

1 NAME OF THE MEDICINE

Indometacin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 25 mg of indometacin as the active ingredient.

Excipients with known effect: sugars as lactose and trace quantities of sulfites.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ARTHREXIN capsules are size 3 white opaque hard gelatin capsules, marked “IN-25” on both body and cap.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ARTHREXIN is indicated in active stages of:

- Rheumatoid arthritis
- Osteoarthritis
- Degenerative joint disease of the hip
- Ankylosing spondylitis
- Gout

It is also indicated for:

- Acute musculoskeletal disorders, such as bursitis, tendonitis, synovitis, tenosynovitis, capsulitis of the shoulder, sprains and strains
- Low back pain (commonly referred to as lumbago)
- Inflammation, pain and oedema following orthopaedic surgical procedures and nonsurgical procedures associated with reduction and immobilisation of fractures or dislocations
- Pain and associated symptoms of primary dysmenorrhoea

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dosage of ARTHREXIN is 50 to 200 mg daily in divided doses and should be individually adjusted to patient's response and tolerance. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Patients on long term treatment should be reviewed regularly with regards to efficacy, risk factors and ongoing need for treatment.

Unlike some other potent antirheumatic agents, an initial high loading dose of ARTHREXIN 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). This will produce maximum benefit and minimise adverse reactions.

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. It is rarely necessary to exceed a dosage of 200 mg/day.

In the treatment of acute gouty arthritis, the recommended daily dosage is 150 mg to 200 mg until all signs and symptoms subside.

In primary dysmenorrhoea, the recommended dosage is 25 mg three times a day starting with onset of cramps or bleeding and continuing for as long as the symptoms usually last.

To minimise the possibility of gastrointestinal disturbances, ARTHREXIN should be taken with food, milk or an antacid.

4.3 CONTRAINDICATIONS

Indometacin should not be used in:

- Patients who are hypersensitive to any component of this product
- Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by acetylsalicylic acid (aspirin) or other non-steroidal anti-inflammatory agents (NSAIDs)
- Patients with severe heart failure
- Patients with severe hepatic impairment

As with other anti-inflammatory agents, indometacin may mask the signs and symptoms of peptic ulcer. Because indometacin itself may cause peptic ulceration or irritation of the gastrointestinal tract, it should not be given to patients with active peptic ulcer, or with a recurrent history of gastrointestinal ulceration.

Indometacin is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

For use in pregnancy and lactation, see Section 4.6 FERTILITY, PREGNANCY AND LACTATION.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Carefully consider the potential benefits and risks of indometacin and other treatment options before deciding to use indometacin. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Cardiovascular Effects

Cardiovascular Thrombotic Events

Observational studies have indicated that non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with an increased risk of serious cardiovascular thrombotic events, including myocardial infarction, stroke, and heart failure, which may increase with dose and duration of use and patients with cardiovascular disease, history of atherosclerotic cardiovascular disease or cardiovascular risk factors may also be at greater risk. There are a lack of data from randomised, placebo controlled studies. However, to minimise the potential risk of an adverse cardiovascular event (CV), especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration.

Physicians and patients should remain alert for such CV events even in the absence of previous CV symptoms. Patients should be informed about signs and/or symptoms of serious CV toxicity and the steps to take if they occur.

There is no evidence that the concurrent use of acetylsalicylic acid mitigates the increased risk of serious cardiovascular events associated with NSAID use. However, the concurrent use of NSAIDs and acetylsalicylic acid does increase the risk of serious GI events.

Hypertension

NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of cardiovascular events. Patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response and hence NSAIDs should be administered with caution in patients with hypertension. Furthermore, when given to patients with hypertension, blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Congestive Heart Failure, Fluid Retention and Oedema

Congestive heart failure, fluid retention and peripheral oedema have been observed in some patients taking indometacin. Therefore, as with other NSAIDs, ARTHREXIN should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions predisposing to fluid retention.

Serious Gastrointestinal Effects

All NSAIDs can cause gastrointestinal discomfort and serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use; but can occur at any time without warning. Upper GI ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months and in about 2 to 4% of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

Single or multiple ulcerations, including perforation and haemorrhage of the oesophagus, stomach, duodenum or small or large intestine have been reported to occur with indometacin. Fatalities have been reported in some instances. Rarely, intestinal ulceration has been associated with stenosis and obstruction.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occurs in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increase the risk of serious gastrointestinal adverse events.

Because of the occurrence and at times severity of gastrointestinal reactions, the risks of continuing therapy with ARTHREXIN in the face of such symptoms must be weighed against the possible benefits to the individual patient.

Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.) have occurred. Increased abdominal pain in ulcerative colitis patients or the development of ulcerative and regional ileitis have been reported to occur rarely. Pancreatitis has been reported with an unknown frequency.

Severe Skin Reactions

NSAIDs, including indometacin, can cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome (see Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)) which can be fatal and may occur without warning. These serious adverse events are idiosyncratic and are independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their physician at the first appearance of a skin rash or any other sign of hypersensitivity.

Drug Reaction with Eosinophilia with Systemic Symptoms (DRESS)

DRESS has been reported in patients taking NSAIDs. 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 the NSAID and evaluate the patient immediately.

Platelet Aggregation

Indometacin, like other NSAIDs, can inhibit platelet aggregation. This effect is of shorter duration than that seen with acetylsalicylic acid and usually disappears within 24 hours after discontinuation of ARTHREXIN. Indometacin has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this effect may be exaggerated in patients with underlying haemostatic defects, ARTHREXIN should be used with caution in persons with coagulation defects.

Anticoagulants

Concurrent use of NSAIDs and warfarin has been associated with severe, sometimes fatal, haemorrhage, especially in the elderly. The exact mechanism is unknown; but may involve enhanced bleeding from NSAID-induced gastrointestinal ulceration, or an additive effect of anticoagulation by warfarin and inhibition of platelet function by NSAIDs. Indometacin should be used in combination with warfarin only if absolutely necessary, and patients taking this combination should be closely monitored. In post marketing experience, bleeding has been reported in patients on concomitant treatment with anticoagulants and indometacin. Caution should be exercised when indometacin and anticoagulants are administered concomitantly. Adjustment of dosage for oral anticoagulants may be required.

Ocular Effects

Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with indometacin. The prescribing physician should be alert to the possible association between the changes noted and ARTHREXIN; however, similar eye changes have been observed in patients with rheumatoid arthritis who have not received indometacin. It is advisable to discontinue therapy if such 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 in whom therapy is prolonged.

Adverse ophthalmological effects have been observed with non-steroidal anti-inflammatory agents; accordingly, patients who develop visual disturbances during treatment with ARTHREXIN should have an ophthalmological examination.

Central Nervous System Effects

Headache, sometimes accompanied by dizziness or light-headedness, may occur, usually early in treatment with indometacin. Although the severity of these effects rarely requires discontinuing therapy, if headache persists, despite dosage reduction, indometacin therapy should be discontinued. Patients should be warned that they may experience dizziness and in this event should not operate motor vehicles and should avoid potentially dangerous activities which require alertness.

ARTHREXIN should be used with caution in patients with psychiatric disturbances, epilepsy or parkinsonism, since it may, in some instances, tend to aggravate these conditions.

Infections

In common with other anti-inflammatory analgesic antipyretic drugs, indometacin possesses the potential for masking the signs and symptoms which ordinarily accompany infectious diseases. The physician should be

alert to this possibility to avoid undue delay in initiating appropriate treatment of the infection. Indometacin should be used with caution in patients with existing, but controlled, infection.

Use in Renal Impairment

As with other NSAIDs, there have been reports of acute interstitial nephritis with haematuria, proteinuria and, occasionally, nephrotic syndrome in patients receiving long-term administration of indometacin.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. In patients with reduced renal blood flow where renal prostaglandins play a major role in maintaining renal perfusion, administration of a NSAID may precipitate overt renal decompensation. 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 drug. Caution should be used when initiating the treatment with indometacin in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with indometacin. Caution is also recommended in patients with pre-existing kidney disease. An NSAID should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of non-steroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Increases in serum potassium concentration, including hyperkalaemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninaemic-hypoaldosteronism state (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Since indometacin 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 drug accumulation. Therefore, treatment with indometacin is not recommended in these patients with advanced renal disease. If indometacin therapy must be initiated, close monitoring of the patient's renal function is advisable.

Use in the Elderly

As advancing years appear to increase the possibility of side effects, ARTHREXIN should be used with greater care in the elderly.

Paediatric Use

Safe conditions for use in children under two years of age have not been established. Children should be monitored closely and periodic evaluations of liver function should be performed at appropriate intervals. Cases of hepatotoxicity including fatalities have been reported.

Effects on Laboratory Tests

As with other NSAIDs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may resolve with continued therapy.

Significant (3 times the upper limit of normal) elevations of SGPT (ALT) or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients receiving therapy with NSAIDs. Physicians and patients should remain alert for hepatotoxicity. Patients should be informed about the signs and/or symptoms of hepatotoxicity. A patient with symptoms and/or signs suggesting liver dysfunction (e.g. nausea, fatigue, lethargy, pruritis, jaundice, abdominal tenderness, in the right upper quadrant and "flu-like" symptoms), or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy 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.), therapy should be discontinued.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Acetylsalicylic Acid

The use of ARTHREXIN in conjunction with acetylsalicylic acid or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of indometacin and acetylsalicylic acid does not produce any greater therapeutic effect than the use of indometacin alone. Furthermore, in one of these clinical studies, the incidence of gastrointestinal side effects was significantly increased with combined therapy. In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of acetylsalicylic acid per day decreases indometacin blood levels approximately 20%.

Diflunisal

The combined use of indometacin and diflunisal has been associated with fatal gastrointestinal haemorrhage. The co-administration of diflunisal and indometacin results in an increase of about 30 to 35% in indometacin plasma levels and a concomitant decrease in renal clearance of indometacin and its conjugate. Therefore, ARTHREXIN and diflunisal should not be used concomitantly.

Other NSAIDs

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

Anticoagulants

Although clinical studies suggest that indometacin does not influence the hypoprothrombinaemia induced by anticoagulants, patients also receiving anticoagulants should be closely observed for alterations of the prothrombin time.

Probenecid

When ARTHREXIN is given to patients receiving probenecid, the plasma levels of indometacin are likely to be increased. Therefore, a lower total daily dosage of ARTHREXIN may produce a satisfactory therapeutic effect. When increases in the dose of ARTHREXIN are made under these circumstances, they should be made cautiously and in small increments.

Methotrexate

Caution should be used if ARTHREXIN is administered simultaneously with methotrexate. Indometacin has been reported to decrease the tubular secretion of methotrexate and to potentiate toxicity.

Ciclosporin

Administration of NSAIDs concomitantly with ciclosporin has been associated with an increase in ciclosporin-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. In patients taking ciclosporin, NSAIDs should be used with caution and the patients' renal function monitored carefully.

Lithium

Indometacin 50 mg three times daily produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when indometacin and lithium are given concomitantly, the patient should be carefully observed for signs of lithium toxicity. (Refer to literature for lithium preparations before use of such concomitant therapy). In addition, the frequency of monitoring serum lithium concentrations should be increased at the outset of such combination drug treatment.

Cardiac glycosides/Digoxin

Indometacin given concomitantly with digoxin has been reported to raise the serum concentration and prolong the half-life of digoxin. Therefore, when ARTHREXIN and digoxin are used concomitantly, serum levels of digoxin should be closely monitored.

Diuretics

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

Indometacin reduces basal plasma renin activity (PRA) as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

It has been reported that the addition of triamterene to a maintenance schedule of indometacin resulted in reversible acute renal failure in two of four healthy volunteers. ARTHREXIN and triamterene should not be administered together.

ARTHREXIN and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of ARTHREXIN and potassium sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by indometacin.

Antihypertensive Medications

Co-administration of indometacin and some antihypertensive agents has resulted in an attenuation of the latter's hypotensive effect acutely, due at least in part to indometacin's inhibition of prostaglandin synthesis. Therefore, caution should be exercised by the prescriber when considering the addition of ARTHREXIN to the patient's medication regimen when the patient is taking any of the following antihypertensive agents: an alpha-adrenergic blocking agent (such as prazosin), an angiotensin converting enzyme inhibitor (such as captopril or lisinopril), a beta-adrenergic blocking agent, a diuretic (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS – Diuretics), hydralazine or losartan (an angiotensin II receptor antagonist). In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy), the co-administration of an NSAID and an ACE inhibitor or angiotensin II antagonist may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible.

These interactions should be considered in patients taking an NSAID concomitantly with diuretics and ACE inhibitors. Therefore, the combination should be administered with caution, especially in the elderly.

β-Adrenergic Receptor Blocking Agents

A decrease in the antihypertensive effect of β-adrenergic receptor blocking agents by non-steroidal anti-inflammatory drugs including indometacin has been reported. Therefore, when using a β-blocking agent to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained.

Combination Use of ACE inhibitors or Angiotensin Receptor Antagonists, Anti-Inflammatory Drugs and Thiazide Diuretics

The use of an ACE inhibiting drug (ACE-inhibitor or angiotensin receptor antagonist), an anti-inflammatory drug (NSAID or cyclooxygenase-2 COX-2 inhibitor) and a thiazide diuretic at the same time increases the risk of renal impairment. This includes use in fixed-combination products containing more than one class of drug. Combined use of these medications should be accompanied by increased monitoring of serum creatinine,

particularly at the institution of the combination. The combination of drugs from these three classes should be used with caution particularly in elderly patients or those with pre-existing renal impairment.

Phenylpropanolamine

Hypertensive crises have been reported due to oral phenylpropanolamine alone and rarely (< 1/1000) to phenylpropanolamine given with indometacin. This additive effect is probably due partly to indometacin's ability to inhibit prostaglandin synthesis. Caution should be exercised when ARTHREXIN and phenylpropanolamine are administered together.

Corticosteroids

The risk of gastro-intestinal bleeding and ulceration associated with NSAIDs is increased when used with corticosteroids.

Mifepristone

NSAIDs and aspirin should be avoided until at least 8 to 12 days after administration of mifepristone.

Quinolone antibiotics

There have been reports that 4-quinolones may induce convulsions in patients with or without a history of convulsions; taking NSAIDs at the same time may also induce them.

Vancomycin

Studies in premature neonates being treated for patent ductus arteriosus have shown that concomitant administration of indometacin and vancomycin may have additive nephrotoxic effects. As such, caution is advised during concurrent or subsequent use of indometacin and vancomycin, as indometacin may increase the risk of vancomycin related toxicities. Where possible, monitor vancomycin levels and adjust the vancomycin dose and/or dosing interval accordingly.

Gold Preparations

Gold preparations increase nephrotoxicity (due to inhibition of prostaglandin synthesis in the kidneys).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Indometacin should be used with caution in women of child-bearing age who are thinking to get pregnant. Consider withdrawal of NSAIDs, including indometacin, in women who have difficulties conceiving or who are being medically evaluated for infertility.

Prostaglandins have been reported to play an important role in human ovulation and implantation. Inhibition of prostaglandin synthesis may adversely affect the pregnancy and/or the embryo/fetal development.

Clinical studies have shown that NSAIDs including indometacin have an inhibitory (delay) reversible effect on healthy women ovulation.

Use in Pregnancy

Pregnancy category: C

Non-steroidal anti-inflammatory drugs have an inhibitory effect on prostaglandin synthesis and, when given during the third trimester of pregnancy, may cause closure of the fetal ductus arteriosus, tricuspid incompetence and pulmonary hypertension, non-closure of ductus arteriosus postnatally which may be resistant to medical management, myocardial degenerative changes, platelet dysfunction with resultant bleeding, intracranial bleeding, renal dysfunction or failure, renal injury/dysgenesis which may result in prolonged or permanent renal failure, oligohydramnios (see Oligohydramnios and Neonatal Renal

Impairment), gastrointestinal bleeding or perforation, increased risk of necrotising enterocolitis and delayed labour and birth.

Indometacin should not be given to pregnant women since safety for this use has not been established.

Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy.

Oligohydramnios and Neonatal Renal Impairment:

Use of NSAIDs from about 20 weeks gestation may cause fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment.

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 initiation. Oligohydramnios is often, but not always, reversible with treatment discontinuation.

Complications of prolonged oligohydramnios may, for example, 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, after careful consideration of alternative treatment options for pain management, NSAID treatment is necessary from about 20 weeks, limit use to the lowest effective dose and shortest duration possible. Consider ultrasound monitoring of amniotic fluid if treatment extends beyond 48 hours. Discontinue treatment with NSAIDs if oligohydramnios occurs.

Use in Lactation

Administration of indometacin is not recommended during pregnancy or lactation. Indometacin is excreted in breast milk.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

During the treatment period, care must be taken when driving vehicles and engaging in other activities that require increased attention and rapid psychomotor reactions.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Central Nervous System

Central nervous system adverse effects are headache, dizziness, light-headedness, depression, vertigo and fatigue (including malaise and listlessness). Reactions reported infrequently include mental confusion, anxiety, syncope, drowsiness, convulsions, coma, peripheral neuropathy, muscle weakness, involuntary muscle movements, insomnia, psychic disturbances such as depersonalisation, psychotic episodes and rarely, paraesthesia, dysarthria, aggravation of epilepsy and parkinsonism. These are often transient and disappear frequently with continued treatment or with a reduction in dosage. However, the severity of these may, on occasion, require stopping therapy.

Gastrointestinal

Gastrointestinal reactions which occur most frequently are nausea, anorexia, vomiting, epigastric distress, abdominal pain, constipation and diarrhoea. Others which may develop are ulceration - single or multiple - of oesophagus, stomach, duodenum or small or large intestine, including perforation and haemorrhage with a few fatalities having been reported; gastrointestinal tract bleeding without obvious ulcer formation; and increased abdominal pain when used in patients with pre-existing ulcerative colitis. Rarely, intestinal strictures (diaphragms) and intestinal ulceration followed by stenosis and obstruction has been reported. Reactions which occur infrequently are stomatitis, gastritis, flatulence, bleeding from the sigmoid colon - occult or from a diverticulum, and perforation of pre-existing sigmoid lesions (diverticula, carcinoma). Other gastrointestinal side effects which may or may not be caused by indometacin include ulcerative colitis and regional ileitis.

Studies in humans with radioactive chromate tagged red blood cells indicate that the highest recommended oral dosage of indometacin (50 mg, four times a day) produces less faecal blood loss than average doses of acetylsalicylic acid (600 mg, four times a day).

Hepatic

Reactions reported on rare occasions are jaundice and hepatitis and some fatal cases have been reported.

Cardiovascular - Renal

Cardiovascular – renal reactions which may occur infrequently include oedema, elevation of blood pressure, tachycardia, chest pain, arrhythmia, palpitations, hypotension, congestive heart failure, BUN elevation and haematuria.

Hypersensitivity

Hypersensitivity reactions reported infrequently are pruritus, urticaria, angitis, erythema nodosum, skin rashes, exfoliative dermatitis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, loss of hair, acute respiratory distress, a rapid fall in blood pressure resembling a shock-like state, acute anaphylaxis, angioneurotic oedema, sudden dyspnoea, asthma and pulmonary oedema. Hypersensitivity reactions with unknown frequency are Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome.

Haematological

Haematological reactions which may develop infrequently with indometacin therapy are leucopenia, petechiae or ecchymosis, purpura, aplastic and haemolytic anaemia, thrombocytopenia and disseminated intravascular coagulation. Rarely, agranulocytosis and bone marrow depression have been reported, but a definite relationship to indometacin has not been established.

Some patients may manifest anaemia secondary to obvious or occult gastrointestinal bleeding. Therefore, appropriate blood determinations are recommended.

Eye

Blurred vision, diplopia and orbital and periorbital pain may occur infrequently. Corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients with rheumatoid arthritis on prolonged therapy with indometacin. Similar eye changes have been observed in some patients with this disease who have not received indometacin.

Ear

Tinnitus, hearing disturbances and deafness rarely, have been reported to occur.

Genitourinary

Reported rarely: proteinuria, nephrotic syndrome, interstitial nephritis and renal insufficiency, including renal failure.

Miscellaneous

Miscellaneous adverse reactions reported rarely include vaginal bleeding, hyperglycaemia and glycosuria, hyperkalaemia, flushing and sweating, epistaxis, ulcerative stomatitis and breast changes including enlargement and tenderness, or gynaecomastia.

Pregnancy, puerperium and perinatal conditions

Oligohydramnios, neonatal renal impairment.

Adverse Effects – Causal Relationship Unknown

The following additional adverse effects have been reported; however, a causal relationship to therapy with indometacin has not been established.

Cardiovascular

Thrombophlebitis.

Haematological

Although there have been several reports of leukaemia, the supporting information is weak.

Genitourinary

Urinary frequency.

Miscellaneous

Rare occurrences of fulminant necrotising fasciitis, particularly in association with Group A β -haemolytic streptococcus, have been described in persons treated with non-steroidal anti-inflammatory agents, sometimes with fatal outcome (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

The following symptoms may be observed following overdosage: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation or lethargy. There have been reports of paraesthesias, numbness and convulsions.

No specific information is available on the treatment of overdosage with indometacin. Treatment is symptomatic and supportive. Therapy with indometacin should be discontinued and the patient observed closely. If possible, activated charcoal should be given within 1 hour of ingestion, with then correction of dehydration and electrolyte imbalance by established procedures. The patient should be followed for several days, because gastrointestinal ulceration and haemorrhage have been reported as adverse reactions of indometacin. Use of antacids may be helpful.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Indometacin is a highly effective non-steroidal anti-inflammatory drug (NSAID) with marked analgesic and antipyretic properties.

Indometacin is a potent inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy which have been demonstrated to have an effect *in vivo* as well.

Indometacin has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis and osteoarthritis.

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

Indometacin has been found effective in relieving pain, reducing fever, swelling, redness and tenderness of acute gouty arthritis.

The prostaglandin inhibitory effect of indometacin has been shown to be useful in the relief of pain and associated symptoms of primary dysmenorrhoea.

Prostaglandins sensitise afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Moreover, prostaglandins are known to be among the mediators of inflammation. Since indometacin is an inhibitor of prostaglandin synthesis, the mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Indometacin has been reported to diminish basal and CO₂ stimulated cerebral blood flow in healthy volunteers following acute oral and intravenous administration. In one study after one week of treatment with orally administered indometacin, this effect on basal cerebral blood flow had disappeared. The clinical significance of this effect has not been established.

Clinical Trials

Anti-Inflammatory Action

The anti-inflammatory activity of indometacin was first demonstrated in animals, measuring the ability of the compound to inhibit either granuloma formation or oedema induced by subplantar injection of carrageenin in rats. The latter appears to correlate well with antirheumatic activity in man. Assays of relative potency indicated that indometacin was more potent than acetylsalicylic acid, phenylbutazone or hydrocortisone; the potency ratios differed with the test employed.

The inhibition of carrageenin-induced oedema by indometacin is specific; the compound failed to inhibit oedema induced by a variety of agents other than carrageenin, nor did it reduce oedema if the drug was administered after the oedema had been established.

As with other anti-inflammatory agents, the mechanism of action of indometacin is unknown. Indometacin is fully active in the absence of the adrenals; and its activity is readily demonstrable by direct application of the compound to the site of action. Unlike anti-inflammatory steroids, indometacin in intact animals did not affect the size of the adrenals or the thymus, nor did it retard gain in body weight; these are sensitive indicators of adrenal activation. The anti-inflammatory activity of combinations of indometacin and a steroid was that of either drug alone in comparable doses.

Experiments have shown indometacin to have a favourable effect upon adjuvant-induced polyarthritis in rats; it was more active than phenylbutazone or acetylsalicylic acid in suppressing the delayed manifestations of disseminated arthritis. This response is said to correlate well with clinical antiarthritic activity.

Antipyretic Activity

The antipyretic activity of indometacin has been demonstrated in rabbits and rats injected with bacterial pyrogen and in the classical yeast induced fever assay in rats. A direct comparison of peak antipyretic activity in the yeast fever test showed indometacin to be about 9 times as potent as aminopyrine, 24 times as potent as phenylbutazone, and 43 times as potent as acetylsalicylic acid.

The antipyretic activity of indometacin has been confirmed clinically by observation in patients with a variety of febrile conditions.

Analgesic Activity

Indometacin is active in animal tests designed to assay analgesic activity of non-narcotic analgesics. Moderate doses raise the response threshold when pressure is applied to the yeast inflamed foot of the rat, but do not affect responses to thermal stimuli, or to pressure on a non-inflamed foot. Qualitatively, indometacin behaves like an analgesic of the anti-inflammatory antipyretic type typified by the salicylates, and not of the narcotic type typified by morphine.

When single oral doses of indometacin were assayed in the inflamed foot assay, the compound was found to be about 28 times as potent as acetylsalicylic acid and about 14 times as potent as phenylbutazone.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following single oral doses of indometacin capsules 25 mg or 50 mg, indometacin is readily absorbed, attaining peak plasma concentrations of approximately 1 and 2 microgram/mL, respectively, at about two hours.

Orally administered indometacin capsules are virtually 100% bioavailable, with 90% of the dose absorbed within four hours.

Distribution

Indometacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl metabolites, all in the unconjugated form. About 60% of an oral dosage is recovered in urine as drug and metabolites (26% as indometacin and its glucuronide), and 33% is recovered in faeces (1.5% as indometacin).

About 90% of indometacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations.

Excretion

Indometacin is eliminated via renal excretion, metabolism and biliary excretion. Indometacin undergoes appreciable enterohepatic circulation. The mean half-life of indometacin is estimated to be about 4.5 hours. With a typical therapeutic regimen of 25 mg or 50 mg three times a day, the steady-state plasma concentrations of indometacin average 1.4 times those following the first dose.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

ARTHREXIN capsules contain the following inactive excipients: lactose monohydrate, sodium starch glycollate, sodium lauryl sulfate, magnesium stearate, Empty Hard Gelatin Capsules Bovine Size 3 White-Opaque/White-Opaque G3ICSRA0399 (ARTG PI No: 140186) and Opacode Black A-10259 (ARTG PI No: 1659).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: bottle (HDPE with PP cap) and blister pack (PVC/PVDC)

Pack sizes:

Bottle: 6, 30, 50, 90, 250 and 1000 capsules

Blister pack: 30, 50 and 90 capsules

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 353403 – ARTHREXIN indometacin 25mg capsule bottle

AUST R 353404 – ARTHREXIN indometacin 25mg capsule blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

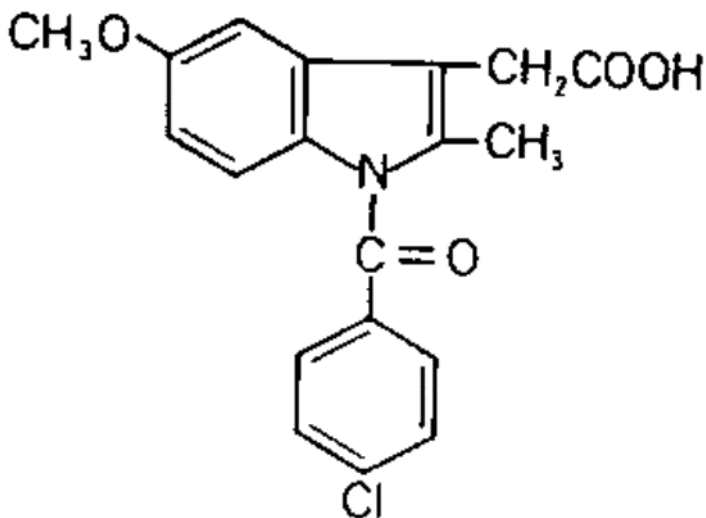
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Indometacin is a white to yellow, crystalline powder; odourless or almost odourless.

Structural Formula



Chemical name: 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid.

Molecular formula: C₁₉H₁₆ClNO₄

Molecular weight: 357.8

CAS Number

53-86-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

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Millers Point NSW 2000

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Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

20/09/1991

10 DATE OF REVISION

12/06/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2	Minor editorial changes to excipient details
4.5	Add interactions to Gold Preparations
4.7	Update to Effects on ability to drive and use machines

ARTHREXIN™ is a Viatris company trade mark

ARTHREXIN_pi\Jun24/00 (CCDS 13-Nov-2023)