1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

ARTHREXIN 100 mg suppositories

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each suppository of ARTHREXIN contains 100 mg indomethacin.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Suppositories

ARTHREXIN is a cream coloured, torpedo-shaped mass.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ARTHREXIN is indicated for:

- The relief of painful symptoms of ankylosing spondylitis and osteoarthritis.
- The relief of pain and swelling in gout, acute gouty arthritis, rheumatoid arthritis.
- The relief of pain and swelling in acute musculoskeletal disorders such as, bursitis, tendonitis, synovitis, tenosynovitis, capsulitis of the shoulder, sprains and strains.
- 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.
- The reduction of fever in Hodgkin's disease when the fever has been refractory to other therapy.
- Fever (as a short-term adjunct to specific therapy).

4.2. Posology and method of administration

Posology

Adults

The recommended dosage of ARTHREXIN is 100 mg to 200 mg daily in divided doses, individually adjusted to the patient’s response and tolerability to the medicines.

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

In patients with persistent night pain and/or morning stiffness, 100 mg may be administered as a suppository on retiring. A dosage of 200 mg per day should not be exceeded.

In the treatment of acute gouty arthritis, 100 mg to 200 mg is the recommended daily dosage until symptoms and signs subside.

In primary dysmenorrhoea, the recommended dosage is 100 mg daily as a single dose, starting at the onset of cramps and bleeding and continuing for as long as symptoms usually last.

Paediatric population

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

Method of administration

For rectal administration

Cut one suppository off, separate the plastic foil and pull to release suppository.

Immerse in water (room temperature) before inserting.

4.3. Contraindications

ARTHREXIN is contraindicated in:

- Patients with hypersensitivity to indomethacin or to any excipients in ARTHREXIN (see section 6.1).
- Patients with a history of gastrointestinal perforation, ulceration or bleeding (PUBs) related to previous non-steroidal anti-inflammatory drugs (NSAIDs), including ARTHREXIN.
- Patients with an active or history of recurrent ulcer/haemorrhage/perforations.
- Patients with a recent history of proctitis or recent rectal bleeding.
- Patients with nasal polyps associated with angioneurotic oedema.
- Patients with a history of acute asthma attacks, urticaria or rhinitis as a result of therapy with aspirin or other NSAIDs, including ARTHREXIN.
- Patients on concurrent triamterene treatment. Addition of triamterene to a maintenance schedule of ARTHREXIN may result in acute renal failure which may be reversible upon discontinuation of treatment. ARTHREXIN and triamterene should not be administered together (see section 4.5).
- Patients taking diflunisal, this medicine should not be used concomitantly with

ARTHREXIN (see section 4.5).

- Patients with a history of angioedema following exposure to NSAIDS such as ARTHREXIN and/or aspirin.
- Patients with peri-operative pain in the setting of coronary artery surgery.
- Patients with heart failure, established ischaemic heart disease and/or cerebrovascular disease (stroke) and peripheral arterial disease.
- Patients with severe hepatic failure and renal failure (see section 4.4).
- 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 ARTHREXIN in children has not been established.

4.4. Special warnings and precautions for use

ARTHREXIN 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, 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.

ARTHREXIN 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 ARTHREXIN. 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 ARTHREXIN and evaluate the patient immediately.

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 ARTHREXIN treatment due to inhibition of prostaglandin synthesis. In view of ARTHREXIN's inherent potential to cause fluid retention, heart failure may be precipitated in some compromised patients.

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 ARTHREXIN (see section 4.3).

Caution is required in patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) and should only be treated with indomethacin, as in ARTHREXIN, after careful consideration.

ARTHREXIN, 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, such as ARTHREXIN. ARTHREXIN, should be used with caution in patients with hypertension.

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

Cardiovascular thrombotic events

ARTHREXIN 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.

To minimise the potential risk for an adverse cardiovascular event in patients treated with ARTHREXIN, the lowest effective dose should be used for the shortest duration possible.

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

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

Renal impairment

In patients with renal, cardiac, hepatic impairment, or conditions predisposing to fluid retention, caution is required since the use of NSAIDs, such as ARTHREXIN, 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. ARTHREXIN may also cause fluid retention which may further aggravate these conditions.

The administration of ARTHREXIN may cause a dose dependent reduction in prostaglandin formation and precipitate renal failure.

In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of ARTHREXIN may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, cardiac impairment, liver dysfunction, those taking diuretics, the elderly, diabetes mellitus, extracellular volume depletion, congestive heart failure, sepsis, or concomitant use of any nephrotoxic medicine. ARTHREXIN should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of ARTHREXIN

therapy is usually followed by recovery to the pre-treatment state.

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.

Acute interstitial nephritis with haematuria, proteinuria, and occasionally nephrotic syndrome can occur in patients receiving long-term administration of ARTHREXIN.

Since indomethacin, as in ARTHREXIN, is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be used to avoid excessive medicine accumulation.

Caution should be used when initiating the treatment with ARTHREXIN in patients with dehydration. Patients should first be hydrated before therapy with ARTHREXIN commences.

Caution is also recommended in patients with pre-existing kidney disease.

Hepatic impairment

ARTHREXIN should be administered with caution to patients with impaired hepatic function.

Patients 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 ARTHREXIN.

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.

Indomethacin, as in ARTHREXIN 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 ARTHREXIN.

Elderly

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

Gastrointestinal effects

The risk of gastrointestinal perforation, ulceration or bleeding (PUBs) is higher with increasing doses of ARTHREXIN, in patients with a history of ulcers, and the elderly. When gastrointestinal bleeding or ulceration occurs in patients receiving ARTHREXIN, treatment with ARTHREXIN should be stopped. ARTHREXIN 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.

Single or multiple ulcerations, including perforation and haemorrhage of the oesophagus, stomach, duodenum or small or large intestine, have been reported to occur with indomethacin, as in ARTHREXIN. Fatalities have been reported. Intestinal ulceration has been associated with stenosis and obstruction (see section 4.8).

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

Caution is advised when indomethacin, as in ARTHREXIN is to be given to patients with gastrointestinal disease.

Combination therapy with protective medicines (e.g., misoprostol or proton pump inhibitors) should be considered for these patients and also for patients requiring concomitant low dose aspirin.

Antipyretic

Single doses of ARTHREXIN are usually adequately tolerated however, because of its potential toxicity, ARTHREXIN is not recommended as a general analgesic-antipyretic.

Use with caution

ARTHREXIN should be used cautiously in patients with psychiatric disorders, epilepsy, or parkinsonism, as ARTHREXIN may tend to aggravate these disorders.

Central nervous system effects

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

Tenesmus

Tenesmus and irritation of the rectal mucosa can occur occasionally with ARTHREXIN (see section 4.8).

Infections

ARTHREXIN may mask the signs and symptoms of infection. ARTHREXIN should be used with caution in patients with existing infection.

Anaemia

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

Platelet aggregation

ARTHREXIN can inhibit platelet aggregation. This effect usually disappears within 24 hours of discontinuing ARTHREXIN. Bleeding time is prolonged (but within normal range) in normal adults. Because this effect may be exaggerated in patients with underlying haemostatic defects, ARTHREXIN should be used cautiously in patients with coagulation defects (see section 4.5).

Lithium

ARTHREXIN may produce a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal patients with steady-state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when ARTHREXIN and lithium are given concomitantly, the patient should be observed carefully for signs of lithium toxicity. In addition, the frequency of monitoring serum lithium concentrations should be increased at the outset of such combination treatment (see section 4.5).

Use in pregnancy

Limit the use of NSAIDs, including ARTHREXIN, between 20 and 30 weeks of pregnancy due to the risk of oligohydramnios/foetal renal dysfunction. Avoid use of NSAIDs, such as ARTHREXIN, 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 ARTHREXIN, 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 ARTHREXIN is necessary between 20 weeks and 30 weeks gestation, limit ARTHREXIN use to the lowest effective dose and shortest duration possible.

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

Female fertility

ARTHREXIN may have a reversible inhibitory effect on women's ovulation. The use of ARTHREXIN 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 ARTHREXIN 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

In patients with rheumatoid arthritis, eye changes may occur which may be related to the underlying disease or to the treatment. Therefore, in chronic rheumatoid disease,

ophthalmological examinations at periodic intervals are recommended.

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

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

Discontinue therapy if eye changes are observed.

General

Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Porphyria:

Safety has not been established.

Paediatric population

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

4.5. Interaction with other medicines and other forms of interaction

Aspirin

The use of indomethacin, as in ARTHREXIN, with aspirin or other salicylates is not recommended. No enhanced therapeutic effect has been shown with concomitant use and a significant increase in the incidence of gastrointestinal side effects have been reported.

Indomethacin, as in ARTHREXIN, inhibits platelet aggregation but is not a substitute for aspirin for cardiovascular prophylaxis (see section 4.4). There is no consistent evidence that concurrent

use of aspirin mitigates the increased risk of serious cardiovascular thrombotic events associated with indomethacin, as in ARTHREXIN.

Diflunisal

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

Other NSAIDs

The concomitant use of indomethacin as in ARTHREXIN, with other NSAIDs is not recommended due to the increased possibility of gastrointestinal toxicity, with little or no increase in efficacy.

Avoid concomitant use of two or more NSAIDs.

Other analgesics including cyclooxygenase-2 selective inhibitors

Avoid concomitant use of two or more NSAIDs (including aspirin) as this may increase the risk of adverse effects (see section 4.4).

Antacids

The bioavailability of indomethacin, as in ARTHREXIN, may be reduced by concomitant antacid therapy.

Anticoagulants

Indomethacin, as in ARTHREXIN, may enhance the effects of anticoagulants such as warfarin. Patients should be closely observed for alterations of prothrombin time, when indomethacin, as

in ARTHREXIN, is given concomitantly with anticoagulants. Caution should be exercised when indomethacin, as in ARTHREXIN and anticoagulants are administered concomitantly.

Probenecid

Co-administration of probenecid may increase plasma levels of indomethacin, as in ARTHREXIN, therefore, a lower total daily dosage in indomethacin, as in ARTHREXIN, may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin, as in ARTHREXIN, are made under these circumstances they should be made cautiously and in small increments. The total plasma concentration of indomethacin, as in ARTHREXIN, plus its inactive metabolites is increased by concurrent administration of probenecid. However, it has not been determined whether the concentration of unchanged indomethacin, as in ARTHREXIN, not bound to plasma protein is altered, or whether the dosage of indomethacin, as in ARTHREXIN, must be adjusted when the two medicines are employed together. Indomethacin, as in ARTHREXIN, does not interfere with the uricosuric effect of probenecid.

Methotrexate

Caution should be exercised with simultaneous use of indomethacin, as in ARTHREXIN, with methotrexate. Indomethacin, as in ARTHREXIN, has been reported to decrease the tubular secretion of methotrexate and to potentiate toxicity. Serious interactions have been reported with the use of high doses of methotrexate with indomethacin, as in ARTHREXIN.

Ciclosporin

Administration of non-steroidal anti-inflammatory medicines (NSAIDs), such as indomethacin, as in ARTHREXIN, concomitantly with ciclosporin, has been associated with an increase in ciclosporin-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. Indomethacin, as in ARTHREXIN, should be used with caution in patients taking ciclosporin, and

renal function should be carefully monitored.

Lithium

Indomethacin, as in ARTHREXIN, may produce a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance (see section 4.4).

Diuretics

In some patients, the administration of indomethacin, as in ARTHREXIN, can reduce the diuretic and antihypertensive effects of loop, potassium-sparing and thiazide diuretics. Therefore, when indomethacin, as in ARTHREXIN and diuretics are used concomitantly, the patient should be closely observed to determine if the desired effect of the diuretic is obtained.

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 indomethacin, as in ARTHREXIN. Therefore, the combination should be administered with caution, especially in the elderly. Patients should be adequately hydrated, and consideration should be given to monitoring of renal function after initiation of concomitant therapy, and periodically thereafter.

Basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion, are reduced by indomethacin, as in ARTHREXIN. These facts should be borne in mind when evaluating plasma renin activity in hypertensive patients.

Addition of triamterene to a maintenance schedule of indomethacin, as in ARTHREXIN, may result in acute renal failure which may be reversible upon discontinuation of treatment. Indomethacin, as in ARTHREXIN and triamterene should not be administered together (see section 4.3).

Indomethacin, as in ARTHREXIN and potassium-sparing diuretics may be associated with increased plasma potassium levels. The potential effects of indomethacin, as in ARTHREXIN and potassium-sparing diuretics on potassium kinetics and renal function should be considered when 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 ARTHREXIN.

Digoxin

Indomethacin, as in ARTHREXIN, given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when indomethacin, as in ARTHREXIN and digoxin are used concomitantly, serum digoxin levels should be monitored closely. NSAIDS, such as indomethacin, as in ARTHREXIN, may exacerbate cardiac failure, reduce GFR and increase plasma digoxin levels.

Antihypertensive medicines

Co-administration of indomethacin, as in ARTHREXIN and some antihypertensive medicines may acutely attenuate the hypotensive effect of the latter, due partly to the inhibition of prostaglandin synthesis by indomethacin, as in ARTHREXIN. Caution should be exercised when considering the addition of indomethacin as in ARTHREXIN, to the regimen of a patient taking any of the following antihypertensive medicines:

- alpha-adrenergic blocking medicines,
- angiotensin converting enzyme (ACE) inhibitors,
- beta-adrenergic blocking medicines,
- diuretics,
- hydralazine, nifedipine or losartan,
- angiotensin II receptor antagonists.

An increased risk of hyperkalaemia has also been reported when NSAIDs such as indomethacin, as in ARTHREXIN, are used with ACE inhibitors.

Antipsychotics

Increased drowsiness has been reported with concomitant use of indomethacin, as in ARTHREXIN and haloperidol.

Phenylpropanolamine

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

Corticosteroids

The risk of gastrointestinal bleeding and ulceration associated with NSAIDs, such as indomethacin, as in ARTHREXIN, is increased when used with corticosteroids.
In a patient receiving corticosteroids concomitantly, a reduction in dosage of these may be possible, but should only be effected slowly under supervision.

Desmopressin

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

Mifepristone

NSAIDs, such as indomethacin, as in ARTHREXIN and aspirin, should be avoided until at least 8 to 12 days after administration of mifepristone as this may reduce the efficacy of mifepristone.

Quinolone antibiotics

Fluoroquinolones may induce convulsions in patients with or without a history of convulsions. Taking NSAIDs, such as indomethacin, as in ARTHREXIN concomitantly, may also induce convulsions.

Muscle relaxants

Concomitant use of indomethacin, as in ARTHREXIN and baclofen may induce baclofen toxicity due to reduced rate of excretion.

Pentoxifylline

Possible increased risk of bleeding when taken with indomethacin, as in ARTHREXIN.

Phenytoin

Indomethacin, as in ARTHREXIN, may increase the effects of phenytoin.

Sulfonylurea antidiabetics

Indomethacin, as in ARTHREXIN, may increase the effects of sulfonylurea antidiabetics. The hypoglycaemic effect of sulfonylureas may be increased by NSAIDs such as indomethacin, as in ARTHREXIN.

Tacrolimus

Possible increased risk of nephrotoxicity when indomethacin, as in ARTHREXIN, is given with tacrolimus.

Tiludronic acid

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

Antiretrovirals

There may be an increased risk of haematotoxicity if zidovudine is used with NSAIDs such as indomethacin, as in ARTHREXIN. Ritonavir may increase the plasma concentrations of indomethacin, as in ARTHREXIN and should thus be avoided. There is evidence of an increased risk of haemarthroses and haematoma in HIV(+) haemophiliacs receiving concurrent treatment with zidovudine and ibuprofen.

Vancomycin

Caution is advised during concurrent or subsequent use of indomethacin, as in ARTHREXIN and vancomycin, indomethacin, as in ARTHREXIN, may increase the risk of vancomycin related toxicities. Where possible, monitor vancomycin levels and adjust the vancomycin dose and/or dosing interval accordingly.

Anti-platelet medicines and selective serotonin reuptake inhibitors (SSRIs)

Indomethacin, as in ARTHREXIN, may increase the risk of gastrointestinal bleeding. Indomethacin, as in ARTHREXIN, 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).

Laboratory tests

False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin, as in ARTHREXIN, 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 ARTHREXIN 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 ARTHREXIN, 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

Regular use of non-steroidal anti-inflammatory medicines, such as ARTHREXIN, during the third trimester of pregnancy;

- may expose the foetus to:
  - cardiopulmonary toxicity (with premature closure of the foetal ductus arteriosus *in utero* 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 ARTHREXIN, 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

ARTHREXIN is excreted into breastmilk. Mothers breastfeeding their infants should not be treated with ARTHREXIN (see section 4.3).

Fertility

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

4.7. Effects on ability to drive and use machines

ARTHREXIN has minor influence the ability to drive or operate machinery.

Since adverse reactions such as dizziness, light-headedness, convulsions, mental confusion, involuntary muscle movements, blurred vision, visual field changes and diplopia have been reported in patients receiving ARTHREXIN, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ARTHREXIN does not adversely affect their ability to do so safely (see section 4.8).

4.8. Undesirable effects

a) *Summary of the safety profile*

The most commonly observed adverse events are gastrointestinal in nature.

b) Tabulated list of adverse reactions

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		Blood dyscrasias, neutropenia, thrombocytopenia, aplastic anaemia[2], leukopenia, purpura, haemolytic anaemia, agranulocytosis, petechiae or ecchymosis, bone-marrow depression, disseminated intravascular coagulation.	
Immune system disorders		Hypersensitivity reactions[3,5] acute anaphylaxis, acute respiratory distress[4].	
Endocrine disorders		Hyperglycaemia, hypoaldosteronism.	
Metabolism and nutrition disorders		Hyperkalaemia.	
Psychiatric disorders		Depression, psychosis, hallucinations, drowsiness, confusion, insomnia, psychiatric disturbances, depersonalisation.	Suicide.
Nervous system disorders	Headache, dizziness, light-headedness, fatigue, malaise, listlessness.	Convulsions, coma, peripheral neuropathy, mental confusion, anxiety, syncope, drowsiness, involuntary muscle movements, paraesthesia, dysarthria, aggravation of	Medication overuse headache (MOH).

		epilepsy and Parkinsonism[6].	
Eye disorders		Corneal opacities, visual field changes, pallor of the optic disc, blurred vision, diplopia, optic neuritis, orbital and peri-orbital pain[7].	
Ear and labyrinth disorders	Vertigo.	Tinnitus.	Hearing disturbances (rarely deafness).
Cardiac disorders		Cardiac failure, oedema, tachycardia, chest pain, dysrhythmia, palpitation, congestive heart failure.	
Vascular disorders		Hypertension, hypotension, flushing.	Thrombophlebitis.
Respiratory, thoracic and mediastinal disorders		Epistaxis[8], sudden dyspnoea, asthma; pulmonary oedema.	Pulmonary eosinophilia, bronchospasm[8].
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, constipation, diarrhoea, anorexia, epigastric distress, ulceration[9].	Flatulence, dyspepsia, melaena, haematemesis, ulcerative stomatitis, Crohn's disease, gastritis, tenesmus, proctitis, rectal bleeding, burning, pain, discomfort, itching, bleeding from the sigmoid colon[9].	Pancreatitis, ulcerative colitis, regional ileitis[9].
Hepatobiliary disorders		Hepatitis, jaundice[10].	Cholestasis, abnormal liver function[10].
Skin and subcutaneous tissue disorders	Angiitis, erythema.	Skin rash, bullous reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), pruritus, urticaria, alopecia, angioedema, erythema nodosum, photosensitivity, exfoliative dermatitis, erythema	Exacerbation of psoriasis, Drug Rash with Eosinophilia and Systemic Syndrome (DRESS).

		multiforme, sweating.	
Musculoskeletal and connective tissue disorders			Muscle weakness, acceleration of cartilage degeneration.
Renal and urinary disorders		Haematuria, renal failure and acute renal failure, proteinuria, nephrotic syndrome, interstitial nephritis, glycosuria.	
Reproductive system and breast disorders		Vaginal bleeding, breast changes including enlargement and tenderness, gynaecomastia.	
General disorders and administrative site conditions		Weight gain, oedema.	Fatigue, chest pain.
Investigations	Blood urea nitrogen (BUN) elevation.		Abnormal laboratory tests[11].

[1,2,3,4,5,6,7,8,9,10,11] see c) below

c) Description of selected adverse reactions

[1]Infections and infestations:

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

[2]Blood and lymphatic system disorders:

Because some patients may develop anaemia secondary to obvious or occult gastrointestinal bleeding, appropriate blood determinations are recommended (see section 4.4).

[3,4,5]Immune system disorders

Hypersensitivity reactions include:

- sudden hypotension (rapid fall in blood pressure resembling a shock-like state),

- acute respiratory distress, including sudden dyspnoea, asthma and pulmonary oedema,
- non-specific allergic reactions and anaphylaxis,
- respiratory tract reactivity comprising asthma, aggravated asthma, bronchospasm or dyspnoea, rhinitis,
- assorted skin disorders, including rashes of various types, pruritus, urticaria, purpura, angioedema and exfoliative and bullous dermatoses (including epidermal necrolysis and erythema multiforme).

[6]*Nervous system disorders:*

These are often transient and disappear frequently with continued treatment or with reduced dosage. However, occasionally, severe reactions require stopping therapy.

[7]*Eye disorders:*

Corneal deposits and retinal disturbances, including those of the macula, can occur in patients with rheumatoid arthritis on prolonged therapy, but similar changes may also be expected in patients with rheumatoid arthritis who have not received ARTHREXIN.

[8]*Respiratory, thoracic and mediastinal disorders:*

Epistaxis and bronchospasm may be precipitated in patients suffering from, or with a history of, bronchial asthma or allergic disease.

[9]*Gastrointestinal disorders:*

Ulceration - single or multiple - of oesophagus, stomach, duodenum or small or large intestine (even with resultant stenosis and obstruction), including perforation and haemorrhage with fatalities having been reported, gastrointestinal tract bleeding without obvious ulcer formation or from a diverticulum, increased abdominal pain when used in patients with pre-existing ulcerative colitis.

Bleeding from the sigmoid colon - occult or from a diverticulum, perforation of pre-existing sigmoid lesions (such as diverticulum or carcinoma).

Rarely, intestinal strictures (diaphragms) and intestinal ulceration followed by stenosis and obstruction has been reported. With suppositories, tenesmus and irritation of the rectal

mucosa have occasionally been reported. Other gastrointestinal side effects which may or may not be caused by indomethacin, as in ARTHREXIN, include: ulcerative colitis and regional ileitis.

[10]*Hepato-biliary disorders:*

Some fatalities reported in patients with jaundice and hepatitis.

Cholestasis, borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT), abnormal liver function, hepatitis and jaundice.

[11]*Investigations:*

Borderline elevations of one or more liver tests may occur, and significant elevations of ALT (SGPT) or AST (SGOT) have been seen. If abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations such as rash or eosinophilia occur, ARTHREXIN should be stopped.

False-negative results in the dexamethasone suppression test (DST) in patients being treated with ARTHREXIN can occur. Thus, results of this test should be used with caution in these patients (see section 4.5).

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/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088/ +27 (0)11 239-6200

4.9. Overdose

Symptoms

Overdosage does not readily occur with the use of suppositories.

The following symptoms may be observed following overdosage: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, lethargy, epigastric pain, gastrointestinal bleeding, diarrhoea, excitation, coma, drowsiness, tinnitus and fainting. There have been reports of paraesthesia, numbness, convulsions, abdominal pain, anorexia, restlessness and agitation. In cases of significant poisoning, kidney injury (acute kidney failure) and liver damage are possible.

Treatment

Treatment is symptomatic and supportive.

Within one hour of ingestion of a potentially toxic amount, activated charcoal should be considered. Good urine output should be ensured. Renal and liver function should be closely monitored. Patients should be observed for at least four hours after ingestion of potentially toxic amounts. Frequent or prolonged convulsions should be treated with intravenous diazepam. Other measures may be indicated by the patient's clinical condition.

The patient should be followed for several days because gastrointestinal ulceration and haemorrhage have been reported as adverse reactions of indomethacin, as in ARTHREXIN. Use of antacids may be helpful.

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 prominent anti-inflammatory, analgesic and antipyretic properties. The anti-inflammatory effects of indomethacin are evident in patients with rheumatoid and other types of arthritis and in acute gout.

The antipyretic effect of indomethacin has also been readily demonstrated in patients with fever. 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. Indomethacin inhibits motility of polymorphonuclear leucocytes and it uncouples oxidative phosphorylation in cartilaginous and hepatic mitochondria.

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

5.2. Pharmacokinetic properties

Absorption

Indomethacin is well absorbed. The bioavailability of rectal suppositories in adults has been reported to be comparable with or slightly less than the bioavailability with oral dosage forms.

Distribution

Indomethacin exists in the plasma as the parent medicine and its dimethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. Peak plasma concentration is attained within 1 to 2 hours in the fasting subject. Indomethacin is 90 % bound to plasma proteins and also extensively bound in tissues. The concentration of indomethacin in the central spinal fluid is low.

Biotransformation

Indomethacin is largely converted to inactive metabolites. About half of a single dose is O-

demethylated and about 10 % is conjugated with glucuronic acid by the hepatic microsomal enzymes. A portion is also N-deacylated by a non-microsomal system.

Since the suppository dissolves rather quickly rather than melting slowly, it is seldom recovered in recognisable form if the patient retains the suppository for more than a few minutes.

Elimination

The plasma half-life of the unchanged medicine is about 2 hours. Some of the metabolites are detectable in plasma, and free and conjugated metabolites are eliminated in the urine, bile and faeces. Enterohepatic cycling of the conjugates occurs. 10 to 20 % of the medicine is excreted unchanged in the urine, in part by tubular secretion.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Suppocire AS2

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.

Keep in original packaging until required for use.

6.5. Nature and contents of container

10 suppositories packed in white opaque polyvinlycloride laminated to polyethylene.

One or more strips are packed into an outer cardboard carton together with a leaflet.

6.6. Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead, 2191

8. REGISTRATION NUMBER

K/3.1/222

9. DATE OF FIRST AUTHORISATION

03 September 1978

10. DATE OF REVISION OF TEXT

23 August 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar.

Mediese Blitslyn: 0800 118 088.

Botswana: BOT0600848 S2

Namibia: NS2 90/3.1/00796

Zimbabwe: P.P.92/3.1/2610

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