PACKAGE INSERT

SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE:

AMDOCIN (capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each AMDOCIN capsule tablet contains Indomethacin 25 mg.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

AMDOCIN capsules are yellow gelatin capsules containing white to off-white powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications:

AMDOCIN is indicated for the symptomatic treatment of

- rheumatoid arthritis,
- ankylosing spondylitis,
- osteoarthritis,
- other musculoskeletal inflammatory disorders and
- acute attacks of gout.
- Degenerative joint disease of the hip.
- Low back pain (commonly referred to as lumbago).
- 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.
- The reduction of symptoms in some febrile conditions.
- Fever (as a short-term adjunct to specific treatment).
- The reduction of fever in Hodgkin's disease when the fever has been refractory to other treatment.

4.2. Posology and method of administration

Posology

Adults

The recommended dosage is 25 mg to 200 mg daily divided in two to four equal doses. Undesirable effects may be minimised by taking the lowest effective dose for the shortest possible duration of treatment (see section 4.4), consistent with individual patient treatment goals, starting with a low dose.

A loading dose of AMDOCIN 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 maximum benefit and minimise adverse reactions.

In chronic conditions start the treatment with a low dosage, increasing as required.

- In chronic musculoskeletal and joint disorders, the usual initial dose is 25 mg two or three times daily with food, increased, if required, by 25 mg to 50 mg daily at weekly intervals, up to 150 mg to 200 mg daily in divided doses.

- 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 acute periarticular disorders and in low back pain 50 mg may be given two or three times daily for about 10 days.
- In the treatment of 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.

The total combined daily dose by mouth should not generally exceed 200 mg.

Paediatric population

The safety and efficacy of indomethacin, as in AMDOCIN, in children has not been established (see section 4.4).

Method of administration

For oral administration.

To minimise or reduce the possibility of gastrointestinal disturbances, it is recommended that AMDOCIN be taken with food, milk or an antacid.

4.3 Contraindications:

AMDOCIN is contra-indicated in:

- Patients with hypersensitivity to indomethacin or to any excipients in AMDOCIN (see section 6.1).
- Patients with severe hepatic failure and renal failure (see section 4.4).
- Patients with gastritis, regional enteritis, ulcerative colitis.

- Patients with bleeding disorders.
- Patients in whom acute asthmatic attacks, urticaria or rhinitis and nasal polyps are precipitated by acetylsalicylic acid or other non-steroidal anti-inflammatory drugs (see section 4.8).
- Patients on concurrent triamterene treatment. Addition of triamterene to a maintenance schedule of AMDOCIN may result in acute renal failure which may be reversible upon discontinuation of treatment. AMDOCIN and triamterene should not be administered together (see section 4.5).
- Patients taking diflunisal, this medicine should not be taken concomitantly with AMDOCIN (see 4.5).
- Patients with heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Patients with a history of angioedema following exposure to NSAIDS, such as AMDOCIN and/or aspirin.
- Patients who require treatment for peri-operative pain relief in the setting of coronary artery surgery.
- Patients with a history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous NSAIDs including AMDOCIN.
- Patients with active or history of recurrent ulcer/haemorrhage/perforations.
- Patients with a history of, or current gastrointestinal lesions.
- Pregnant women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/ foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.4 and 4.6).
- Lactation (see section 4.6).

Safety of AMDOCIN in children has not been established.

4.4. Special warnings and precautions for use:

AMDOCIN may predispose to cardiovascular events, gastrointestinal events, or cutaneous reactions which may be fatal.

Hypersensitivity

Serious skin reactions, some of them fatal, including drug rash with eosinophilia and systemic symptoms (DRESS), exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN) have been reported (see section 4.8).

These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations.

Patients allergic to salicylates may exhibit a cross-reaction to AMDOCIN.

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

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

Patients appear to be at highest risk for these reactions early in the course of treatment, the onset of the reaction occurring in the majority of cases, within the first month of treatment.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) has been reported in patients taking NSAIDs such as AMDOCIN. 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 AMDOCIN and evaluate the patient immediately.

Gastrointestinal effects

The risk of gastrointestinal bleeding or perforation (PUBs) is higher with increasing doses of AMDOCIN, in patients with a history of ulcers, and the elderly. These patients should commence treatment on the lowest dose available.

When gastrointestinal bleeding or ulceration occurs in patients receiving AMDOCIN, treatment with AMDOCIN should be stopped.

AMDOCIN 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. Combination treatment 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.

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

Heart failure and oedema

Caution is required in patients with a history of cardiac dysfunction, hypertension and/or heart failure as fluid retention and oedema have been reported in association with AMDOCIN treatment due to inhibition of prostaglandin synthesis.

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

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 treatment, as in AMDOCIN.

Hypertension

Patients with uncontrolled hypertension, congestive heart failure, established ischaemic heart disease, peripheral arterial disease, and/or cerebrovascular disease should not be treated with indomethacin, as in AMDOCIN (see section 4.3).

Caution is required before initiating longer-term treatment of patients with significant risk factors for cardiovascular disease (e.g., hypertension, hyperlipidaemia, diabetes mellitus, smoking).

AMDOCIN 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, as in AMDOCIN. AMDOCIN should be taken with caution in patients with hypertension.

Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment, as in AMDOCIN and throughout the course of treatment.

Cardiovascular thrombotic events

AMDOCIN 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 AMDOCIN, the lowest effective dose should be taken for the shortest duration possible.

Because of its lack of platelet effect, AMDOCIN is not a substitute for aspirin for cardiovascular prophylaxis.

Renal 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, as in AMDOCIN, 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.

AMDOCIN may also cause fluid retention which may further aggravate these conditions.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of a NSAID, as in AMDOCIN, may precipitate overt renal decompensation. The administration of an NSAID, as in AMDOCIN, may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure. 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 AMDOCIN in patients with dehydration. Patients should first be hydrated before treatment with AMDOCIN commences.
Caution is also recommended in patients with pre-existing kidney disease.
AMDOCIN should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve (see also section 4.3).
Discontinuation of NSAID treatment, as in AMDOCIN, is usually followed by recovery to the pre-treatment state.
Acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome can occur in patients receiving long-term administration of AMDOCIN. Since indomethacin, as in AMDOCIN, is eliminated primarily by the kidneys,
patients with significantly impaired renal function should not be treated with AMDOCIN (see section 4.3).
Increases in plasma potassium concentration, including hyperkalaemia, can occur even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninaemic-hypoaldosteronism state.
Hepatic impairment

AMDOCIN 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 treatment with NSAIDs such as AMDOCIN.

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 treatment with AMDOCIN.

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.), treatment should be discontinued.

Use in pregnancy

Limit the use of NSAIDs, including AMDOCIN, between 20 and 30 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction. Avoid use of NSAIDs, such as AMDOCIN, in women around 30 weeks gestation and later in pregnancy due to the risks of oligohydramnios/foetal renal dysfunction and premature closure of the foetal ductus arteriosus (see section 4.3 and 4.6).

These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID, such as AMDOCIN, initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation. Complications of prolonged oligohydramnios may include limb contractures and delayed lung maturation. In some post marketing cases of impaired neonatal renal function, invasive procedures such as exchange transfusion or dialysis were required.

If AMDOCIN is necessary between 20 weeks and 30 weeks gestation, limit AMDOCIN use to the lowest effective dose and shortest duration possible.

Healthcare professionals should consider ultrasound monitoring of amniotic fluid if AMDOCIN treatment extends beyond 48 hours. Discontinue AMDOCIN if oligohydramnios occurs and follow up according to clinical practice.

Female fertility

AMDOCIN may have a reversible inhibitory effect on women's ovulation. The use of AMDOCIN may impair female fertility and is not recommended in women attempting to conceive. In women who have difficulties conceiving or who are undergoing investigation of infertility, withdrawal of AMDOCIN should be considered (see section 4.6).

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.

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.

Ocular effects

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

In patients with rheumatoid arthritis, eye changes may occur which may be related to the underlying disease or to the treatment. In chronic rheumatoid disease, ophthalmological examinations at periodic intervals are recommended, treatment should be discontinued if eye changes are observed.

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 treatment is prolonged. Discontinue treatment if eye changes are observed.

Prolonged treatment will require regular ophthalmological examination.

Platelet aggregation

AMDOCIN can inhibit platelet aggregation. This effect usually disappears within 24 hours of discontinuation of AMDOCIN. AMDOCIN 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, AMDOCIN should be used with caution in persons with coagulation defects (see section 4.5).

Respiratory disorders

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

Central nervous system effects

Headache, sometimes accompanied by dizziness or light-headedness may occur, usually early in treatment with AMDOCIN.

Starting treatment with a low dosage and increasing it gradually may minimise the incidence of headache. These symptoms may disappear on continuing treatment or

with reducing the dosage. If headache persists despite dosage reduction, AMDOCIN should be withdrawn.

Infections

AMDOCIN may mask the signs and symptoms which ordinarily accompany infectious disease.

AMDOCIN should be used with caution in patients with existing, but controlled infection.

Caution is advised with concomitant use of live vaccines.

Anaemia

Patients should be periodically observed to allow early detection of any unwanted effects on peripheral blood (anaemia), liver function, or gastro-intestinal tract.

General

AMDOCIN should be used cautiously in patients with psychiatric disorders, epilepsy or Parkinsonism, as indomethacin, as in AMDOCIN, may aggravate these disorders.

Porphyria

Safety has not been established.

Elderly

The elderly have an increased frequency of adverse reactions to NSAIDs, including AMDOCIN, especially gastrointestinal bleeding and perforation (PUBs) which may be fatal. An increase in age increases the possibility of side effects. AMDOCIN should be used with greater care in the elderly.

Paediatric population

The safety and efficacy of AMDOCIN in children has not yet been established (see section 4.3).

If AMDOCIN fails to provide benefit in 2 to 3 weeks, alternative treatment must be considered.

AMDOCIN contains lactose:

AMDOCIN contains lactose which may have an effect on the glycaemic control of patients with diabetes mellitus.

Patients with rare hereditary conditions of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take AMDOCIN.

4.5. Interaction with other medicines and other forms of interaction

Diflunisal

When diflunisal and AMDOCIN are given together, the renal clearance of AMDOCIN decreases and the plasma concentration increases, and the combined use can result in fatal gastrointestinal haemorrhage.

The combination should not be used (see section 4.3).

Acetylsalicylic acid

The administration of anti-inflammatory doses of aspirin decreases AMDOCIN blood concentrations by about 20 %.

AMDOCIN 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 AMDOCIN.

The concomitant use of AMDOCIN with aspirin or other salicylates is not recommended. Combined use of AMDOCIN and aspirin does not produce any greater therapeutic effect than the use of AMDOCIN. Furthermore, the incidence of gastrointestinal side effects significantly increases with combined treatment.

NSAIDs

The use of two or more NSAIDs concomitantly could result in the increase in side effects and should therefore be avoided.

Antacids

The bioavailability of indomethacin, as in AMDOCIN, may be reduced by concomitant antacid treatment.

Probenecid

When indomethacin, as in AMDOCIN, is given to patients receiving probenecid, the plasma levels of indomethacin, as in AMDOCIN, are likely to be increased.

Therefore, a lower total daily dosage of indomethacin, as in AMDOCIN, may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin, as in AMDOCIN, are made under these circumstances they should be made cautiously and in small increments.

Anticoagulants

AMDOCIN may enhance the effects of anticoagulants such as warfarin.

Patients should be closely observed for alterations of prothrombin time, when indomethacin, as in AMDOCIN is given concomitantly with anticoagulants. Caution should be exercised when indomethacin, as in AMDOCIN and anticoagulants are administered concomitantly.

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

Corticosteroids

Increased risk of gastrointestinal ulceration or bleeding (PUBs). In a patient receiving corticosteroids concomitantly, a reduction in dosage of these may be possible, but should only be effected slowly under supervision.

Anti-platelet medicines

Increased risk of gastrointestinal bleeding.

Indomethacin, as in AMDOCIN 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/selective serotonin reuptake inhibitors (SSRIs)

Increased risk of bleeding.

Antidiabetics

The hypoglycaemic effect of sulfonylureas may be increased by NSAIDs, such as AMDOCIN.

Methotrexate

Caution should be exercised with concomitant use of indomethacin, as in AMDOCIN, with methotrexate. Indomethacin, as in AMDOCIN, 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 indomethacin, as in AMDOCIN.

Ciclosporin

Administration of NSAIDs such as AMDOCIN, concomitantly with ciclosporin has been associated with an increase in ciclosporin-induced toxicity, possibly due to decreased

synthesis of renal prostacyclin. Indomethacin, as in AMDOCIN should be used with caution in patients taking ciclosporin, and renal function should be monitored carefully.'

Lithium

Decreased elimination of lithium; Indomethacin, as in AMDOCIN, 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 treatment, plasma lithium concentration should be monitored more frequently.

Antihypertensives

Reduced anti-hypertensive effect; AMDOCIN may acutely reduce the antihypertensive effect of antihypertensives due partly to the inhibition of prostaglandin synthesis of indomethacin, as in AMDOCIN. Patients receiving
concomitant treatment should have the antihypertensive effect of their treatment reassessed. Therefore, caution should be exercised when considering the addition of indomethacin, as in AMDOCIN, 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 antagonists,

• hydralazine or nifedipine.

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

Phenytoin

AMDOCIN may increase the effects of phenytoin.

Antipsychotics

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

Antivirals

There is an increased risk of haematological toxicity when NSAIDs, such as AMDOCIN are given with zidovudine. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrenttreatment with zidovudine and ibuprofen. There is a risk of indomethacin toxicity with concomitant use of AMDOCIN with ritonavir and should thus be avoided.

False negative results in the dexamethasone suppression test have been reported in patients taking AMDOCIN.

Diuretics

AMDOCIN antagonises the natriuretic and antihypertensive effects of furosemide, the antihypertensive effects of thiazide diuretics, ß-adrenergic blocking medicines, or inhibitors of angiotensin converting enzyme may also be reduced. Therefore, when AMDOCIN and diuretics are used concomitantly, the patient should be closely observed to determine whether the desired effect of the diuretic is being obtained.

Reversible acute renal failure associated with the concomitant administration of indomethacin, as in AMDOCIN and triamterene has been reported. Indomethacin, as in AMDOCIN and triamterene should not be administered concomitantly.

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 AMDOCIN. 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 treatment, and periodically thereafter.

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

In patients with compromised renal function (e.g., the elderly or patients who are volume depleted, including those on diuretic treatment) who are being treated with NSAIDs, such as AMDOCIN, including selective cyclooxygenase-2 inhibitors, the co-administration of angiotensin II receptor antagonists or ACE inhibitors may result in further deterioration of renal function, including possible acute renal injury (renal failure). These effects are usually reversible. Therefore, the combination should be administered with caution in patients with compromised renal function.

Both indomethacin, as in AMDOCIN and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin, as in AMDOCIN 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 indomethacin, as in AMDOCIN.

Cardiac glycosides/digoxin

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

NSAIDs, such as AMDOCIN, 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 indomethacin, as in AMDOCIN.
This additive effect is probably due at least in part to inhibition of prostaglandin synthesis by indomethacin, as in AMDOCIN and may lead to water intoxication.
Caution should be exercised when indomethacin, as in AMDOCIN and phenylpropanolamine are administered concomitantly.

Desmopressin

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

Mifepristone

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

Quinolone antibiotics

Concomitant use of fluoroquinolones and indomethacin, as in AMDOCIN may induce convulsions in patients with or without a history of convulsions/seizures.

Muscle relaxants

Concomitant use of NSAIDs such as AMDOCIN and baclofen may induce baclofen toxicity due to reduced rate of excretion.

Pentoxifylline

Possible increased risk of bleeding when taken with NSAIDs such as AMDOCIN.

Tacrolimus

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

Tiludronic acid

The bioavailability of tiludronic acid is increased by indomethacin, as in AMDOCIN.

Laboratory tests

False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin, as in AMDOCIN have been reported. Thus, results of the DST should be interpreted with caution in these patients (see section 4.8).

4.6. Fertility, pregnancy and lactation

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

Pregnancy

First trimester

Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/foetal development.

Data from epidemiological studies suggests an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor, such as AMDOCIN, 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.

Second and third trimester

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 oligohydramnios'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.

Because of these risks, the use of AMDOCIN, dose and duration, between 20 and 30 weeks of gestation should be limited and avoided at around 30 weeks of gestation and later in pregnancy (see sections 4.3 and 4.4).

Breastfeeding

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

Fertility

The use of AMDOCIN 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 AMDOCIN should be stopped (see section 4.4).

4.7. Effects on ability to drive and use machines

AMDOCIN has major influence on the ability to drive or operate machinery.

AMDOCIN may interfere with driving and the operation of machines, as it may cause dizziness, drowsiness, visual disturbances and headaches. Patients on treatment with AMDOCIN should not drive or operate machines until they know how they are affected by AMDOCIN (see section 4.8).

4.8. Undesirable effects

a) Summary of the safety profile

The most common side effects are gastrointestinal disturbances, headache and dizziness. Gastrointestinal perforation, ulceration and bleeding, sometimes fatal, may occur.

System organ class	**Frequent**	**Less frequent**	**Frequency unknown** (cannot be estimated from the available data)
Infections and infestations		Fulminant necrotising fasciitis[1].	
Neoplasm benign, malignant and unspecified (including cysts and polyps)			Leukaemia.
Blood and the lymphatic system disorders		Neutropenia, haemolytic anaemia, thrombocytopenia, agranulocytosis, leucopenia, aplastic anaemia,	

		purpura, petechiae or ecchymosis, bone marrow depression, disseminated intravascular coagulation [2].	
Immune system disorders		Acute anaphylaxis.	Allergic reactions, anaphylaxis, skin rashes, itching, urticaria, pruritus, purpura, angioed ema, erythema multiforme, acute asthma, aggravated asthma, rhinitis[3].
Endocrine disorders			Hyperglycaemia.
Metabolism and nutrition disorders			Hyperkalaemia.
Psychiatric disorders	Hallucinations, confusion, anxiety, depersonalisation[4].	Depression.	

Nervous system disorders	Headache, dizziness, light headedness.	Drowsiness, insomnia, vertigo, fatigue (malaise and listlessness), syncope, convulsions, coma, peripheral neuropathy, dysarthria, epilepsy, parkinsonism, involuntary muscle movement, muscle weakness.	Aseptic meningitis[5], aggravation of epilepsy and parkinsonism, paraesthesias[4],
Eye disorders		Blurred vision, visual disturbances, optic neuritis, orbital and peri- orbital pain.	Corneal opacities, visual- field changes, pallor of the optic disc.
Ear and labyrinth disorders			Tinnitus. hearing disturbances, deafness.
Cardiac disorders		Myocardial infarction, cardiovascular thrombotic events.	Peripheral oedema, cardiac failure, tachycardia,

			dysrhythmia, palpitations, congestive heart failure, chest pain.
Vascular disorders			Hypertension, flushing, hypotension, thrombophlebitis.
Respiratory, thoracic and mediastinal disorders		Epistaxis acute respiratory distress, sudden dyspnoea, asthma, pulmonary oedema.	Pulmonary eosinophilia, bronchospasm.
Gastrointestinal disorders	Epigastric distress, abdominal laceration[6]	Acute pancreatitis, regional ileitis, anorexia, ulceration[6]	Peptic ulcers, perforation, GI bleeding, nausea, vomiting, abdominal pain, diarrhoea, flatulence, constipation, dyspepsia, melaena, haematemesis, ulcerative stomatitis, exacerbation of

			colitis and Crohn's disease, gastritis.
Hepatobiliary disorders	Hepatitis, jaundice.		Cholestasis, abnormal liver function[7].
Skin and subcutaneous tissue disorders	Erythema, angiitis, photosensitivity.	Exfoliative dermatitis.	Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, Drug Rash with Eosinophilia and Systemic Syndrome (DRESS). angioneurotic oedema, alopecia, sweating, exacerbation of psoriasis.
Musculoskeletal and connective tissue disorders			Muscle weakness, acceleration of cartilage degeneration
Renal and urinary disorders		Glycosuria, urinary frequency	Haematuria, renal failure8.

Reproductive system and breast disorders			Vaginal bleeding, breast change including enlargement, tenderness or gynaecomastia.
General disorders and administrative site conditions			Weight gain, Oedema.
Investigations	BUN elevation.	A rapid fall in blood pressure resembling a shocklike state, false-negative results in the dexamethasone suppression test (DST).	

a) Description of selected adverse reactions

[1] Infections and infestations

Fulminant necrotising fasciitis, particularly in association with Group A β-haemolytic streptococcus.

[2] Blood and the lymphatic system disorders

Blood dyscrasias may occur, including leukopenia, petechiae or ecchymosis, purpura, aplastic and haemolytic anaemia, agranulocytosis, bone marrow

depression, disseminated intravascular coagulation, and thrombocytopenia.

Patients may develop anaemia secondary to obvious appropriate blood determinations are recommended.

Platelet function is impaired by AMDOCIN.

[3] *Immune system disorders*

Hypersensitivity reactions are manifested in skin rashes, itching, urticaria, and, more seriously, acute attacks of asthma.

Hypersensitivity reactions (a) non-specific allergic reactions and anaphylaxis, (b) respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, rhinitis (see section 4.3) or (c) assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and exfoliative and bullous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme).

[4]*Psychiatric disorders*

Mental confusion, anxiety, psychic disturbances such as depersonalisation, psychotic episodes, paraesthesias; aggravation of psychiatric disturbances,

Nervous system disorders

Severe frontal headache may occur in patients using AMDOCIN for long periods.

[5]Aseptic meningitis, (especially in patients with existing autoimmune disorders, such as systemic lupus erythematosus or mixed connective tissue disease) with symptoms such as stiff neck, headache, nausea, vomiting, fever or disorientation depression, vertigo, fatigue, malaise, dysarthria, coma, cerebral oedema, nervousness, confusion, anxiety and other psychiatric disturbances, depersonalisation, hallucinations, drowsiness, convulsions and aggravation of

epilepsy and parkinsonism, peripheral neuropathy, paraesthesia, involuntary movements and insomnia.

[6]*Gastrointestinal disorders*

Abdominal laceration, single or multiple, of oesophagus; stomach, duodenum or small or large intestine including perforation and haemorrhage.

Ulceration at any point in the gastro-intestinal tract (even with resultant stenosis and obstruction), bleeding (even without obvious ulceration or from a diverticulum) and perforation of pre-existing sigmoid lesions (such as diverticulum or carcinoma), increased abdominal pain or exacerbation of the condition in patients with ulcerative colitis intestinal strictures and regional gastritis.

[7]*Hepato-biliary disorders*

Borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT),

[8]*Renal and urinary disorders*

Nephrotoxicity in various forms, including interstitial nephritis, nephrotic syndrome, renal failure, renal insufficiency, proteinuria.

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. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

4.9. Overdose Symptoms

Symptoms include headache, nausea, vomiting, dyspepsia, epigastric pain, ulceration and/or gastrointestinal bleeding, diarrhoea, disorientation, excitation,

coma, drowsiness, dizziness, tinnitus, fainting, occasionally convulsions, abdominal pain, anorexia, restlessness and agitation, vertigo and, gastrointestinal irritation resulting in, peptic ulceration often with bleeding and acute pancreatitis. In cases of significant poisoning, kidney injury (acute kidney failure) and liver damage are possible.

Treatment

In acute poisoning, the stomach should be emptied by inducing emesis or by aspiration and lavage.

Blood-electrolyte balance should be maintained.

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.

Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and Class: A 3.1 Antirheumatics (anti-inflammatory agents)

Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, acetic acid derivatives and related substances.

ATC code: M01AB01

Mechanism of action

Indomethacin has analgesic, anti-inflammatory and antipyretic properties.

Like the salicylates and related anti-inflammatory medicines, indomethacin inhibits the biosynthesis of prostaglandins; this action may be the basis of its anti- inflammatory and antipyretic properties and certain of its other effects. Since indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues. It inhibits motility of polymorphonuclear leucocytes and like salicylates, it uncouples oxidative phosphorylation in supratherapeutic concentrations and depresses the biosynthesis of mucopolysaccharides.

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 from the gastrointestinal tract, 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 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).

Peak plasma concentrations are reached about 2 hours after a dose. About 99 % of indomethacin is bound to plasma proteins and indomethacin is distributed into synovial fluid, the central nervous system and the placenta. Low concentrations can be detected in breast milk.

Biotransformation

Equal fractions of indomethacin are eventually absorbed following I.M. or oral administration. However, indomethacin is significantly more rapidly absorbed following I.M. administration with peak plasma levels appearing one hour sooner than following oral administration.

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose, maize starch, microcrystalline cellulose, sodium starch glycolate,

Hard gelatin capsule, with a yellow cap and body:

Quinoline yellow, sunset yellow, titanium dioxide.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months.

6.4. Special precautions for storage

Store at or below 25 °C.

Protect from light and moisture.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

Aluminium foil/PVC film blister strip of 15 capsules and a package insert in a printed carton.

4 Aluminium foil/PVC film blister strip of 21 capsules and a package insert in a printed carton.

Bottles containing 100, 500 and 1 000 capsules.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

No special requirements

7. HOLDER OF CERTIFICATE OF REGISTRATION

Innovata Pharmaceuticals (Pty) Ltd

Crownwood Office Park, Block D, Ground Floor,

100 Northern Parkway, Ormonde, Johannesburg

2091, South Africa

8. REGISTRATION NUMBER

A 27/3.1/0169

9. DATE OF FIRST AUTHORISATION

21 December 1992

10. DATE OF REVISION OF TEXT

24/01/2024