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.

Date of PI: 28/04/2024

- 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

28 April 2024

VOUBILJET

SKEDULERINGSTATUS: **S3**

1. NAAM VAN DIE MEDISYNE:

AMDOCIN (kapsules)

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING:

Elke **AMDOCIN** kapsule tablet bevat Indometasien 25 mg.

Vir volledige lys van eksipiënte, sien afdeling 6.1.

3. FARMASEUTIESE VORM

AMDOCIN kapsules is geel gelatien kapsules bevattende wit tot naaswit poeier.

4. KLINIESE BESONDERHEDE

4.1. Terapeutiese indikasies:

AMDOCIN word aangedui vir die simptomatiese behandeling van

- Rumatoïede artritis,
- Ankiloserende spondilitis,
- Osteoartritis,
- Ander muskuloskeletale inflammatoriese siektes en
- akute aanvalle van jig.
- Degeneratiewe gewrigsiekte van van die heup.
- Lae rugpyn (dit word algemeen na verwys as lumbago).
- Inflammasie, pyn, trismus en swelsel na tande prosedures.
- Inflammasie, pyn en swelsel na ortopediese sjirurgiese prosedures.

- en nie-sjirurgiese prosedures geassosieer met afname en immobilisering van frakture van dislokasies.
- Pyn en geassosieerde simptome van primêre dismenoree.
- Die afname van simptome in sommige febriele toestande.
- Koors (as ‘n kort-termyn toevoeging tot spesifieke behandeling).
- Die afname van koors in Hodgkin se siekte wanneer die koors weerstandbiedend was tot enige ander behandeling.

4.2. Posologie en metode van toediening

Posologie

Volwassenes

Die aanbevole dosering is 25 mg tot 200 mg per dag verdeel in twee tot vier gelyke doserings.

Ongewenste effekte kan verminder word deur die inname van die laagste effektiewe dosis vir die kortste moontlike tydperk (sien afdeling 4.4), ooreenstemmend met individuele pasiënt behandeling doelwitte, met die begin van ‘n lae dosis.

‘n Ladingdosis van AMDOCIN is nie nodig nie. In chroniese rumatoïede siektes, begin terapie met lae doserings, verhoog geleidelik wanneer nodig en gaan voort vir ‘n voldoende periode (tot een maand word aanbeveel), wat maksimum voordeel sal gee en ongunstige reaksies verminder.

By chroniese toestande begin die behandeling met ‘n lae dosering en verhoog soos nodig.

- In chroniese muskuloskeletale en gewrigsafwykings, is die gewone aanvangsdosis 25 mg twee of drie keer per dag met voedsel, en verhoog, indien

moontlik, met 25 mg tot 50 mg per dag by weeklikse intervalle, op tot 150 mg tot 200 mg per dag, in verdeelde doserings.

- In pasiënte met aanhoudende nagpyn en/of oggend styfheid, mag ‘n dosering van tot 100 mg met slapenstyd help vir die verligting van pyn. ‘n Dosis van 200 mg per dag moet nie oorskry word nie.
- In akute peri-artikulêre siektes en in lae rugpyn kan 50 mg toegedien word twee of drie keer per dag vir ongeveer 10 dae.
- In die behandeling van jigagtige artritis is die aanbevole daaglikse doserings 150 mg tot 200 mg in verdeelde doserings, totdat simptome en tekens afneem.
- In primêre dismenoree, is die aanbevole dosering 75 mg per dag as ‘n enkel dosis of verdeelde dosering, wat begin word met die begin van krampe en bloeding en voortduur vir so lank as wat die simptome gewoonlik aanhou.

Die totale gekombineerde daaglikse dosis per mond moet gewoonlik nie 200 mg oorskry nie.

Pediatriese bevolking

Die veiligheid en effektiwiteit van indometasien, soos in AMDOCIN, by kinders is nog nie vasgestel nie (sien afdeling 4.4).

Metode van toediening

Vir orale toediening.

Om die moontlikheid kleiner te maak of die moontlikheid van gastroïntestinale versteurings te verminder, word dit aanbeveel dat AMDOCIN met voedsel geneem word, met melk of ‘n teensuurmiddel.

4.3 Kontra-indikasies:

AMDOCIN word teenaangedui by:

- Pasiënte met hipersensitiwiteit vir indometasien of vir enige eksipiënte in AMDOCIN (sien afdeling 6.1).
- Pasiënte met ernstige hepatiese versaking en renale versaking (sien afdeling 4.4).
- Pasiënte met gastritis, streeksenteritis, ulseratiewe kolitis.
- Pasiënte met bloedingsafwykings.
- Pasiënte by wie akute asmatiese aanvalle, urtikarie of rinitis en nasale poliepe gepresipiteer word deur asetielsalisielsuur of ander nie-steroïed anti-inflammatoriese middels (sien afdeling 4.8).
- Pasiënte op meegaande triamtereen behandeling. Die toevoeg van triamtereen tot ‘n instandhouding-skedule van AMDOCIN kan tot gevolg hê in akute renale versaking, wat omkeerbaar kan wees met die staak van behandeling. AMDOCIN en triamtereen moet nie saam toegedien word nie (sien afdeling 4.5).
- Pasiënte wat diflunisal gebruik, omdat hierdie medisyne nie saam met AMDOCIN geneem moet word nie (sien 4.5).
- Pasiënte met hartversaking, bevestigde isgemiese hartsiekte en/of serebrovaskulêre siekte (beroerte) en perifere ateriële siekte.
- Pasiënte met ‘n geskiedenis van angio-edeem na blootstelling aan NSAIMs, soos AMDOCIN en/of aspirien.
- Pasiënte wat behandeling benodig vir peri-operatiewe pynverligting in die opset van koronêre arteriese sjirurgie.
- Pasiënte met ‘n geskiedenis van gastroïntestinale perforasie, ulserasie of bloeding (PUBs) verwant aan vorige NSAIMs, insluitend AMDOCIN.

- Pasiënte met aktiewe of ’n geskiedenis van herhalende ulkusse/hemoragie/perforasies.
- Pasiënte met ‘n geskiedenis van, of huidige gastroïntestinale letsels.
- Swanger vrouens van ongeveer 30 weke swangerskap, of later in swangerskap, weens die risikos van oligohidramniose/fetale renale disfunksie en premature sluiting van fetale ductus arteriosus (sien afdelings 4.4 en 4.6).
- Laktasie (sien afdeling 4.6).

Veiligheid van AMDOCIN by kinders is nog nie vasgestel nie.

4.4. Spesiale waarskuwings en voorsorgmaatreëls vir gebruik:

AMDOCIN kan geneig wees tot kardiovaskulêre voorvalle, gastroïntestinale voorvalle, of kutaneuse reaksies, wat noodlottig kan wees.

Hipersensitiwiteit

Ernstige velreaksies, sommige noodlottig, insluitend medisyne uitslag met esinofilie en sistemiese simptome (DRESS), eksfoliatiewe dermatitis, Stevens-Johnson se sindroom en toksiese epidermale nekrolise (TEN) is gerapporteer (sien afdeling 4.8).

Hierdie ernstige voorvalle kan voorkom sonder waarskuwing. Pasiënte moet ingelig word omtrent die tekens en simptome van ernstige vel manifestasies.

Pasiënte wat allergies is vir salisilate, kan ‘n kruis-reaksie wys met AMDOCIN.

AMDOCIN moet gestaak word met die eerste voorkoms van veluitslag, mukosale letsels, of enige ander tekens van hipersensitiwiteit.

Pasiënte moet versigting waargeneem word om enige ongewone manifestasies van medisyne sensitiwiteit te bespeur.

Pasiënte blyk om die hoogste risiko van hierdie reaksies te hê vroeg gedurende die begin van behandeling, wanneer die meeste gevalle vir die aanvang van reaksies voorkom binne die eerste maand van behandeling.

Medisyne Uitslag met Esinofilie en Sistemiese Simptome (DRESS)

Medisyne Reaksie met Esinofilie en Sistemiese Simptome (DRESS) was gerapporteer in pasiënte wat NSAIMs neem, soos AMDOCIN. Sommige van hierdie voorvalle was noodlottig of lewensgevaarlik. DRESS kan tipies, alhoewel nie ekslusief nie, presenteer met koors, uitslag, limfadenopatie, en/of opswel van gesig. Ander kliniese manifestasies kan insluit hepatitis, nefritis, hematologiese abnormaliteite, miokarditis, of miositis. Soms kan simptome van DRESS ooreenkom met ‘n akute virale infeksie. Esinofilie is dikwels teenwoordig. Omdat hierdie afwyking veranderlik is in sy voorkoms kan ander orgaanstelstels wat nie gemeld is nie betrokke wees. Dit is belangrik om te merk dat vroeë manifestasies van hipersensitiwiteit, soos koors of limfadenopatie teenwoordig kan wees, selfs sonder duidelike uitslag. Indien sulke tekens of simptome teenwoordig is moet AMDOCIN gestaak en die pasiënt onmiddellik ge-evalueer word.

Gastroïntestinale effekte

Die risiko van gastroïntestinale bloeding of perforasie (PUBs) is hoër met verhoogde doserings van AMDOCIN, by pasiënte met ‘n geskiedenis van ulkusse en by bejaardes. Hierdie pasiënte moet behandeling begin op die laagste dosis beskikbaar.

Wanneer gastroïntestinale bloeding of ulserasie voorkom by pasiënte wat AMDOCIN ontvang, moet behandeling met AMDOCIN gestaak word.

AMDOCIN moet versigtig toegedien word aan pasiënte met ‘n geskiedenis van gastroïntestinale siekte (bv. ulseratiewe kolitis, Crohn se siekte, hiatus hernia, gastro-esofageale refluks siekte, angiodisplasie) omdat hierdie toestand erger kan word.

Kombinasie behandeling met beskermende medisynes (bv. misoprostol of protonpompremmers) moet oorweeg word vir hierdie pasiënte en ook by pasiënte wat meegaande lae dosis aspirien benodig.

Enkel of veelvuldige ulserasies, insluitend perforasie en hemoragie van die esofagus, maag, duodenum of dun- of dikderm is gerapporteer om voor te kom met AMDOCIN. Noodlottige gevalle is gerapporteer. Intestinale ulserasie was geassosieer met stenose en obstruksie (sien afdeling 4.8).

Gastroïntestinale bloeding sonder opmerklike ulkus-vorming en perforasie van voorafgaande sigmoïede letsets (divertikulum, karsinoom, ens.) het voorgekom.

Toename in abdominale pyn in pasiënte met ulseratiewe kolitis of die ontwikkeling van ulseratiewe kolitis en streeks ileïtis is gerapporteer (sien afdeling 4.8).

Hartversaking en edeem

Omsigtigheid is nodig by pasiënte met ‘n geskiedenis van kardiale disfunksie, hipertensie en/of hartversaking omdat vloeistof retensie en edeem gerapporteer is in assosiasie met AMDOCIN-behandeling, weens inhibisie van prostaglandien-sintese. Weens AMDOCIN se inherente potensiaal om vloeistofretensie te veroorsaak, kan hartversaking gepresipiteer word in sommige gekompromiteerde pasiënte.

Toepaslike monitering en advies is nodig vir pasiënte met ‘n geskiedenis van hipertensie en/of ligte tot matige kongestiewe hartversaking omdat vloeistof retensie en edeem gerapporteer is in assosiasie met NSAIM-behandeling, soos in AMDOCIN.

Hipertensie

Pasiënte met ongekontrolleerde hipertensie, kongestiewe hartversaking, bevestigde isgemiese hartsiekte, perifere arteriële siekte, en/of serebrovaskulêre siekte moet nie behandel word met indometasien nie, soos in AMDOCIN (sien afdeling 4.3).

Omsigtigheid is nodig voordat langer-termyn behandeling begin word by pasiënte met beduidende risiko faktore vir kardiovaskulêre siekte (bv. hipertensie, hiperlipidemie, diabetes mellitus, rook).

AMDOCIN kan tot gevolg hê die begin of opvlamming van hipertensie, wat beide kan bydra tot die verhoogde insidensie van kardiovaskulêre voorvalle.

Pasiënte wat tiasiede neem of lus diuretika kan ingekorte respons hê tot hierdie terapie wanneer NSAIMs gebruik word, soos in AMDOCIN. AMDOCIN moet versigtig gebruik word deur pasiënte met hipertensie. .

Bloeddruk (BP) behoort versigtig gemonitor te word gedurende die begin van NSAIM-behandeling, soos in AMDOCIN, en regdeur die tydperk van behandeling.

Kardiovaskulêre trombotiese voorvalle

AMDOCIN en ander NSAIMs kan ‘n verhoogde risiko veroorsaak van ernstige kardiovaskulêre trombotiese voorvalle, miokardiale infarksie en beroerte, wat noodlottig kan wees. Beide COX-2 selektiewe en nie-selektiewe kan ‘n soortgelyke risiko hê.

Hierdie risiko kan toeneem met die tydperk van behandeling.

Pasiënte met kardiovaskulêre siekte of risiko faktore vir kardiovaskulêre siekte kan ‘n groter risiko hê. Om die potensiële risiko vir ‘n ongunstige kardiovaskulêre voorval te verminder by pasiënte wat behandel word met AMDOCIN, moet die laagste effektiewe dosis geneem word vir die kortste tydperk moontlik.

Weens sy gebrek aan plaatjie effek is AMDOCIN nie geskik as vervanging vir aspirien vir kardiovaskulêre profilakse nie.

Renale inkorting

By pasiënte met renale, kardiale, hepatiese inkorting, hipertensie, hartversaking of toestande ontvanklik vir vloeistof-retensie, is omsigtigheid nodig omdat die gebruik van

NSAIMs, soos in AMDOCIN, tot gevolg kan hê die agteruitgang van renale funksie (sien afdeling 4.8). Die dosering moet so laag as moontlik gehou word en renale funksie moet gemonitor word. AMDOCIN kan ook vloeistof-retensie veroorsaak wat hierdie toestande erger kan maak.

By pasiënte met verminderde renale bloedvloei waar renale prostaglandiene ‘n groot rol speel in handhawing van renale perfusie, kan toediening van ‘n NSAIM, soos in AMDOCIN, overte renale dekompensasie presipiteer. Die toediening van ‘n NSAIM, soos in AMDOCIN, kan ‘n dosis-afhanklike afname veroorsaak in prostaglandienvorming en nierversaking presipiteer. Pasiënte met die grootste risiko van hierdie reaksie is dié met renale of hepatiese disfunksie, diabetes mellitus, gevorderde ouderdom, ekstrasellulêre volume uitputting, kongestiewe hartversaking, sepsis, of meegaande gebruik van enige nefrotoksiese medisynes.

Omsigtigheid is nodig wanneer behandeling begin word by pasiënte net dehidrasie. Pasiënte moet eers gehidreer word voordat behandeling begin word met AMDOCIN.

Omsigtigheid word ook aanbeveel by pasiënte met voorafbestaande niersiekte. AMDOCIN moet versigtig toegedien word en nierfunksie moet gemonitor word by enige pasiënt met verminderde renale reserwe (sien ook afdeling 4.3).

Staak van NSAIM-behandeling, soos in AMDOCIN, word gewoonlik gevolg deur herstel tot die voor-behandeling status.

Akute interstisiële nefritis met hematurie, proteïenurie, en soms nefrotiese sindroom kan voorkom by pasiënte wat langtermyn toediening van AMDOCIN ontvang. Omdat indometasien, soos in AMDOCIN, hoofsaaklik uitgeskei word deur die niere, moet pasiënte met beduidende ingekorte renale funksie nie behandel word met AMDOCIN nie (sien afdeling 4.3).

Toenames in plasma-kaliumkonsentrasie, insluitend hiperkalemie, kan voorkom selfs in sommige pasiënte sonder renale inkorting. By pasiënte met normale renale funksie, was hierdie effekte toegeskryf aan ‘n hipo-reninemiese - hipo-aldesteronisme staat.

Hepatiese inkorting

AMDOCIN kan ‘n toename in lewerensieme veroorsaak. Beduidende (3 keer die boonste limiet van normaal) verhogings van ALT (SGPT) of AST (SGOT) in gekontrolleerde kliniese studies is gerapporteer in minder as 1 % van pasiënte wat behandeling ontvang met NSAIMs, soos AMDOCIN.

‘n Pasiënt met simptome en/of tekens wat lewerdisfunksie suggereer, of by wie ‘n abnormale lewertoets voorgekom het, moet ge-evalueer word vir bewyse vir ontwikkeling van meer ernstige hepatiese reaksies terwyl hulle op behandeling is met AMDOCIN.

Indien abnormale lewertoetse aanhou of agteruitgaan, indien kliniese tekens en simptome ooreenstemmend met lewersiekte ontwikkel, of indien sistemiese manifestasies voorkom (bv. esinofilie, uitslag, ens), moet behandeling gestaak word.

Gebruik gedurende swangerskap

Beperk die gebruik van NSAIMs, insluitend AMDOCIN, tussen 20 en 30 weke van swangerskap weens die risiko van oligohidramnios/fetale renale disfunksie. Vermy gebruik van NSAIMs, soos AMDOCIN, by vrouens van ongeveer 30 weke swangerskap en later gedurende swangerskap, weens die risikos van oligohidramnios/fetale renale disfunksie en premature sluiting van die fetale ductus arteriosus (sien afdelings 4.3 en 4.6).

Hierdie ongunstige gevolge word gemiddeld waargeneem dae tot weke na begin van behandeling, alhoewel oligohidramnios soms gerapporteer word so gou as 48 uur na ‘n

NSAIM, soos in AMDOCIN. Oligohidramnios is dikwels, maar nie altyd nie, omkeerbaar met die staak van behandeling. Komplikasies van verlengde oligohidramnios kan insluit ledemate kontraktuur en vertraagde long-maturasie. In sommige na-bemarking gevalle van ingekorte neonatale renale funksie, was indringende prosedures soos ruil-transfusie of dialise benodig.

Indien AMDOCIN nodig is tussen 20 weke en 30 weke swangerskap beperk AMDOCIN gebruik tot die laagste effektiewe dosis en kortste tydperk moontlik.

Gesondheidsorg professionele persone moet 'ultraklank' monitering van amniotiese vloeistof oorweeg indien AMDOCIN-behandeling langer is as 48 uur. Staak AMDOCIN indien oligohidramnios voorkom en volg op volgens kliniese praktyk.

Vroulike fertiliteit

AMDOCIN kan 'n omkeerbare inhiberende effek hê op 'n vrou se ovulasie. Die gebruik van AMDOCIN kan vroulike fertiliteit inkort en word nie aanbeveel by vrouens wat swangerskap beplan nie. By vrouens wat probleme het om swanger te word of wie ondersoeke ondergaan vir infertiliteit, moet onttrekking van AMDOCIN oorweeg word (sien afdeling 4.8).

SLE en gemengde bindweefsel-siekte

In pasiënte met sistemiese lupus erythematosus (SLE) en gemengde bindweefsel-afwykings kan daar 'n verhoogde risiko wees van aseptiese meningitis.

Medikasie oorgebruik hoofpyn (MOH)

Na langtermyn behandeling met analgetiese middels, kan medikasie-oorgebruik hoofpyn (MOH) ontwikkel of agteruitgaan. MOH moet vermoed word by pasiënte wat dikwelse of daaglike hoofpyne het, ten spyte van (of weens) gereëlde gebruik van analgetiese middels. Pasiënte met MOH moet nie behandel word deur die dosis te

verhoog nie. In sulke gevalle van die gebruik van analgetiese middels gestaak word in konsultasie met ‘n dokter.

Okulêre effekte

Korneale aanpaksel en retinale versteurings, insluitend die van die makula, is waargeneem by pasiënte wat verlengde behandeling ontvang het met AMDOCIN.
In pasiënte met rumatoïede artritis, kan oog-veranderings voorkom wat verwant kan wees aan die onderliggende siekte of met die behandeling. In chroniese rumatoïede siekte word oftalmologiese ondersoeke by periodieke intervalle aanbeveel, behandeling moet gestaak word indien oog-veranderinge waargeneem word.
Dowwe visie kan ‘n beduidende simptoom wees en regverdig ‘n deeglike oftalmologiese ondersoek. Omdat hierdie veranderinge asimptomaties kan wees is oftalmologiese ondersoek by periodieke intervalle wenslik by pasiënte waar behandeling verleng word.
Staak behandeling indien oogveranderinge waargeneem word.
Verlengde behandeling sal gereëlde oftalmologiese ondersoeke benodig.

Plaatjie-aggregasie

AMDOCIN kan plaatjie-aggregasie inhibeer. Hierdie effek verdwyn gewoonlik binne 24 uur na die staak van AMDOCIN. AMDOCIN het gewys om bloedingstyd te verleng (maar binne die normale omvang) by normale volwassenes. Omdat hierdie effek erger kan wees by pasiënte met onderliggende homeostatiese defekte, behoort AMDOCIN gebruik te word by persone met koagulasie defekte (sien afdeling 4.5).

Respiratoriese afwykings

Versigtigheid is nodig wanneer AMDOCIN toegedien word aan pasiënte met, of wat ‘n vorige geskiedenis het, van brongiale asma, omdat NSAIMs, soos in AMDOCIN, gerapporteer word om brongospasma te presipiteer by sulke pasiënte.

Sentrale senuweestelsel effekte

Hoofpyn, soms vergesel deur duiseligheid of lighoofdigheid kan voorkom, gewoonlik vroeg gedurende behandeling met AMDOCIN.

Deur behandeling te begin met ‘n lae dosis en geleidelik te verhoog kan die insidensie van hoofpyn verminder word. Hierdie simptome kan verdwyn met voortgesette behandeling of met afname in dosering. Indien hoofpyn voortduur ten spyte van doseringsafname, moet AMDOCIN onttrek word.

Infeksies

AMDOCIN kan tekens en simptome maskeer wat gewoonlik infektiewe siekte vergesel.

AMDOCIN moet versigtig gebruik word by pasiënte met voorafbestaande, maar gekontroleerde infeksie.

Versigtigheid word aanbeveel met meegaande gebruik van ‘n lewendige vaksiene.

Anemie

Pasiënte moet periodiek waargeneem word vir vroeë opsporing van enige ongewenste effekte op perifere bloed (anemie), lewerfunksie of gastroïntestinale traktus.

Algemeen

AMDOCIN moet versigtig gebruik word by pasiënte met psigiatriese afwykings, epilepsie of Parkinsonisme, omdat indometasien, soos in AMDOCIN, hierdie afwykings erger kan maak.

Porfirie

Veiligheid is nog nie vasgestel nie.

Bejaardes

Bejaardes het ‘n verhoogde frekwensie van ongunstige reaksies tot NSAIMs, insluitend met AMDOCIN, veral gastroïntestinale bloeding en perforasie (PUBs), wat noodlottig kan wees. ‘n Toename in ouderdom verhoog die moontlikheid van newe-effekte. AMDOCIN moet met meer omsigtigheid gebruik word by bejaardes.

Pediatriese bevolking

Die veiligheid en effektiwiteit van AMDOCIN is nog vasgestel by kinders nie (sien afdeling 4.3).

Indien AMDOCIN nie verligting gee binne 2 tot 3 weke nie, moet alternatiewe behandeling oorweeg word.

AMDOCIN bevat laktose:

AMDOCIN bevat laktose wat ‘n effek kan hê op die glisemiese kontrole van pasiënte met diabetes mellitus.

Pasiënte met rare oorerflike toestande van galaktose intoleransie, totale laktase-tekort of glukose-galaktose wanabsorpsie, moet nie AMDOCIN gebruik nie.

4.5. Interaksie met ander medisynes en ander vorms van interaksie

Diflunisal

Wanneer diflunisal en AMDOCIN saam toegedien word, verminder die renale opruiming van AMDOCIN en die plasma-konsentrasie neem toe en die gekombineerde gebruik kan tot gevolg hê in noodlottige gastroïntestinale hemoragie.

Die kombinasie moet nie gebruik word nie (sien afdeling 4.3).

Asetielsalisielsuur

Die toediening van anti-inflammatoriese doserings van aspirien verminder AMDOCIN bloed-konsentrasies met ongeveer 20 %.

AMDOCIN inhibeer plaatjie-aggregasie maar is nie ‘n substituut vir aspirien vir kardiovaskulêre profilakse nie.

Daar is geen konsekwente bewys dat meegaande gebruik van aspirien die verhoogde risikos van ernstige kardiovaskulêre trombotiese voorvalle geassosieer met AMDOCIN mitigeer nie.

Die meegaande gebruik van AMDOCIN met aspirien of ander salisilate word nie aanbeveel nie. Gekombineerde gebruik van AMDOCIN en aspirien gee nie enige groter terapeutiese effek as die gebruik van AMDOCIN nie. Ook word die insidensie van gastroïntestinale newe-effekte beduidend verhoog met gekombineerde behandeling.

NSAIMs

Die gebruik van twee of meer NSAIMs saam kan tot gevolg hê in die toename in newe-effekte en moet dus vermy word.

Teensuurmiddels

Die biobeskikbaarheid van indometasien, soos in AMDOCIN, kan afneem deur meegaande teensuurmiddel-behandeling.

Probenesied

Wanneer indometasien, soos in AMDOCIN, toegedien word aan pasiënte wat probenesied ontvang, is dit moontlik dat die plasmavlakke van indometasien, soos in AMDOCIN, kan toeneem.

Dus kan ‘n laer totale daaglikse dosis van indometasien, soos in AMDOCIN, ‘n voldoende terapeutiese effek gee. Wanneer toenames in die dosering van indometasien, soos in AMDOCIN, gedoen word onder hierdie omstandighede, moet dit versigtig gebeur en in klein inkremente.

Antikoagulante

AMDOCIN kan effekte van antikoagulante, soos warfarien, laat toeneem.

Pasiënte moet versigtig waargeneem word vir veranderinge van protrombientyd wanneer indometasien, soos in AMDOCIN, toegedien word saam met antikoagulante.

Omsigtigheid is nodig wanneer indometasien, soos in AMDOCIN, en antikoagulante saam toegedien word.

Meegaande toediening van orale antikoagulant-medisynes het tot gevolg ‘n verhoogde risiko van gastroïntestinale bloeding.

Kortikosteroïede

Verhoogde risiko van gastroïntestinale ulserasie of bloeding (PUBs). In ‘n pasiënt wat meegaande kortikosteroïede ontvang, is ‘n afname in dosering van hierdie moontlik, maar moet slegs stadig gedoen word onder toesig.

Anti-plaatjie medisynes

Toename in risiko van gastroïntestinale bloeding.

Indometasien, soos in AMDOCIN, kan plaatjie-aggregasie inhibeer, ‘n effek wat verdwyn binne 24 uur na onttrekking; die bloedingstyd kan verleng word en hierdie effek kan erger wees by pasiënte met ‘n onderliggende hemostatiese defek (sien afdeling 4.4).

Antidepressante/selektiewe serotonien heropname inhibeerders (SSRIs)

Verhoogde risiko van bloeding.

Antidiabetiese middels

Die hipoglisemiese effek van sulfonielureums kan verhoog word met NSAIMs, soos AMDOCIN.

Metotreksaat

Omsigtigheid is nodig met meegaande gebruik van indometasien, soos in AMDOCIN, met metotreksaat. Indometasien, soos in AMDOCIN, was gerapporteer om die tubulêre sekresie te laat afneem van metotreksaat en daardeur die metotreksaat toksisiteit te potensieer.

Ernstige interaksies is gerapporteer met die gebruik van hoë doserings van metotreksaat met indometasien, soos in AMDOCIN.

Siklosporien

Toediening van NSAIMs soos AMDOCIN, saam met siklosporien was geassosieer met ‘n toename in siklosporien-geïnduseerde toksisiteit, moontlik weens verminderde sintese van renale prostasiklien. Indometasien, soos in AMDOCIN, moet versigtig gebruik word by pasiënte wat siklosporien neem en renale funksie moet versigtig gemonitor word.

Litium

Verminderde eliminasie van litium: Indometasien, soos in AMDOCIN, inhibeer prostaglandien-sintese en kan dus plasma-litiumvlakke verhoog en verminder litium-opruiming in pasiënte met vaste vlak plasma-litiumkonsentrasies. By die aanvang van sulke gekombineerde behandeling, moet plasma-litiumkonsentrasie meer dikwels gemonitor word.

Antihipertensiewe middels

Verminderde antihipertensiewe effek: AMDOCIN kan akuut die antihipertensiewe effek verminder van antihipertensiewe middels, gedeeltelik weens die hihibisie van prostaglandien sintese van indometasien, soos in AMDOCIN. Pasiënte wat meegaande behandeling ontvang moet die antihipertensiewe effek van hulle behandeling weer laat

vasstel. Dus is omsigtigheid nodig wanneer die toevoeging van indometasien, soos in AMDOCIN, oorweeg word tot die regimen van ‘n pasiënt wat enige van die volgende antihipertensiewe medisynes neem:

• alfa-adrenergiese blokker-medisynes,

• AOE-inhibeerders,

• beta-adrenergiese blokker-medisynes,

• angiotensien-2-reseptor antagoniste,

• hidralasien of nifedipien.

‘n Verhoogde risiko van hiperkalemie is ook gerapporteer wanneer NSAIMs, soos in AMDOCIN, geneem word met AOE-inhibeerders.

Fenitoïen

AMDOCIN kan die effekte van fenitoïen laat toeneem.

Antipsigotiese middels

Toename in lomerigheid is gerapporteer met meegaande gebruik van AMDOCIN en haloperidol.

Antivirale middels

Daar is ‘n verhoogde risiko van hematologiese toksisiteit wanneer NSAIMs, soos in AMDOCIN, toegedien word met sidovudien. Daar is bewys van ‘n verhoogde risiko van hemartrose en hematoon in MIV(+) hemofilie pasiënte wat meegaande behandeling ontvang met sidovudien en ibuprofeen. Daar is ‘n risiko vir indometasien toksisiteit met meegaande gebruik van AMDOCIN met ritonavir en moet dus vermy word.

Vals negatiewe resultate in die deksametasoon onderdrukkingstoets is gerapporteer by pasiënte met AMDOCIN.

Diuretiese middels

AMDOCIN antagoniseer die natriuretiese en antihipertensiewe effekte van furosemied, die antihipertensiewe effekte van tiasied diuretika, ß-adrenergiese blokker-medisynes, of inhibeerders van angiotensien-omskakeling-ensiem kan ook afneem. Dus wanneer AMDOCIN en diuretiese middels saam geneem word, moet die pasiënt noukeurig gemonitor word om te bepaal of die verlangde effek van die diuretiese produk verkry word.

Omkeerbare akute renale versaking geassosieer met die meegaande toediening van indometasien, soos in AMDOCIN, en triamtereen is gerapporteer. Indometasien, soos in AMDOCIN, en triamtereen moet nie saam toegedien word nie.

Die risiko van akute renale ontoereikendheid, wat gewoonlik omkeerbaar is, kan toeneem met gekomprommiteerde renale funksie (bv. gedehidreerde pasiënte of bejaarde pasiënte) wanneer angiotensien II reseptor antagoniste gekombineer word met NSAIMs, soos AMDOCIN. Dus moet die kombinasie versigtig toegedien word, veral by bejaardes. Pasiënte moet voldoende gehidreer word en oorweging moet gegee word aan monitering van renale funksie na begin van meegaande behandeling en periodiek daarna.

Diuretiese middels kan die risiko van nefrotoksisiteit van NSAIMs, soos in AMDOCIN, laat toeneem.

In pasiënte met gekompromitteerde renale funksie (bv. by bejaardes of pasiënte met volume uitputting, insluitend die op diuretiese behandeling) wat behandel was met NSAIMs, soos AMDOCIN, insluitend selektiewe siklo-oksigenase-2 inhibeerders, kan die meegaande toediening van angiotensien II reseptor antagoniste of AOE-reseptor antagoniste of AOE-inhibeerders tot gevolg hê in verdere agteruitgang van renale funksie, insluitend moontlike akute renale skade (nierversaking). Hierdie effekte is

gewoonlik omkeerbaar. Dus moet die kombinasie versigtig toegedien word by pasiënte met gekomprommiteerde renale funksie.

Beid indometasien, soos in AMDOCIN, en kalium-sparende diuretiese middels kan geassosieer word met ‘n toename in serumkaliumvlakke. Die potensiële effekte van indometasien, soos in AMDOCIN, en kalium-sparende diuretiese middels op kalium kinetika en renale funksie moet oorweeg word wanneer hierdie medisynes saam toegedien word. Meeste van die bogemelde effekte verwant aan diuretiese middels was toegeskryf ten minste gedeeltelik, aan meganismes met betrokkenheid tot inhibisie van prostaglandien sintese in indometasien, soos in AMDOCIN.

Kardiale glikosiede/digoksien

Wanneer AMDOCIN toegedien was saam met digoksien, is toename in serumkonsentrasie en verlengde halfleeftyd van digoksien gerapporteer. Dus wanneer indometasien, soos in AMDOCIN, en digoksien saam gebruik word, moet plasma-digoksienvlakke noukeurig gemonitor word.

NSAIMs, soos AMDOCIN, kan hartversaking laat agteruitgaan, GFR laat afneem en plasma-digoksienvlakke verhoog.

Fenielpropanolamien

Hipertensiewe krisis is gerapporteer weens orale fenielpropanolamien en tot fenielpropanolamien toegedien saam met indometasien, soos in AMDOCIN.

Hierdie additiewe effek is moontlik gedeeltelik weens inhibisie van prostaglandien sintese deur indometasien, soos in AMDOCIN, en kan water-intoksikasie tot gevolg hê.

Omsigtigheid is nodig wanneer indometasien, soos in AMDOCIN, en fenielpropanolamien saam toegedien word.

Desmopressien

Effek word gepotensieer deur indometasien, soos in AMDOCIN, en kan tot gevolg hê in water-intoksikasie.

Mifepristoon

NSAIMs, soos AMDOCIN, en aspirien moet vermy word tot ten minste 8 tot 12 dae na toediening van mifepristoon omdat NSAIMs, soos AMDOCIN, die effek kan verminder van mifepristoon.

Kinoloon antibiotika

Meegaande gebruik van fluorokinolone en indometasien, soos in AMDOCIN kan konvulsies induseer in pasiënte met of sonder ‘n geskiedenis van konvulsies/siekte aanvalle.

Spierverslappers

Meegaande gebruik van NSAIMs, soos in AMDOCIN, en baklofen kan baklofen toksisiteit induseer weens tempo van ekskresie.

Pentoksifillien

Moontlike verhoogde risiko van bloeding wanneer geneem word met NSAIMs, soos in AMDOCIN.

Takrolimus

Moontlike verhoogde risiko van nefrotoksisiteit wanneer NSAIMs, soos AMDOCIN, toegedien word met takrolimus.

Tiludroniese suur

Die biobeskikbaarheid van tiludroniese suur word verhoog deur indometasien, soos in AMDOCIN.

Laboratoriumtoetse

Vals-negatiewe resultate in die deksametasoon onderdrukking-toets (DST) in pasiënte wat behandel was met indometasien, soos in AMDOCIN, is gerapporteer. Dus moet resultate van die DST versigtig geinterpreteer word in hierdie pasiënte (sien afdeling 4.8)

4.6. Fertiliteit, swangerskap en laktasie

Die gebruik van AMDOCIN is teenaangedui in swangerskap en laktasie (sien afdeling 4.3).

Swangerskap

Eerste trimester

Inhibisie van prostaglandien sintese kan die swangerskap ongunstig beïnvloed en/of die embrio/fetale ontwikkeling.

Data van epidemiologiese studies suggereer ‘n verhoogde risiko van miskraam en van kardiale misvorming en gastroschisis na gebruik van ‘n prostaglandien sintese inhibeerder, soos AMDOCIN, in vroeë swangerskap. Die absolute risiko vir kardiovaskulêre misvorming was verhoog van minder as 1 % op tot ongeveer 1,5 %. Die risiko word geglo om toe te neem met dosering en tydperk van terapie.

In diere het die toediening van ‘n prostaglandien sintese inhibeerder gewys om verhoogde pre- en post-inplant verlies en embrio-fetale sterfte tot gevolg te hê. Addisioneel was verhoogde insidente van verskillende misvormings, insluitend kardiovaskulêr, gerapporteer by diere wat prostaglandien sintese inhibeerder toegedien was gedurende die organogenetiese periode.

Tweede en derde trimester

Gedurende die derde trimester van swangerskap met alle prostaglandien sintese inhibeerders

• kan die fetus blootstel aan:

- kardiopulmonêre toksisiteit (met premature sluiting van die ductus arteriosus en pulmonêre hipertensie);
- renale disfunksie, wat kan voortgaan tot renale versaking met oligohidramnios.

• kan die moeder en die neonaat blootsel, aan die einde van swangerskap aan:

- moontlike verlenging van bloedingstyd, ‘n anti-sameklomping effek wat kan voorkom selfs by baie lae doserings.
- inhibisie van uteriene sametrekkings met gevolglike vertraging of verlengde kraam.

Weens hierdie risikos, moet die gebruik van AMDOCIN, die dosering en tydperk, tussen 20 en 30 weke van swangerskap beperk en vermy word teen ongeveer 30 weke van swangerskap of later gedurende swangerskap (sien afdelings 4.3 en 4.4).

Borsvoeding

Indometasien, soos in AMDOCIN, word uitgeskei in borsmelk. Moeders wat hulle kleuters borsvoed moet nie behandel word met AMDOCIN nie (sien afdeling 4.3).

Fertiliteit

Die gebruik van AMDOCIN kan vroulike fertiliteit beïnvloed en word nie aanbeveel by vrouens wat probeer om swanger te raak nie. In vrouens wat probleme het om swanger te raak of wat ondersoeke ondergaan vir fertiliteit, moet behandeling met AMDOCIN gestaak word (sien afdeling 4.4).

4.7. Effekte op vermoë om te bestuur en masjinerie te gebruik

AMDOCIN het groot invloed op die vermoë om te bestuur of masjinerie te gebruik. AMDOCIN kan ‘n invloed hê op bestuur en die gebruik van masjinerie, omdat dit duiseligheid, lomerigheid, visuele versteurings en hoofpyne kan veroorsaak. Pasiënte

wat behandel word met AMDOCIN moenie bestuur of masjinerie gebruik nie totdat hulle bewus is tot watter mate hulle beïnvloed word deur AMDOCIN (sien afdeling 4.8).

4.8. Ongewenste effekte

a) Opsomming van die veiligheidsprofiel

Die mees algemene newe-effekte is gastroïntestinale versteurings, hoofpyn en duiseligheid. Gastroïntestinale perforasie, ulserasie en bloeding, soms noodlottig, kan voorkom.

Sistem orgaan klas	**Dikwels**	**Minder dikwels**	**Frekwensie onbekend** (kan nie bereken word van die data beskikbaar nie)
Infeksies en infestasies		Fulminante nekrotiserende fasiitis[1].	
Neoplasme benigne, maligne en ongespesifiseer (insluitend kiste en poliepe)			Leukemie.
Bloed- en die limfatiese sisteem-afwykings		Neutropenie, hemolitiese anemie, trombositopenie, agranulositose, leukopenie, aplastiese anemie,	

		purpura, puntbloeding of eggimose, beenmurg-onderdrukking, g e dissemineerde intravaskulêre koagulasie [2].	
Immuunstelsel-afwykings		Akute anafilakse.	Allergiese reaksies, anafilakse, veluitslag, jeuk, urtikarie, pruritus, purpura, angio-edeem, erythema multiforme, akute asma, agteruitgang van asma, rinitis[3].
Endokrien-afwykings			Hiperglisemie.
Metabolisme en voedings-afwykings			Hiperkalemie.
Psigiatriese afwykings	Hallusinasies, verwarring,	Depressie.	

	angstigheid, depersonalisering[4].		
Senuweestelsel-afwykings	Hoofpyn, duiseligheid, lighoofdigheid.	Lomerigheid, insomnie, vertigo, uitputting (malaise en lusteloosheid), sinkopie, konvulsies, koma, perifere neuropatie, disartrie, epilepsie, parkinsonisme, onwillekeurige spier-beweging, spier-swakheid.	Aseptiese meningitis[5], agteruitgang van epilepsie en parkinsonisme, parestesie[4],
Oogafwykings		Dowwe visie, visuele versteurings, optiese neuritis, orbitale en peri-orbitale pyn.	Korneale donkerheid, visuele veld-veranderinge, bleekheid van die optiese skyf.
Oor- en labirint-afwykings			Tinnitus. gehoor-versteurings, doofheid.
Kardiale afwykings		Miokardiale infarkt, kardiovaskulêre	Perifere edeem,

		trombotiese voorvalle.	kardiale versaking, tagikardie, disritmie, hartkloppings, kongestiewe hart - versaking, borspyn.
Vaskulêre afwykings			Hipertensie, blosing, hipotensie, tromboflebitis.
Respiratoriese, torakale en mediastinale afwykings		Epistaksis akute respiratories distres, skielike dispnee, asma, pulmonêre edeem.	Pulmonêre esinofilie, brongospasma.
Gastroïntestinale afwykings	Epigastriese distres, abdominale wond[6]	Akute pankreatitis, streeks ileitis, anoreksie, ulserasie[6]	Peptiese ulkus, perforasie GI, bloeding, naarheid, braking, abdominale pyn, diarree, winderigheid, hardlywigheid, dispepsie, melena, hematemese, ulseratiewe stomatitis,

			opvlamming van kolitis en Crohn se siekte, gastritis.
Hepatobiliêre afwykings	Hepatitis, geelsug.		Cholestase, abnormale lewer-funksie[7].
Vel- en subkutaneuse weefselafwykings	Eriteem, angiitis, fotosensitiwiteit.	Eksfoliatiewe dermatitis.	Bulleuse reaksies, insluitend Stevens-Johnson se sindroom en toksiese epidermale nekrolise, Medisyne Uitslag met Esinofilie en Sistemiese Sindroom (DRESS), angioneurotiese edeem, alopesie, sweet, opvlamming van psoriase.

Muskuloskeletale en bindweefsel-afwykings			Spierswakheid, versnelling van kraakbeen-degenerasie
Renale en urinêre afwykings		Glikosurie, urinêre frekwensie	Hematurie, nier-versaking8.
Reproduktiewe stelsel en bors-afwykings			Vaginale bloeding, borsveranderinge insluitend vergroting, teerheid of ginekomastie.
Algemene afwykings en toe-dieningsitus toestande			Massatoename, edeem.
Ondersoeke	BUN verhoging.	'n Vinnige val in bloeddruk gelykend tot 'n skok-tipe staat, vals-negatiewe resultate in die deksametasoon onderdrukkingtoets (DST).	

a) Beskrywing van geselekteerde ongunstige reaksies

[1]Infeksies en infestasies

Fulminante nekrotiserende fassiitis, veral in assosiasie met Groep A β-hemolitiese streptokokkus.

[2]*Bloed- en die limfatiese stelselafwykings*

Bloed-diskrasie kan voorkom, insluitend leukopenie, petegia of eggimose, purpura, aplastiese en hemolitiese anemie, agranulositose, beenmurg-onderdrukking, gedissemineerde intravaskulêre koagulasie en trombositopenie. Pasiënte kan anemie ontwikkel sekondêr tot duidelike toepaslike bloed-bepalings word aanbeveel.

Plaatjie-funksie word ingekort deur AMDOCIN.

[3]*Immuunstelselafwykings*

Hipersensitiwiteitsreaksies manifesteer in veluitslag, jeuk, urtikarie en meer ernstige, akute aanvalle van asma.

Hipersensitiwiteitsreaksies (a) nie-spesifieke allergiese reaksies en anafilakse, (b) asemhalingskanaal reaktiwiteit van asma, agteruitgang van asma, brongospasma of dispnee, rinitis (sien afdeling 4.3) of (c) verskillende velafwykings, insluitend uitslag van verskillende tipes, pruritus, urtikarie, purpura, angio-edeem en eksfoliatiewe en bulleuse reaksies, insluitend Stevens-Johnson se sindroom, toksiese epidermale nekrolise en erythema multiforme.

[4]*Psigiatriese afwykings*

Geestesverwarring, angstigheid, psigiese versteurings soos verontpersoonliking, psigotiese episodes, parestesie; agteruitgang van psigiatriese versteurings.

Senuweestelselafwykings

Ernstige frontale hoofpyn kan voorkom by pasiënte wat AMDOCIN gebruik vir lang tydperke. [5]Aseptiese meningitis, (veral by pasiënte met bestaande outo-immuun

afwykings, soos sistemiese lupus erythematosus of gemengde bindweefsel-siekte) met simptome soos stywe nek, hoofpyn, naarheid, braking, koors of disoriëntasie, depressie, vertigo, uitputting, malaise, disartrie, koma, serebrale edeem, senuweeagtigheid, verwarring, angstigheid en ander psigiatriese versteurings, hallusinasies, lomerigheid, konvulsies en agteruitgang van epilepsie en parkinsonisme, perifere neuropatie, parestesie, onwillekeurige bewegings en insomnie.

[6]*Gastroïntestinale afwykings*

Abdominale laserasie, enkel of veelvuldig, van esofagus; maag, duodenum of dun- of dikderm, insluitend perforasie en hemoragie. Ulserasie by enige punt in die gastroïntestinale kanaal (selfs met gevolglike stenose en obstruksie), bloeding (selfs sonder opmerklike ulserasie of van ‘n divertikulum) en perforasie van voorafbestaande sigmoïed letsels (soos divertikulum of karsinoom), het abdominale pyn of opvlamming van die toestand by pasiënte met ulseratiewe kolitis intestinale vernouings en streeks-gastritis.

[7]*Hepato-biliêre afwykings*

Grenslyn verhogings van een of meer lewertoetse kan voorkom en beduidende verhogings van ALT (SGPT) of AST (SGOT),

[8]*Renale en urinêre afwykings*

Nefrotoksisiteit in verskillende vorms, insluitend interstisiële nefritis, nefrotiese sindroom, renale versaking, renale ontoereikendheid, proteïenurie.

Rapporteer van vermoedelike ongunstige reaksies

Rapporteer van vermoedelike ongunstige reaksies na goedkeuring van die medisyne is belangrik. Dit laat toe vir volgehoue monitering van die voordeel/risiko balans van die

medisyne. Gesondheidsorgvoorsieners word versoek om enige vermoedelike ongunstige reaksies te rapporteer aan: https://www.sahpra.org.za/Publications/Index/8

4.9. Oordosering Simptome

Simptome sluit in hoofpyn, naarheid, braking, dispepsie, epigastriese pyn, ulserasie en/of gastroïntestinale bloeding, diarree, disoriëntasie, prikkeling, koma, lomerigheid, duiseligheid, tinnitus, floute, soms konvulsies, abdominale pyn, anoreksie, rusteloosheid en opgewondenheid, vertigo en gastroïntestinale irritasie, met gevolglike peptiese ulserasie, dikwels met bloeding en akute pankreatitis. In gevalle van beduidende vergiftiging is nierskade (akute nierversaking) en lewerskade moontlik.

Behandeling

In akute vergifting moet die maag geledig word deur emese te induseer of deur aspirasie en uitspoeling.

Bloed-elektroliet balans moet gehandhaaf word.

Binne een uur na inname van ‘n potensiële toksiese hoeveelheid, moet geaktiveerde houtskool oorweeg word. Goeie uriene uitset moet verseker word. Renale en lewerfunksie moet versigtig gemonitor word. Pasiënte moet waargeneem word vir ten minste vier uur na inname van potensiële toksiese hoeveelhede. Dikwelse of verlengde konvulsies moet behandel word met intraveneuse diasepam. Ander maatreëls kan aangedui word volgens die pasiënt se kliniese toestand.

Behandeling is ondersteunend en simptomaties.

5. FARMAKOLOGIESE EIENSKAPPE

5.1. Farmakodinamiese eienskappe

Kategorie en Klas: A 3.1 Antirumatiek (anti-inflammatoriese middels)

Farmakoterapeutiese groep: Anti-inflammatoriese en antirumatiek produkte, nie-steroïede, asetiese suur derivative en verwante substanse.

ATC kode: M01AB01

Werkingsmeganisme

Indometasien het analgetiese, anti-inflammatoriese en antipiretiese eienskappe.

Soos die salisilate en verwante anti-inflammatoriese medisynes, inhibeer indometasien die biosintese van prostaglandiene; hierdie werking kan die basis wees van sy anti-inflammatoriese en antipiretiese eienskappe en sekere van sy ander effekte. Daar indometasien ‘n inhibeerder is van prostaglandien sintese, kan sy wyse van werking wees weens ‘n afname van prostaglandiene in perifere weefsels. Dit inhibeer motiliteit van polimorfonukleêr leukosiete en soos salisilate, ontkoppel dit oksidatiewe fosforilasie in supraterapeutiese konsentrasies en onderdruk die biosintese van mukopolisaggariedes.

Indometasien verskaf verligting van simptome; dit verander nie die koers van die onderliggende siekte nie.

5.2. Farmakokinetiese eienskappe

Absorpsie

Na ‘n enkel orale dosis, word indometasien geredelik geabsorbeer vanuit die

gastroïntestinale kanaal en bereik piek plasma-konsentrasies van ongeveer 1 en 2 mkg/mL, respektiewelik, by ongeveer 2 uur. Indometasien oraal toegedien is omgeveer 100 % biobeskikbaar, met 90 % van die dosis geabsorbeer binne 4 uur.

Distribusie

Indometasien is in plasma as die moedersamestelling en sy dimetiel, desbensoïel en desmetiel-desbensoïel metaboliete, in die ongekonjugeerde vorm. Ongeveer 60 % van ‘n orale dosering word herwin in uriene as medisyne en metaboliete (26 % as indometasien en sy glukuronied) en 33 % word herwin in fesies (1,5 % as indometasien).

Piek plasma-konsentrasies word bereik ongeveer 2 uur na ‘n dosering. Ongeveer 99 % van indometasien is gebonde aan plasma-proteïene en indometasien word versprei in die sinoviale vloeistof, die sentrale senuweestelsel en die plasenta. Lae konsentrasies kan waargeneem word in borsmelk.

Biotransformasie

Gelyke fraksies van indometasien word uiteindelik geabsorbeer na IM of orale toediening. Indometasien word egter vinniger geabsorbeer na IM toediening met piek plasmavlakke wat waargeneem word een uur vinniger as na orale toediening.

Eliminasie

Indometasien word uitgeskei via renale ekskresie, metabolisme en biliêre ekskresie. Indometasien ondergaan merkbare enterohepatiese sirkulasie. Die gemiddelde halfleeftyd van indometasien word bereken om ongeveer 4,5 uur te wees. Met ‘n tipiese

terapeutiese regimen van 25 of 50 mg drie keer per dag, is die vaste vlak plasmakonsentrasies van indometasien gemiddeld 1,4 keer van dié na die eerste dosis.

6. FARMASEUTIESE BESONDERHEDE

6.1. Lys van eksipiënte

Laktose, mieliestysel, mikrokristallyn sellulose, natriumstysel glikolaat.

Harde gelatien kapsule, met 'n geel doppie en romp:

Kinolien geel, "sunset" geel, titaniumdioksied.

6.2. Onverenigbaarhede

Nie van toepassing nie

6.3. Rakleeftyd

24 maande.

6.4. Spesiale voorsorgmaatreëls vir berging

Berg by of benede 25 °C.

Beskerm teen lig en vog.

Hou in oorspronklike verpakking totdat dit benodig word vir gebruik.

HOU BUITE DIE BEREIK VAN KINDERS.

6.5. Aard en inhoud van houer

Aluminiumfoelie/PVC film stolpstrokie met 15 kapsules en 'n voubiljet in 'n gedrukte karton.

4 Aluminiumfoelie/PVC film stolpstrokie met 21 kapsules en 'n voubiljet in 'n gedrukte karton.

Bottels bevattende 100, 500 en 1 000 kapsules.

Nie alle pakgroottes sal bemark word nie.

6.6. Spesiale voorsorgmaatreëls vir weggooi en ander hantering

Geen spesiale vereistes nie.

7. HOUER VAN SERTIFIKAAT VAN REGISTRASIE

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8. REGISTRASIENOMMER

A 27/3.1/0169

9. DATUM VAN EERSTE GOEDKEURING

21 Desember 1992

10. DATUM VAN REVISIE VAN TEKS

28 April 2024