirin for cardiovascular prophylaxis.

Due to inhibition of prostaglandin synthesis, fluid retention and oedema have been observed in patients taking FLAMARET, therefore FLAMARET should be used with caution in patients with compromised cardiac function and other conditions predisposing to, or worsened by, fluid retention.

**Cardiovascular thrombotic events**

FLAMARET and other NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. Both COX-2 selective and nonselective, may have a similar risk. This risk may increase with duration of use.

Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimise the potential risk for an adverse cardiovascular event in patients treated with FLAMARET, the lowest effective dose should be used for the shortest duration possible.

Caution is advised when FLAMARET is prescribed to patients with cardiovascular risk factors e.g. hypertension, diabetes, smoking and hypercholesterolaemia.

FLAMARET is contraindicated in patients with heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke), and peripheral arterial disease (see section 4.3).

**Hypertension**

NSAIDs, including FLAMARET, can lead to onset or exacerbation of hypertension, either of which may contribute to the increased incidence of cardiovascular events.

Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including FLAMARET, should be used with caution in patients with hypertension.

Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

**Congestive heart failure, fluid retention and oedema**

Congestive heart failure, fluid retention and peripheral oedema have been observed in some patients taking FLAMARET. Thus, FLAMARET should be used with caution in patients with cardiac dysfunction, hypertension or other conditions predisposing to fluid retention.

In view of FLAMARET's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

**Gastrointestinal effects**

Gastrointestinal disturbances may be minimised by giving FLAMARET orally with food, milk or an antacid (see section 4.2).

Gastrointestinal disturbances usually disappear on reducing the dosage, if not, the risks of continuing therapy should be weighed against the possible benefits.

If gastrointestinal bleeding does occur, FLAMARET should immediately be discontinued.

Single or multiple ulcerations, including perforation and haemorrhage of the oesophagus, stomach, duodenum or small or large intestine, have been reported to occur with FLAMARET.

Fatalities have been reported. Intestinal ulceration has been associated with stenosis and obstruction (see section 4.8).

Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred. Increased abdominal pain in patients with ulcerative colitis or the development of ulcerative colitis and regional ileitis have been reported (see section 4.8).

Caution is advised in patients with pre-existing sigmoid lesions (such as diverticulum or carcinoma), or the development of these conditions, as FLAMARET can aggravate these conditions.

Patients with a history of GI toxicity, particularly the elderly, should report any unusual abdominal symptoms (especially GI bleeding) particularly during the initial stages of treatment. 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 previous history of serious GI events. When GI bleeding or ulceration occurs in patients receiving FLAMARET, the treatment should be withdrawn.

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 medicines (e.g. misoprostol or proton pump inhibitors) should be considered for these patients, and also for patients requiring concomitant low dose aspirin, or other medicines likely to increase gastrointestinal risk (see section 4.5).

Caution should be advised in patients receiving concomitant medicines which could increase the risk of ulceration or bleeding, such as oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors, or antiplatelet medicines such as aspirin (see section 4.5).

**Renal function**

There have been reports of acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome in patients receiving long-term administration of FLAMARET. Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of FLAMARET may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotoxic medicines.

Caution should be used when initiating the treatment with FLAMARET in patients with dehydration. Patients should first be hydrated before therapy with FLAMARET commences. Caution is also recommended in patients with pre-existing kidney disease.

NSAIDs, including FLAMARET should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of NSAIDs therapy should usually be followed by recovery to the pre-treatment state.

Since FLAMARET is eliminated primarily by the kidneys (see section 5: Elimination), patients with significantly impaired renal function should not be treated with FLAMARET.

Severe hypokalaemia and renal tubular acidosis have been reported due to prolonged use of NSAIDs at higher than recommended doses. Presenting signs and symptoms included reduced level of consciousness and generalised weakness (see section 4.8 and 4.9). NSAID induced renal tubular acidosis should be considered in patients with unexplained hypokalaemia and metabolic acidosis.

**Ovulation**

Indomethacin, as in FLAMARET may have a reversible inhibitory effect on women's ovulation (see section 4.6).

**Skin reactions**

Serious skin reactions, which can be fatal, may occur (see section 4.8).
NSAIDs, including FLAMARET, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the medicines should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Patients appear to be at highest risk for 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. FLAMARET should be discontinued at the first appearance of skin rash, mucosal lesions, and any other sign of hypersensitivity.

**Systemic lupus erythematosus (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).

**Anaemia**

Patients should be periodically observed to allow for early detection of unwanted effects on peripheral blood (anaemia), liver function (see section 4.8), or gastrointestinal tract especially during prolonged therapy.

**Medication overuse headache (MOH)**

After long-term treatment with analgesics, medication-overuse headache (MOH) may develop or be aggravated. MOH should be suspected in patients who have frequent or daily headaches despite (or because of) regular use of analgesics. Patients with MOH should not be treated by increasing the dose. In such cases the use of analgesics should be discontinued in consultation with a doctor.

Avoid concomitant use of two or more NSAIDs.

**Plasma potassium**

Increases in plasma potassium concentration, including hyperkalaemia have been reported, in patients with or without renal impairment.

In patients with normal renal function, these effects have been attributed to a hyporeninaemic-hypoaldosteronism state.

**Ocular effects**

Corneal deposits and retinal disturbances, including those of the macula, have been observed in patients who had received prolonged therapy with FLAMARET.

In patients with rheumatoid arthritis, eye changes may occur which may be related to the underlying disease or to the therapy.
Therefore, in chronic rheumatoid disease, ophthalmological examinations at periodic intervals are recommended.

Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmological examination at periodic intervals is desirable in patients where therapy is prolonged.

Discontinue therapy if eye changes are observed.

**Central nervous system effects**

Headache, sometimes accompanied by dizziness or light-headedness may occur, usually early in treatment with FLAMARET**.** Starting therapy with a low dosage and increasing it gradually may minimise the incidence of headache. These symptoms may disappear on continuing therapy or with reducing the dosage. If headache persists despite dosage reduction, FLAMARET should be withdrawn.

**Infections**

FLAMARET may mask the signs and symptoms which ordinarily accompany infectious disease. FLAMARET should be used with caution in patients with existing, but controlled

infection. Antibiotic therapy should be initiated promptly if an infection occurs during therapy with FLAMARET**.** Caution is advised with concomitant use of live vaccines.

**Hepatic effects**

FLAMARET may cause a rise in liver enzymes.

Significant (3 times the upper limit of normal) elevations of ALT (SGPT) or AST (SGOT) in controlled clinical trials have been reported in less than 1 % of patients receiving therapy with NSAIDs such as FLAMARET.

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 development of more severe hepatic reactions while on therapy with FLAMARET.

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.), therapy should be discontinued.

**Platelet aggregation**

FLAMARET can inhibit platelet aggregation. This effect usually disappears within 24 hours of discontinuation of FLAMARET. FLAMARET has been shown to prolong bleeding time (but within the normal range) in normal adults. Because this effect may be exaggerated in patients with underlying homeostatic defects, FLAMARET should be used with caution in persons with coagulation defects.

Caution is required in post-operative patients as bleeding time is prolonged (but within normal range) in normal adults.

**Respiratory disorders**

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

**Drug reaction with eosinophilia and systemic symptoms (DRESS)**

DRESS has been reported in patients taking NSAIDs, such as FLAMARET**,** some of these events have been fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, lymphadenopathy, and/or facial swelling. Other clinical manifestations may include hepatitis, nephritis, haematological abnormalities, myocarditis, or myositis. Sometimes symptoms of DRESS may resemble an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its presentation, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, discontinue FLAMARET and evaluate the patient immediately.

**General**

FLAMARET should be used cautiously in patients with psychiatric disorders, epilepsy or parkinsonism, as indomethacin may aggravate these disorders.
Patients should be periodically observed to allow early detection of any unwanted effects on peripheral blood (anaemia), liver function, or gastrointestinal tract especially during prolonged therapy.

**Use in pregnancy**

FLAMARET is contraindicated during pregnancy (see section 4.3). The use of NSAIDs, such as FLAMARET, around 20 weeks gestation or later in pregnancy may cause a rare but

serious foetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Complications of prolonged oligohydramnios include limb contractures and delayed lung maturation, which may require invasive procedures such as exchange transfusion or dialysis, in some cases (see section 4.6).

**Elderly**

Elderly patients may be especially susceptible to the toxic effects of FLAMARET**.**

Elderly patients show an increased frequency of adverse reactions to NSAIDs, such as FLAMARET, especially gastrointestinal ulceration, bleeding and perforation (PUBS), which may be fatal (see section 4.2).

**Paediatric population**

The safety of FLAMARET in children has not been established (see section 4.3).

**Lactose intolerance**

FLAMARET capsules contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take FLAMARET capsules.

**4.5 Interaction with other medicines and other forms of interaction:**

FLAMARET inhibits platelet aggregation but is not a substitute for aspirin for cardiovascular prophylaxis.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with FLAMARET.

**Acetylsalicylic acid**

The concomitant use of FLAMARET with aspirin or other salicylates is not recommended.

Combined use of FLAMARET and aspirin does not produce any greater therapeutic effect than the use of FLAMARET. Furthermore, the incidence of gastrointestinal side effects significantly increases with combined therapy. Moreover, coadministration of aspirin may decrease the blood concentration of FLAMARET**.**

**Diflunisal**

Co-administration of diflunisal and FLAMARET increases the plasma level of indomethacin by about a third, with a concomitant decrease in renal clearance. Fatal gastrointestinal haemorrhage has occurred. The combination should not be used (see section 4.3).

**Diuretics**

FLAMARET may reduce the effect of diuretics and antihypertensive medicines. The risk of acute renal insufficiency, which is usually reversible, may be increased with compromised renal function (e.g. dehydrated patients or elderly patients) when angiotensin II receptor antagonists are combined with NSAIDs such as FLAMARET. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

FLAMARET may reduce the diuretic, natriuretic and antihypertensive effects of loop, potassium sparing, thiazides diuretics and furosemide. Therefore, when FLAMARET and diuretics are used concomitantly, the patient should be closely observed to determine whether the desired effect of the diuretic is being obtained.

FLAMARET may cause blocking of the furosemide-induced increase in plasma renin activity.

FLAMARET reduces basal plasma renin activity as well as those elevations of plasma renin activity induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of FLAMARET resulted in reversible acute renal injury (acute renal failure). FLAMARET and triamterene should not be administered concomitantly.

Both FLAMARET and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of FLAMARET and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these medicines are administered concurrently.
Most of the above effects relating to diuretics have been attributed at least in part, to mechanisms involving inhibition of prostaglandin synthesis in FLAMARET**.**

Diuretics can increase the risk of nephrotoxicity of NSAIDs, such as FLAMARET.

**Other NSAIDS**

The concomitant use of FLAMARET with other NSAIDs is not recommended, due to the increased possibility of gastrointestinal toxicity, with little or no increase in efficacy.
Other analgesics including cyclooxygenase-2 selective inhibitors: Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

**Antacids**

The bioavailability of FLAMARET may be reduced by concomitant antacids therapy containing aluminium hydroxide, magnesium carbonate and magnesium hydroxide.

**Anticoagulants**

FLAMARET did not influence the hypoprothrombinaemia produced by anti-coagulants in patients and in normal subjects. Patients should, however, be closely observed for alterations of prothrombin time, when FLAMARET is given concomitantly with anticoagulants. Caution should be exercised when FLAMARET and anticoagulants are administered concomitantly. NSAIDs may enhance the effects of anti-coagulants, such as warfarin (see section 4.4).

Concurrent administration of oral anticoagulant medicines leads to increased risk of gastrointestinal bleeding.

**Antiplatelet medicines**

Increased risk of gastrointestinal bleeding. Indomethacin, as in FLAMARET can inhibit platelet aggregation, an effect which disappears within 24 hours of discontinuation; the bleeding time may be prolonged, and this effect may be exaggerated in patients with an underlying haemostatic defect (see section 4.4).

**Antidepressants (SSRI)**

Increased risk of bleeding (see section 4.4).

**Antidiabetics**

The hypoglycaemic effect of sulfonylureas may be increased by NSAIDs.

**Probenecid**

When FLAMARET is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, a lower total daily dosage in FLAMARET may produce a satisfactory therapeutic effect. When increases in the dose of FLAMARET

are made under these circumstances they should be made cautiously and in small increments. The total plasma concentration of indomethacin plus its inactive metabolites is increased by concurrent administration of probenecid.

**Methotrexate**

*C*aution should be exercised with concomitant use of FLAMARET, with methotrexate. Indomethacin, as in FLAMARET, has been reported to decrease the tubular secretion of methotrexate and thereby to potentiate methotrexate toxicity.
Serious interactions have been reported with the use of high doses of methotrexate with FLAMARET.

**Ciclosporin**

Administration of NSAIDs such as FLAMARET concomitantly with ciclosporin has been associated with an increase in ciclosporin-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. FLAMARET should be used with caution in patients taking ciclosporin, and renal function should be monitored carefully.

**Lithium**

Decreased elimination of lithium. FLAMARET inhibits prostaglandin synthesis and may therefore raise plasma lithium levels and reduce lithium clearance in patients with steady state plasma lithium concentrations. At the onset of such combined therapy, plasma lithium concentration should be monitored more frequently.

**Antihypertensives**

Reduced antihypertensive effect. FLAMARET may acutely reduce the antihypertensive effect of antihypertensives due partly to FLAMARET's inhibition of prostaglandin synthesis. Patients receiving concomitant therapy should have the antihypertensive effect of their

therapy reassessed. Therefore, caution should be exercised when considering the addition of FLAMARET to the regimen of a patient taking any of the following antihypertensive medicines:

- alpha-adrenergic blocking medicines,
- ACE inhibitors,
- beta-adrenergic blocking medicines,
- angiotensin-2-receptor antagonist,
- hydralazine or nifedipine.

An increased risk of hyperkalaemia has also been reported when NSAIDs such as FLAMARET are taken with ACE inhibitors.

**Antipsychotics**

Increased drowsiness has been reported with concomitant use of FLAMARET and haloperidol.

**Antivirals**

There is an increased risk of haematological toxicity when NSAIDs, such as FLAMARET 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. There is a risk of indomethacin toxicity with concomitant use of FLAMARET with ritonavir, and should thus be avoided.

**Cardiac glycosides/digoxin**

FLAMARET given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when FLAMARET and digoxin are used concomitantly, plasma digoxin levels should be closely monitored.

NSAIDs may exacerbate cardiac failure, reduce GFR and increase plasma digoxin levels.

**Phenylpropanolamine**

Hypertensive crises have been reported due to oral phenylpropanolamine, and to phenylpropanolamine given concomitantly with FLAMARET. This additive effect is probably due at least in part to inhibition of prostaglandin synthesis by indomethacin, as in FLAMARET, and may lead to water intoxication. Caution should be exercised when FLAMARET and phenylpropanolamine are administered concomitantly.

**Corticosteroids**

The risk of gastrointestinal bleeding and ulceration and perforation (PUBS) associated with NSAIDs such as FLAMARET is increased when used with corticosteroids.

In a patient receiving corticosteroids concomitantly, a reduction in dosage of these may be possible, but should only be effected slowly under supervision.

**Cytotoxic medicines**

FLAMARET may decrease the tubular secretion of methotrexate thus potentiating toxicity; simultaneous use should be undertaken with caution.

**Desmopressin**

Effect potentiated by indomethacin, as in FLAMARET and may lead to water intoxication.

**Mifepristone**

NSAIDs, as in FLAMARET**,** and aspirin should be avoided until at least 8 to 12 days after administration of mifepristone as NSAIDs can reduce the effect of mifepristone.

**Quinolone antibiotics**

Concomitant use of fluoroquinolones and FLAMARET may induce convulsions in patients with or without a history of convulsions/seizures.

**Muscle relaxants**

Concomitant use of NSAIDs (FLAMARET) and baclofen may induce baclofen toxicity due to reduced rate of excretion.

**Pentoxifylline**

Possible increased risk of bleeding when taken with NSAIDs.

**Tacrolimus**

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

**Tiludronic acid**

The bioavailability of tiludronic acid is increased by indomethacin.

**Triamterene**

Acute kidney injury (acute renal failure) has been reported with concomitant indomethacin therapy.

**Laboratory tests**

False-negative results in the dexamethasone suppression test (DST) in patients being treated with FLAMARET have been reported. Thus, results of the DST should be interpreted with caution in these patients.

**4.6 Fertility, pregnancy and lactation:**

The use of FLAMARET is contraindicated in pregnancy and lactation (see section 4.3).

**Pregnancy:**

FLAMARET is contraindicated in pregnant women (see section 4.3 and 4,4). Regular use of non-steroidal anti-inflammatory drugs, such as FLAMARET**,** during the third trimester of pregnancy, may result in premature closure of the foetal ductus arteriosus in utero, and possibly, in persistent pulmonary hypertension of the new-born. The onset of labour may be delayed and its duration increased.

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation after use of a prostaglandin synthesis inhibitor in early pregnancy. The absolute risk for cardiovascular malformation was increased from less than 1 %, up to approximately 1,5 %. The risk is believed to increase with dose and duration of therapy. In animals, administration of a prostaglandin synthesis inhibitor has been shown to result in increased pre- and post-implantation loss and embryo-foetal lethality. In addition, increased incidences of various malformations, including cardiovascular, have been reported in animals given a prostaglandin synthesis inhibitor during the organogenetic period.

During the third trimester of pregnancy, all prostaglandin synthesis inhibitors

- may expose the foetus to:

- cardiopulmonary toxicity (with premature closure of the ductus arteriosus and pulmonary hypertension);
- renal dysfunction, which may progress to renal failure with oligo-hydramnios's;

- may expose 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.

**Breastfeeding:**

Indomethacin, as in FLAMARET is excreted into breast milk. Mothers breastfeeding their infants should not be treated with FLAMARET (see section 4.3).

**Fertility:**

The use of FLAMARET may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulty conceiving or who are undergoing investigation of infertility, treatment with FLAMARET should be stopped.

**4.7 Effects on ability to drive and use machines:**

FLAMARET may interfere with driving and the operation of machines, as it may cause dizziness, drowsiness, visual disturbances and headaches.

FLAMARET is contraindicated in persons operating machinery (see section 4.3).

**4.8 Undesirable effects:**

**Table 1: Tabulated list of adverse reactions**

| System Organ Class | Adverse reactions | Frequency |
|---|---|---|
| Infections and infestations | Fulminant necrotising fasciitis, particularly in association with Group A β-haemolytic streptococcus | *Less frequent* |
| Neoplasm benign, malignant and unspecified (including cysts and polyps) | Leukaemia | *Frequency unknown* |
| Blood and lymphatic system disorders | Blood dyscrasia may occur including leukopenia, petechiae or ecchymosis, purpura, aplastic and haemolytic anaemia, neutropenia, agranulocytosis, bone-marrow depression, disseminated intravascular coagulation, and thrombocytopenia.<br>As some patient's manifest anaemia secondary to obvious or occult gastrointestinal bleeding, appropriate blood determinations are recommended. | *Less frequent* |
| Immune system disorders | Acute Anaphylaxis | *Less frequent* |
| | Hypersensitivity reactions (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract reactivity compromising asthma, aggravated asthma, bronchospasm or dyspnoea, rhinitis or (c) assorted skin disorders, including rashes of various types, pruritis, urticaria, purpura, angioedema and exfoliative and bullous dermatoses (including epidermal | *Frequency unknown* |

| | | |
|---|---|---|
| | necrolysis and erythema multiforme) | |
| Metabolism and nutrition disorders | Hyperglycaemia, glycosuria, hyperkalaemia | *Less frequent* |
| | Weight gain, hypokalaemia* | *Frequency unknown* |
| Psychiatric disorders | Mental confusion, anxiety, psychic disturbances such as depersonalisation, psychotic episodes, paraesthesias, aggravation of psychiatric disturbances | *Frequent* |
| | Depression, insomnia | *Frequency unknown* |
| Nervous system disorders | Headache, dizziness and light-headedness,<br>Starting therapy with a low dose and increasing gradually minimises the incidence of headache. These symptoms frequently disappear on continued therapy or reducing the dosage, but if headache persists despite dosage reduction, FLAMARET should be withdrawn. | *Frequent* |
| | Vertigo, fatigue (including malaise and listlessness), syncope, drowsiness, convulsions, coma, peripheral neuropathy, involuntary muscle movement, dysarthria, epilepsy, parkinsonism, mental confusion, anxiety, muscle weakness | *Less frequent* |
| | Aseptic meningitis (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus or mixed connective tissue disease) with | *Frequency unknown* |

| | | |
|---|---|---|
| | symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation (see section 4.4), depression, dysarthria, coma, cerebral oedema, nervousness, hallucinations, drowsiness, convulsions and aggravation of epilepsy and parkinsonism, paraesthesia, involuntary movements.<br><br>These effects are often transient and abate or disappear on reduced or stopping treatment. However, the severity of these may, on occasion, require cessation of therapy. | |
| Eye disorders | Optic neuritis | *Frequent* |
| | Visual disturbances, blurred vision, diplopia, and orbital and peri-orbital pain | *Less frequent* |
| | Corneal deposits, retinal disturbances, including those of the macula | *Frequency unknown* |
| Ear and labyrinth disorders | Tinnitus | *Frequent* |
| | Hearing disturbances, deafness | *Frequency unknown* |
| Cardiac disorders | Myocardial infarction, cardiovascular thrombotic events<br><br>The 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 | *Less frequent* |

| | | |
|---|---|---|
| | example myocardial infarction or stroke) (see section 4.4). | |
| | Peripheral oedema, tachycardia, dysrhythmia, palpitations, congestive heart failure, chest pain, cardiac failure | *Frequency unknown* |
| Vascular disorders | Flushing | *Less frequent* |
| | Hypertension, hypotension, thrombophlebitis | *Frequency unknown* |
| Respiratory, thoracic and mediastinal disorders | Epistaxis, acute respiratory distress, sudden dyspnoea, asthma, pulmonary oedema | *Less frequent* |
| | Pulmonary eosinophilia, bronchospasm | *Frequency unknown* |
| Gastrointestinal disorders | The most common side effects with indomethacin are gastrointestinal disturbances.<br><br>Epigastric distress, abdominal laceration (single or multiple) of oesophagus, stomach, duodenum or small or large intestine, including perforation and haemorrhage | *Frequent* |
| | Tenesmus proctitis, rectal bleeding, burning, pain, discomfort, itching, irritation, pancreatitis, regional ileitis, anorexia, epigastric discomfort, ulceration at any point in the gastrointestinal tract (even with resultant stenosis and obstruction), bleeding (even without obvious ulceration or from a diverticulum) and perforation of pre-existing sigmoid lesions (such | *Less frequent* |

| | | |
|---|---|---|
| | as diverticulum or carcinoma), increased abdominal pain, or exacerbation of the condition in patients with ulcerative colitis, intestinal strictures and regional gastritis | |
| | Peptic ulcers, perforation, gastrointestinal bleeding, nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melaena, haematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease | *Frequency unknown* |
| Hepatobiliary disorders | Jaundice and hepatitis | *Frequent* |
| | Cholestasis, borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT), abnormal liver function, hepatitis, jaundice.<br><br>If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations such as rash or eosinophilia occur, FLAMARET should be stopped. | *Frequency unknown* |
| Skin and subcutaneous tissue disorders | Erythema, angiitis, photosensitivity | *Frequent* |
| | Petechiae, ecchymosis, purpura, flushing, exfoliative dermatitis, bullous reactions, Stevens Johnson syndrome, erythema | *Less frequent* |

| | | |
|---|---|---|
| | multiforme, toxic epidermal necrolysis | |
| | Pruritis, urticaria, angioedema, photosensitivity, rash, hair loss, sweating, exacerbation of psoriasis | *Frequency unknown* |
| Musculoskeletal and connective tissue disorders | Muscle weakness, acceleration of cartilage degeneration | *Frequency unknown* |
| Renal and urinary disorders | Elevation of blood urea | *Frequent* |
| | Glycosuria, urinary frequency | *Less frequent* |
| | Haematuria, nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, renal failure, renal insufficiency, proteinuria, renal tubular acidosis* | *Frequency unknown* |
| Reproductive system and breast disorders | Breast changes (including enlargement, tenderness or gynaecomastia), vaginal bleeding | *Frequency unknown* |
| General disorders and administrative site conditions | Fatigue, chest pain | *Frequency unknown* |
| Investigations | BUN elevation | *Frequent* |
| | A rapid fall in blood pressure resembling a shock-like state, borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT), false-negative results in the dexamethasone suppression test (DST) | *Less frequent* |

*Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of higher than recommended doses.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

**4.9 Overdose**

**Symptoms**

Symptoms include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, diarrhoea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions, abdominal pain, anorexia, restlessness and agitation. In cases of significant poisoning kidney injury (acute kidney failure) and liver damage are possible. Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis. Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

**Treatment**

Treatment is symptomatic and supportive.
Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. 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 Pharmacodynamics properties:**

A. 3.1 Antirheumatics (anti-inflammatory agents).

*Mechanism of action*

Indomethacin is a non-steroidal anti-inflammatory drug with anti-inflammatory, analgesic and antipyretic properties which are mediated through its mode of action as an inhibitor of prostaglandin synthesis.

Indomethacin affords relief of symptoms; it does not alter the course of the underlying disease.

**5.2 Pharmacokinetic properties**

**Absorption**

Following a single oral dose, indomethacin is readily absorbed, attaining peak plasma concentrations of approximately 1 and 2 mcg/mL, respectively, at about 2 hours. Orally administered indomethacin is virtually 100 % bioavailable, with 90 % of the dose absorbed within 4 hours.

**Distribution**

Indomethacin exists in the plasma as the parent medicine and its dimethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60 % of an oral dosage is recovered in urine as medicine and metabolites (26 % as indomethacin and its glucuronide), and 33 % is recovered in faeces (1,5 % as indomethacin).

About 99 % of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. Indomethacin crosses the blood-brain barrier and the placenta.

**Biotransformation**

It is metabolised in the liver primarily by demethylation and deacetylation, it also undergoes glucuronidation and enterohepatic circulation. Enterohepatic cycling of metabolites, and probably indomethacin itself, occurs. Half-life in plasma is variable from 2 - 11 hours.

**Elimination**

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean half-life of indomethacin is estimated to be about 4,5 hours. With a typical therapeutic regimen of 25 or 50 mg three times daily, the steady-state plasma concentrations of indomethacin are an average 1,4 times those following the first dose.

**Special population**

**Elderly**

An increase in age increases the possibility of side effects. Indomethacin should be used with greater care in the elderly.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Maize starch

Sodium starch glycolate

Microcrystalline cellulose

Lactose monohydrate

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 Years

### 6.4 Special precautions for storage

Store in a dry place, at or below 25 $^{0}$C. Protect from light.

### 6.5 Nature and contents of container

Round white polypropylene securitainer containing 100 and 500 capsules.

## 7. HOLDER OF CERTIFICATE OF REGISTRATION

Unimed Healthcare (Pty) Ltd

Corner Birch Road & Bluegum Avenue,

Anchorville,

Lenasia

1827, South Africa

## 8. REGISTRATION NUMBER:

Y/3.1/425

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of registration: 17 May 1993

## 10. DATE OF REVISION OF THE TEXT

05 April 2024