SCHEDULING STATUS

SOUTH AFRICA: S3

1. NAME OF THE MEDICINE

FLAMARYX 7,5 mg (tablet).

FLAMARYX 15 mg (tablet).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

FLAMARYX 7,5 mg: Each uncoated tablet contains 7,5 mg meloxicam.

FLAMARYX 15 mg: Each uncoated tablet contains 15 mg meloxicam.

Excipients with known effect:

Contains sugar:

FLAMARYX 7,5 mg: lactose monohydrate 23,50 mg per tablet

FLAMARYX 15 mg: lactose monohydrate 20, 00 mg per tablet).

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

FLAMARYX 7,5 mg: Light yellow, round, uncoated tablets with score line between ‘F’ and ‘1’ debossed on one side and plain on the other side.

FLAMARYX 15 mg: Light yellow, round, uncoated tablets with score line between ‘F’ and ‘2’ debossed on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

FLAMARYX is indicated for the symptomatic treatment of:

- Rheumatoid arthritis.
- Painful osteoarthritis.
- Ankylosing spondylitis.

- Episodes of acute sciatica.

4.2 Posology and method of administration

Use the lowest effective dose for the shortest possible duration of treatment, as the potential for adverse reactions increases with dose and duration of exposure.

The maximum daily dose of **FLAMARYX** is 15 mg.

Adults:

Acute sciatica: 7,5 mg once daily. If there is no improvement the dose can be increased to 15 mg a day.

Ankylosing spondylitis: 15 mg once daily. According to the therapeutic response, the dose may be reduced to 7,5 mg/day.

Osteoarthritis: 7,5 mg once daily. Increase to 15 mg if necessary.

Rheumatoid arthritis: 15 mg once daily. Reduce dose if possible to 7,5 mg per day (provided therapeutic response is maintained).

Special populations

Elderly population

In patients with an increased risk of adverse reactions, e.g. the elderly, a history of gastrointestinal disease or risk factors for cardiovascular disease, the treatment should be started at the dose of 7,5 mg per day (see section 4.4).

Renal impairment

The dose of **FLAMARYX** in patients with end stage renal disease on haemodialysis should not be greater than 7,5 mg/day. No dosage reduction is necessary in patients with mild to moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 mL/min). In non-dialysed

patients with severe renal impairment **FLAMARYX** is contraindicated (see section 4.3).

Paediatric population

Safety and efficacy in children under the age of 12 years has not been established.

Method of administration

Oral administration.

The tablet should be taken with a glass of water and together with a meal.

4.3 Contraindications

- Hypersensitivity to **FLAMARYX** or to any ingredients of the formulation (see section 6.1).
- Patients in who attacks of asthma, urticaria, nasal polyps, angioedema or acute rhinitis are precipitated by acetylsalicylic acid/ aspirin or by other non-steroidal anti-inflammatory agents.
- Peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery
- Active peptic ulcer disease.
- Active or history of recurrent gastrointestinal ulceration/haemorrhage/perforations.
- Active inflammatory bowel disease (Crohn's disease or ulcerative colitis).
- History of gastrointestinal perforation, bleeding or perforation (PUBs) related to previous NSAIDs.
- Severe hepatic impairment.
- Severe non-dialysed renal impairment.
- Overt gastrointestinal bleeding, recent cerebrovascular bleeding or established systemic bleeding disorders
- Heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Pregnancy and lactation (see section 4.6).
- Use in children under 12 years of age.
- In case of rare hereditary conditions that may be incompatible with an excipient of **FLAMARYX**, the use of this medicine is contraindicated (see section 4.4.).

4.4 Special warnings and precautions for use

FLAMARYX 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, and gastrointestinal (GI) and cardiovascular risks below).

The recommended maximum daily dose should not be exceeded in case of insufficient therapeutic effect, nor should an additional NSAID be added to the therapy because this may increase the toxicity while therapeutic advantage has not been proven.

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

FLAMARYX is not appropriate for the treatment of patients requiring relief from acute pain.

In the absence of improvement after several days, the clinical benefit of the treatment with **FLAMARYX** should be reassessed.

- **Paediatric population**

  Children under the age of [~~18~~] 12 years – safety and efficacy have not been established (see section 4.3).

- **Elderly population**

  Adverse reactions are often less well tolerated in the elderly or weakened individuals, who therefore require careful monitoring. As with other NSAIDs, particular caution is required in the elderly, in whom renal, hepatic and cardiac functions are frequently impaired. The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal.

- ***Gastrointestinal (GI) effects***

  Any history of oesophagitis, gastritis and/or peptic ulcer must be sought before starting treatment

with **FLAMARYX** (see section 4.3).

Gastrointestinal bleeding, ulceration or perforation, potentially fatal, can occur at any time during treatment, with or without warning symptoms or a previous history of serious gastrointestinal events. The consequences of such events are generally more serious in the elderly. The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of **FLAMARYX**, in patients with a history of ulcers, and 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 below and section 4.5).

Caution should be exercised in patients receiving treatment with anticoagulants. When gastrointestinal bleeding or ulceration occurs in patients receiving **FLAMARYX**, treatment with **FLAMARYX** should be stopped.

FLAMARYX should be given with caution to patients with a history of gastrointestinal disease (e.g. ulcerative colitis, Crohn's disease, hiatus hernia, gastro-oesophageal reflux disease, angiodysplasia) as the condition may be exacerbated (see section 4.3).

Patients with a history of GI toxicity, particularly the 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 medicines which could increase the risk of ulceration or bleeding, such as heparin, as curative treatment or given in the elderly, oral corticosteroids, anticoagulants such as warfarin, selective serotonin reuptake inhibitors or other NSAIDs, including aspirin, given at anti-inflammatory doses (≥ 500 mg per dose or ≥ 3 g as total daily amount) (see section 4.5).

Patients with a history of gastrointestinal disease should be monitored very carefully while on **FLAMARYX** and therapy should be discontinued if any ulceration or bleeding occurs.

- ***Skin reactions***

  Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported.

  Patients appear to be at higher 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.

FLAMARYX should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

If the patient has developed SJS or TEN with the use of **FLAMARYX**, therapy with **FLAMARYX** must not be re-started in this patient at any time.

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in patients taking NSAIDs, such as **FLAMARYX**. 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 **FLAMARYX** and evaluate the patient immediately.

- ***Functional renal failure***

  NSAIDs, such as **FLAMARYX**, may cause a dose dependent inhibition of the synthesis of renal prostaglandins involved in the maintenance of renal perfusion. In patients with decreased renal blood flow and blood volume, taking **FLAMARYX** may result in the decompensation of latent renal failure. However, renal function returns to its initial status when treatment is stopped.

  Patients who are dehydrated, have hepatic or renal dysfunction, taking diuretics or have undergone surgery leading to hypovolaemia, are at particular renal decompensation and renal function should be carefully monitored.

  Patients who have heart failure are at particular renal decompensation (see section 4.3). This particularly concerns patients with the following risk factors where monitoring of diuresis and renal function during treatment is necessary (see sections 4.2 and 4.3):

  - Elderly patients.

- Dehydrated patients.
- Concomitant treatment with medicines such as ACE inhibitors, angiotensin-II antagonists, sartans or diuretics (see section 4.5).
- Hypovolaemia (whatever the cause).
- Renal failure.
- Nephrotic syndrome.
- Lupus nephropathy.
- Those with congestive heart failure
- Liver cirrhosis

NSAIDs, such as **FLAMARYX**, may be the cause of interstitial nephritis, glomerulonephritis, renal medullary necrosis or nephrotic syndrome.
Congestive heart failure increases the risk of renal decompensation (see section 4.3).
The dose of **FLAMARYX** in patients with end-stage renal failure on haemodialysis should not exceed 7,5 mg. No dose reduction is required in patients with mild or moderate renal impairment (i.e. in patients with a creatinine clearance of greater than 25 mL/min).

- ***Cardiovascular and cerebrovascular effects***

FLAMARYX may increase the risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use.

Caution is advised when **FLAMARYX** is prescribed to patients with cardiovascular risk factors (e.g. diabetes, smoking hypercholesterolaemia and hypertension) and they should only be treated with **FLAMARYX** after careful consideration.

Caution is required in patients with a history of hypertension and/or heart failure as fluid retention and oedema have been reported in association with **FLAMARYX** therapy due to inhibition of prostaglandin synthesis.
In view of **FLAMARYX's** inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

Clinical monitoring of blood pressure for patients at risk is recommended at baseline and especially during treatment initiation with **FLAMARYX.**

Because of its lack of platelet effects, **FLAMARYX** is not a substitute for aspirin for cardiovascular prophylaxis (see section 4.5).

- ***Parameters of liver and renal function***

  FLAMARYX should be used with caution in patients with:

  - Hepatic impairment- Increases risk of renal decompensation.
  - Renal impairment- Increases risk of renal decompensation.

  Increases in serum transaminase levels, increases in serum bilirubin or other liver function parameters, as well as increases in serum creatinine and blood urea and other laboratory disturbances, have been reported.

  In most cases these have been small and transient increases above the normal range.

  If the abnormality is significant or persistent, **FLAMARYX** should be stopped and follow up tests carried out.

  No dose reduction is required in patients with clinically stable liver cirrhosis.

  Frail or debilitated patients may tolerate side-effects less well and such patients should be carefully supervised. Caution should be used in the treatment of elderly patients who are more likely to be suffering from impaired renal, hepatic or cardiac function.

- ***Sodium, potassium and water retention***

  Induction of sodium, potassium and water retention and interference with the natriuretic effects of diuretics may occur with **FLAMARYX**.

  Furthermore, a decrease of the antihypertensive effect of antihypertensive medicines may occur (see section 4.5). Oedema or hypertension may be precipitated or exacerbated. Clinical monitoring is therefore necessary for patients at risk. In view of the ~~product's~~ **FLAMARYX's**

inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients (see sections 4.2 and 4.3). For patients at risk, clinical monitoring is recommended.

- ***Hyperkalaemia***

  Hyperkalaemia can be favoured by diabetes or concomitant treatment known to increase serum potassium levels (see section 4.5). Regular monitoring of potassium values should be performed in such cases.

- ***Combination with pemetrexed***

  In patients with mild to moderate renal insufficiency receiving pemetrexed, **FLAMARYX** should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following pemetrexed administration (see section 4.5).

- ***Underlying infections***

  FLAMARYX, may mask the symptoms of an underlying infectious disease.

- ***Pregnancy***

  Regular use of NSAIDs such as **FLAMARYX** 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 (see section 4.6).

- ***Fertility***

  FLAMARYX can inhibit cyclooxygenase / prostaglandin synthesis, which may impair fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving, or who are undergoing investigation of infertility, **FLAMARYX** should be stopped (see section 4.6).

- ***Lithium***

  FLAMARYX has been reported to increase plasma lithium levels (via decreased renal excretion of lithium), which may reach toxic values. The concomitant use of lithium and **FLAMARYX** is not recommended. If this combination appears necessary, lithium plasma concentrations should be monitored carefully during the initiation, adjustment and withdrawal of **FLAMARYX** treatment.

For relevant medicine interactions that require particular attention, see section 4.5.

Excipient warning

FLAMARYX contains lactose monohydrate (see section 2 and section 6.1), which may have an effect on the glycaemic control of diabetes mellitus.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

Risks related to hyperkalaemia -Certain medicines or therapeutic groups may promote hyperkalaemia: potassium salts, potassium-sparing diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, non-steroidal anti-inflammatory medicines, low-molecular-weight or unfractionated heparins, ciclosporin, tacrolimus and trimethoprim.
The onset of hyperkalaemia may depend on whether there are associated factors.
The onset of hyperkalaemia may depend on whether there are associated factors. This risk is increased when the above-mentioned medicines are co-administered with **FLAMARYX.**

Acetylsalicylic acid/ Aspirin and other NSAIDS - Use of two or more NSAIDs concomitantly, given at anti-inflammatory doses (≥ 500 mg per dose or ≥ 3 g as total daily amount)is not recommended could result in an increase in side-effects and may result in an increase in gastric ulceration and/or bleeding (see section 4.4), via inhibition of platelet function and damage to the gastroduodenal mucosa.
There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious

cardiovascular thrombotic events associated with **FLAMARYX**.

Because of its lack of platelet effects, **FLAMARYX** is not a substitute for aspirin for cardiovascular prophylaxis (see section 4.4).

Concomitant administration of aspirin (1000 mg t.i.d.) to healthy volunteers led to increases in the AUC (10 %) and C_{max} (24 %) of **FLAMARYX**. The clinical significance of this interaction is not known.

Anticoagulants, heparin and thrombolytics - FLAMARYX may enhance the effects of anti-coagulants such as warfarin, thrombolytics and heparin with an increased risk of bleeding, via inhibition of platelet function and damage to the gastroduodenal mucosa (see section 4.4).

The concomitant use of **FLAMARYX** and anticoagulants or heparin administered in the elderly or at curative doses is not recommended (see section 4.4).

If such prescribing cannot be avoided, close monitoring of their effects on coagulation is required (see section 4.4).

In remaining cases of heparin use, caution is necessary due to an increased bleeding risk. Careful monitoring of the international normalized ratio (INR) is required if it proves impossible to avoid such combination.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) - increased risk of gastrointestinal ulcers and bleeding, via inhibition of platelet function.

Concomitant use of **FLAMARYX** with other NSAIDs and antiplatelet medicines, including aspirin (acetylsalicylic acid) given at anti-inflammatory doses (≥ 500 mg per dose or ≥ 3 g as total daily amount) is not recommended.

Corticosteroids – The concomitant use of **FLAMARYX** with corticosteroids may increase the risk of gastrointestinal side effects, such as increase the risk of gastrointestinal side effects, such as increased risk of gastrointestinal ulceration or bleeding (PUBs). Use with caution.

Lithium - May result in an increase in plasma lithium concentrations (via decreased renal excretion of lithium) which may reach toxic values. The concomitant use is not recommended. Monitor lithium

plasma concentrations carefully when therapy with **FLAMARYX** is initiated or withdrawn.

Methotrexate – FLAMARYX can reduce the tubular secretion of methotrexate thereby increasing the plasma concentrations of methotrexate. For this reason, for patients on high dosages of methotrexate (more than 15 mg/week) the concomitant use of **FLAMARYX** is not recommended.
The risk of an interaction between **FLAMARYX** and methotrexate should be considered, also in patients on a low dosage of methotrexate, especially in patients with impaired renal function. When combination treatment is necessary, the blood cell count and renal function should be monitored.
When **FLAMARYX** and methotrexate are given within 3 days of each other, the plasma level of methotrexate may increase and cause increased toxicity.
Although the pharmacokinetics of methotrexate (15 mg/week) may not relevantly be affected by concomitant **FLAMARYX** treatment, may result in increased haematological toxicity due to methotrexate toxicity.

Angiotensin-converting enzyme (ACE) inhibitors, ARBs and other anti-hypertensive agents - May result in a decrease in antihypertensive effects and an increased risk of renal failure. **FLAMARYX** and angiotensin-II receptor antagonists as well as ACE inhibitors exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment the co-administration of an ACE inhibitor or angiotensin-II antagonists and medicines that inhibit cyclooxygenase may result in further detoriation of renal function, this may lead to acute renal failure, which is usually reversible. 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 (see section 4.4.).

Cardiac glycosides - May result in an increase in plasma cardiac glycosides (e.g. digoxin) concentrations.

Cholestyramine - Accelerates the elimination of meloxicam (as in **FLAMARYX**), by interrupting the enterohepatic circulation so that clearance for meloxicam increases and may result in a reduced increased therapeutic effect of **FLAMARYX.** Cholestyramine binds meloxicam in the gastrointestinal

tract leading to a faster elimination of **FLAMARYX.**

Calcineurin inhibitors **(e.g. [*C*]ciclosporin, tacrolimus) -** Increases the risk of nephrotoxicity via renal prostaglandin mediated effects. During combined treatment renal function should be assessed regularly. Tacrolimus should not be combined with **FLAMARYX**.

Alcohol - Simultaneous intake may increase the risk of bleeding.

Diuretics - May result in renal impairment if the patient is dehydrated (see section 4.4).
In some patients with compromised renal function (e.g. dehydrated patients or elderly patients with compromised renal function), the co-administration of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II antagonists and medicines that inhibit cyclooxygenase may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible. 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 (see section 4.4). Concomitant use may decrease the antihypertensive effect of beta-blockers (due to inhibition of prostaglandins with vasodilatory effect).

Intrauterine device - NSAIDS may decrease the efficacy of intrauterine devices.

Probenecid - Concomitant treatment with probenecid leads to reduced excretion and thereby increased effects of **FLAMARYX.**

Pemetrexed **-** For the concomitant use of **FLAMARYX** with pemetrexed in patients with creatinine clearance from 45 to 79 mL/min, the administration of **FLAMARYX** should be paused for at 5 days before, on the day of, and 5 days following pemetrexed administration. If a combination of **FLAMARYX** with pemetrexed is necessary, patients should be closely monitored, especially for myelosuppression and gastrointestinal adverse reactions. In patients with severe renal impairment (creatinine clearance below 45 mL/min), the concomitant administration of **FLAMARYX** with pemetrexed is not recommended.

In patients with normal renal function (creatinine clearance ≥ 80 mL/min), doses of 15 mg meloxicam (as in **FLAMARYX**) may decrease the elimination of pemetrexed and therefore increase the occurrence of adverse events due to pemetrexed. Therefore, caution should be taken when co-administering 15 mg doses of meloxicam with pemetrexed in patients with normal renal function (creatinine clearance ≥ 80 mL/min).

***Mifepristone* – FLAMARYX** should not be used for 8 – 12 days after taking mifepristone as it can reduce the effect of mifepristone.

Quinolone antibiotics - -Concomitant use with quinolone antibiotics may have an increased risk of developing convulsions.

Zidovudine - There is an increased risk of haematological toxicity when **FLAMARYX** is taken with zidovudine.

Medicines known to inhibit, or to be metabolised by cytochrome (CYP) 2C9 and/or CYP 3A4

FLAMARYX is eliminated almost entirely by hepatic metabolism, of which approximately two thirds are mediated by cytochrome (CYP) P450 enzymes (CYP 2C9 major pathway and CYP 3A4 minor pathway) and one third by other pathways, such as peroxidase oxidation. The potential for a pharmacokinetic interaction should be taken into account when **FLAMARYX** and medicines known to inhibit, or to be metabolised by CYP 2C9 and/or CYP 3A4 are administered concurrently. Interactions via CYP 2C9 can be expected in combination with medicinal products such as oral antidiabetics (sulphonylureas, nateglinide), which may lead to increased plasma levels of these medicines and **FLAMARYX**. Patients concomitantly using **FLAMARYX** with sulphonylureas or nateglinide should be carefully monitored for hypoglycaemia.

Other medicines - No relevant pharmacokinetic interactions were detected with respect to the concomitant administration of antacids, cimetidine, digoxin and furosemide.

4.6 Fertility, pregnancy and lactation

Safety and efficacy in pregnancy and lactation has not been established.

FLAMARYX Is contraindicated during pregnancy.

Inhibition of prostaglandin synthesis may adversely affect pregnancy and/or the embryo-foetal development. Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastrochisis after use of a prostaglandin synthesis inhibitor in early pregnancy.

The use of **FLAMARYX** during the third trimester is not recommended because of possible adverse effects on the foetus, such as:

- cardiopulmonary toxicity (premature closure of the ductus arteriosus, which may lead to persistent pulmonary hypertension in the newborn).
- renal dysfunction, which may progress to renal failure with oligohydramnios.

  At the end of pregnancy, **FLAMARYX** may expose the mother and the neonate to the following:
  - prolongation of bleeding time, an anti-aggregating effect which may occur even at very low doses.
  - the onset of labour may be delayed and its duration increased (see section 4.3).

Breastfeeding

FLAMARYX is contraindicated during lactation (see section 4.3).

While no specific experience exists for **FLAMARYX** in humans, NSAIDs are known to pass into mother's milk. Administration is therefore contraindicated in women who are breastfeeding.

Fertility

FLAMARYX can inhibit cyclooxygenase / prostaglandin synthesis, which may impair fertility and is not recommended in women attempting to conceive. **FLAMARYX** may delay ovulation. In women who have difficulties conceiving, or who are undergoing investigation of infertility, **FLAMARYX** should be stopped (see section 4.4).

4.7 Effects on ability to drive and use machines

Patients should not operate machinery or drive a vehicle if they experience drowsiness, blurred vision or any other central nervous system effect.

FLAMARYX may cause side effects, such as visual disturbances including blurred vision, dizziness, drowsiness, vertigo and other central nervous system disturbances (see section 4.8) and therefore affect the ability to drive a vehicle or use machinery. Caution is advised before driving a vehicle or operating machinery until the effects of **FLAMARYX** are known.

4.8 Undesirable effects

b. Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Frequent	Anaemia,
	Less frequent	Thrombocytopenia, agranulocytosis, leucopoenia, abnormal blood count (including differential white cell count), neutropenia, eosinophilia
Concomitant administration of a potentially myelotoxic medicine in particular methotrexate, appears to be a predisposing factor to the onset of cytopenia.		
Immune system disorders	Less frequent	Hypersensitivity reactions including anaphylaxis, angioedema and bronchospasm (especially if patient is aspirin-sensitive and has

		asthma and/or nasal polyps **FLAMARYX** should be withdrawn immediately)
	Frequency unknown	Anaphylactoid reactions
Psychiatric disorders	Less frequent	Altered mood, confusional state, insomnia, nightmares
	Frequency unknown	Disorientation
Nervous system disorders	Frequent	Headache, dizziness, light-headedness
	Less frequent	Drowsiness, somnolence
	Frequency unknown	Insomnia, nightmares, erebrovascular incidents (strokes).
Eye disorders	Less frequent	Visual disturbances (such as blurred vision), conjunctivitis
Ear and labyrinth disorders	Less frequent	Vertigo, tinnitus
Cardiac disorders	Less frequent	Oedema, palpitations, elevated blood pressure (hypertension), congestive cardiac failure
	Frequency unknown	Dysrhythmia tachycardia, congestive cardiac failure,

		myocardial infarction, cardiovascular thrombotic events
Vascular disorders	Less frequent	Elevated blood pressure (hypertension), flushing
	Frequency unknown	Aggravated hypertension
Respiratory, thoracic and mediastinal disorders	Less frequent	Bronchospasm, asthma in individuals allergic to aspirin or other NSAIDs
Gastrointestinal disorders	Frequent	Dyspepsia, diarrhoea, nausea, vomiting, abdominal pain
	Less frequent	Peptic ulcers, perforation or gastrointestinal bleeding (sometimes fatal), perforation or ulceration ~~(is~~ generally more serious in the elderly), melaena, haematemesis, ulcerative stomatitis, induction or exacerbation of colitis, stomatitis gastritis, eructation oesophagitis, flatulence, constipation,

		exacerbation of Crohn's disease
	Frequency unknown	Pancreatitis
The most commonly observed adverse events are gastrointestinal in nature.		
Hepato-biliary disorders	Less frequent	Hepatitis, abnormal liver function test (e.g., raised transaminases or billirubin
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, rash,
	Less frequent	Angioedema urticaria, photosensitivity, bullous reactions, including erythema multiforme and Stevens-Johnson syndrome, toxic epidermal necrolysis

Renal and urinary disorders	Less frequent	Nephrotic syndrome, glomerulonephritis, interstitial nephritis and papillary necrosis, acute renal failure, (particularly in patients with risk factors – see section 4.4), sodium and water retention, hyperkalaemia (see sections 4.4 and 4.5), abnormal renal function test (increased serum creatinine and/or serum urea), micturition disorders including acute urinary retention
Reproductive system and breast disorders	Less frequent	Delayed ovulation
General disorders and administration site conditions	Frequent	Peripheral oedema.

Post-marketing experience

System Organ Class	Frequency	Side effects
Immune system disorders	Frequency unknown	Anaphylactoid reaction and anaphylactic reaction, including anaphylactic shock, Drug Reaction with Eosinophillia and Systemic Symptoms (DRESS) (see section 4.5)
Psychiatric disorders	Frequency unknown	Confusional state, disorientation
Skin and subcutaneous tissue disorders	Frequency unknown	Photosensitivity reaction, medicine reaction with eosinophilia and systemic symptoms (DRESS) (see section 4.4)
Reproductive system and breast disorders	Frequency unknown	Female infertility

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

Symptoms following acute NSAID (such as **FLAMARYX**) overdose are usually limited to lethargy, drowsiness, nausea, vomiting and epigastric pain, which may be reversible with supportive care. Gastrointestinal bleeding can occur.

Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs (such as **FLAMARYX**) and may occur following an overdose.

Treatment of overdosage:

- Treatment is symptomatic and supportive as there is no known antidote. Absorption should be reduced by:
- Activated charcoal if patient presents 1 to 2 hours after overdose
- Cholestyramine

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification:

A 3.1 Antirheumatics (anti-inflammatory agents).

ATC code: M01AC06

PHARMACOLOGICAL ACTION:

Mechanism of action

Meloxicam, an oxicam (enolic acid) derivative, is a non-steroidal anti-inflammatory compound (NSAID) with analgesic, antipyretic and anti-inflammatory activities. The action of meloxicam is related to inhibition of the enzyme cyclo-oxygenase (COX), resulting in the decreased formation of prostaglandins (mediators of inflammation) and thromboxanes. A selective COX-2 inhibitory (anti-inflammatory effect) *in vitro* in relation to COX-1 has been demonstrated. Inhibition of COX-1 (gastrointestinal, renal and platelet effects) *in vivo* occurs. It is suggested that the extent of inhibition of

COX-1 *in vivo* is a function of dose and inter-individual variability of meloxicam concentrations.

5.2 Pharmacokinetic properties

Absorption:

Meloxicam is well absorbed from the gastrointestinal tract.

Following single dose administration of meloxicam, mean maximum plasma concentrations are achieved within 5 to 6 hours. Extent of absorption for meloxicam following oral administration is not altered by concomitant food intake or the use of inorganic antacids.

Dose linearity was demonstrated after oral administration in the therapeutic dose range of 7,5 to 15 mg. The extent of absorption after oral administration is 89 % and concomitant administration with food does not affect absorption.

With multiple dosing, steady state conditions were reached within 3 to 5 days.

Once daily dosing leads to mean meloxicam plasma concentrations with a relatively small peak-trough fluctuation in the range of 0,4 – 1,0 µg/mL for 7,5 mg doses and 0,8 – 2,0 µg/mL for 15 mg doses, respectively (C_{min} and C_{max} at steady state, correspondingly).

Mean maximum plasma concentrations of meloxicam at steady state, are achieved within five to six hours

Distribution:

Meloxicam is 99 % protein bound, essentially albumin.

Meloxicam penetrates into synovial fluid to give concentrations approximately half of those in plasma.

Volume of distribution is low, i.e. approximately 11 L after i.m. or i.v. administration, and shows interindividual variation in the order of 7 – 20 %.

The volume distribution of distribution after administration of multiple oral doses of meloxicam (7,5 mg to 15 mg) is approximately 16 L with coefficients of variation ranging from 11 % to 32 %.

Biotransformation:

Meloxicam is extensively metabolized in the liver (mainly by oxidation).

Four different metabolites were identified in urine, which were all pharmacodynamically inactive.

The major metabolite, 5'-carboxymeloxicam (60 % of dose), is formed by oxidation of an intermediate

metabolite 5'- hydroxymethylmeloxicam, which is also excreted to a lesser extent (9 % of dose). In vitro studies suggest that CYP 2C9 plays an important role in this metabolic pathway, with a minor contribution from the CYP 3A4 isoenzyme. The patient's peroxidase activity is probably responsible for the other two metabolites, which account for 16 % and 4 % of the administered dose, respectively.

Elimination:

Meloxicam is excreted predominantly in the form of metabolites and occurs to equal extents in urine and faeces. Less than 5 % of the daily dose is excreted unchanged in the faeces, while only traces of the parent compound are excreted in urine.

The mean elimination half-life varies between 13 and 25 hours . after oral, IM and IV administration.

Total plasma clearance is 7 to 12 mL/min after a single dose.

Linearity/non-linearity:

Meloxicam demonstrates linear pharmacokinetics in the therapeutic dose range of 7,5 mg to 15 mg following oral or intramuscular administration.

Special populations

Hepatic/renal impairment

Neither hepatic nor mild or moderate renal impairment have a substantial effect on meloxicam pharmacokinetics. Moderate renal impairment had significantly higher total medicine clearance. Protein binding is reduced in patients with end stage renal disease. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam concentrations, and a daily dose of 7,5 mg must not be exceeded (see section 4.2).

Elderly population

Patients with hepatic/renal insufficiency: Mild or moderate hepatic insufficiency and mild renal insufficiency do not have a substantial effect on meloxicam pharmacokinetics.

Subjects with moderate renal impairment had significantly higher total meloxicam clearance. A reduced protein binding is observed in patients with terminal renal failure. In terminal renal failure, the increase in the volume of distribution may result in higher free meloxicam

concentrations.

Elderly males exhibited mean pharmacokinetic parameters similar to those of young males. Elderly females showed higher AUC values and longer elimination half-life compared to younger subjects of both sexes. Mean plasma clearance at steady state in elderly subjects was slightly lower than that reported for younger subjects

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Monohydrate

Cellulose Microcrystalline

Sodium Citrate

Crospovidone

Povidone

Purified water

Silica, Colloidal Anhydrous

Magnesium stearate

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at or below 25 °C. Do not remove the blister from the carton until required for use.

KEEP OUT OF THE REACH OF CHILDREN

6.5. Nature and contents of container

FLAMARYX 7,5 mg:

Tablets are packed in 250 micron white opaque PVC coated with 60 gsm PVdC and printed aluminium foil with 7 gsm heat seal lacquer. 3 blisters containing 10 tablets each are packed into a printed cardboard carton.

Pack size: 30's (3 x 10's)

FLAMARYX 15 mg:

Tablets are packed in 250 micron white opaque PVC coated with 60 gsm PVdC and printed aluminium foil with 7 gsm heat seal lacquer. 3 blisters containing 10 tablets each are packed into a printed cardboard carton.

Pack size: 30's (3 x 10's)

7. HOLDER OF CERTIFICATE OF REGISTRATION

Aurogen South Africa (Pty) Ltd

Woodhill Office Park, Building 1,

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg,

South Africa

8. REGISTRATION NUMBER

FLAMARYX 7,5 mg: 42/3.1/0469

FLAMARYX 15 mg: 42/3.1/0470

NAMIBIA:

FLAMARYX 7,5 mg: 10/30.1/0078

FLAMARYX 15 mg: 10/30.1/0079

9. DATE OF FIRST AUTHORISATION

23 July 2010

10. DATE OF REVISION OF TEXT

13 August 2025