APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

SOUTH AFRICA: S3

PROPRIETARY NAME (and dosage form):

FLAMARYX 7,5 mg (tablet)

FLAMARYX 15 mg (tablet)

COMPOSITION:

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

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

PHARMACOLOGICAL CLASSIFICATION:

A 3.1 Antirheumatics (anti-inflammatory agents).

PHARMACOLOGICAL 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.

Pharmacokinetics:

The extent of absorption after oral administration is 89 % and concomitant administration with food does not affect absorption. Meloxicam is 99 % protein bound and has an elimination half-life of 15 -

20 hours. Meloxicam is extensively metabolized in the liver (mainly by oxidation) and less than 5 % of the daily dose is excreted unchanged in the faeces and urine.

INDICATIONS:

FLAMARYX is indicated for the symptomatic treatment of:

- Rheumatoid arthritis.
- Painful osteoarthritis.
- Ankylosing spondylitis.
- Episodes of acute sciatica.

CONTRA-INDICATIONS:

- Hypersensitivity to **FLAMARYX** or to any components of the formulation.
- Patients in who attacks of asthma, urticaria, nasal polyps or acute rhinitis are precipitated by acetylsalicylic acid/ aspirin or by other non-steroidal anti-inflammatory agents.
- Active peptic ulcer disease.
- Active or history of recurrent ulcer/haemorrhage/perforations.
- History of gastrointestinal bleeding or perforation (PUBs) related to previous NSAIDs.
- Severe hepatic impairment.
- Severe renal impairment.
- Heart failure.
- Pregnancy (see "**PREGNANCY AND LACTATION"**).

WARNINGS AND SPECIAL PRECAUTIONS:

- Children under the age of 18 years - Safety and efficacy have not been established.
- Elderly: The elderly have an increased frequency of adverse reactions to NSAIDs, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal.
- 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.

- 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.
- Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported. **FLAMARYX** should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.
- 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.
- Congestive heart failure increases the risk of renal decompensation (see "**CONTRA-INDICATIONS"**).
- **FLAMARYX** should be used with caution in patients with:-
    - Hepatic impairment- Increases risk of renal decompensation.
    - Renal impairment- Increases risk of renal decompensation.

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.

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 "**CONTRA-INDICATIONS"**).

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

Effects on the ability to drive and use machinery

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

INTERACTIONS:

Acetylsalicylic acid/ Aspirin and other NSAIDS- Use of two or more NSAIDs concomitantly could result in an increase in side-effects. May result in an increase in gastric ulceration and/or bleeding.

Anticoagulants - FLAMARYX may enhance the effects of anti-coagulants such as warfarin, and increase the risk of bleeding complications.

Anti-platelet agents and selective serotonin reuptake inhibitors (SSRIs) - increased risk of gastrointestinal bleeding.

Corticosteroids - increased risk of gastrointestinal ulceration or bleeding (PUBs).

Lithium - May result in an increase in plasma lithium concentrations. Monitor lithium plasma concentrations carefully when therapy with **FLAMARYX** is initiated or withdrawn.

Methotrexate - 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.

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

Cholestyramine - May result in a reduced therapeutic effect of **FLAMARYX.**

Ciclosporin - Increases the risk of nephrotoxicity.

Alcohol - Simultaneous intake may increase the risk of bleeding.

Diuretics - May result in renal impairment if the patient is dehydrated (see "**WARNINGS AND SPECIAL PRECAUTIONS"**).

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

PREGNANCY AND LACTATION:

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

The use of **FLAMARYX** during the third trimester is not recommended because of possible adverse effects on the foetus, such as premature closure of the ductus arteriosus, which may lead to

persistent pulmonary hypertension in the newborn. The onset of labour may be delayed and its duration increased (see "**CONTRA-INDICATIONS"**).

DOSAGE AND DIRECTIONS FOR USE:

Safety and efficacy in children under the age of 18 years has not been established.

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

Use the lowest effective dose for the shortest possible duration of treatment.

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).

Adults:

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

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.

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

Rheumatoid arthritis: 15 mg once daily. Reduce dose if possible (provided therapeutic response is maintained).

SIDE EFFECTS:

Blood and the lymphatic system disorders:

Less frequent: Anaemia, thrombocytopenia, agranulocytosis, leucopoenia.

The following side effects have been reported and frequencies are unknown: Neutropenia, eosinophilia.

Nervous system disorders:

Less frequent: Headache, dizziness, light-headedness, vertigo, drowsiness, confusion.

The following side effects have been reported and frequencies are unknown: Insomnia, nightmares.

Eye disorders:

Less frequent: Visual disturbances (such as blurred vision), conjunctivitis.

Cardiac disorders:

Less frequent: Oedema, palpitations, elevated blood pressure (hypertension), cardiac failure.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Bronchospasm.

Gastrointestinal disorders:

The most commonly observed adverse events are gastrointestinal in nature.

Frequent: Dyspepsia, diarrhoea, flatulence.

Less frequent: Peptic ulcers, perforation or gastrointestinal bleeding, sometimes fatal. Perforation or ulceration is generally more serious in the elderly. Nausea and vomiting, constipation and abdominal pain, melaena, haematemesis, ulcerative stomatitis, induction or exacerbation of colitis, gastritis.

The following side effects have been reported and frequencies are unknown: exacerbation of Crohn's disease.

Hepato-biliary disorders:

Less frequent: Hepatitis.

Skin and subcutaneous tissue disorders:

Less frequent: Pruritus, rash, flushing, urticaria, stomatitis, 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, renal failure.

Other:

Less frequent: Tinnitus, 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).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms of overdosage:

(See "**SIDE EFFECTS"**)

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
- Gastric lavage if within 1 hour of overdose

IDENTIFICATION:

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.

PRESENTATION:

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)

STORAGE INSTRUCTIONS:

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.

REGISTRATION NUMBER:

SOUTH AFRICA:

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

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF

REGISTRATION:

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