PRODUCT INFORMATION

Name of the Medicine

Active ingredient: Indomethacin
Chemical name: [1-(4-chlorobenzoyl)-5-methoxy-2-methylindol-3-yl] acetic acid
Structural formula:

Molecular formula: C_{19}H_{16}ClNO_{4}    Molecular weight: 357.8
CAS Registry No.: 53-86-1

Description

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

Arthrexin capsules contain the following inactive excipients: lactose, sodium starch glycollate, sodium lauryl sulfate, magnesium stearate, silica - colloidal anhydrous, gelatin and titanium dioxide CI77891.

Pharmacology

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

Indomethacin is a potent inhibitor of prostaglandin synthesis \textit{in vitro}. Concentrations are reached during therapy which have been demonstrated to have an effect \textit{in vivo} as well.

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

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

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

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

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 indomethacin is an inhibitor of prostaglandin synthesis, the mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Indomethacin 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 indomethacin, this effect on basal cerebral blood flow had disappeared. The clinical significance of this effect has not been established.

Anti-Inflammatory Action. The anti-inflammatory activity of indomethacin 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 indomethacin was more potent than acetylsalicylic acid, phenylbutazone or hydrocortisone; the potency ratios differed with the test employed.

The inhibition of carrageenin induced oedema by indomethacin 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 indomethacin is unknown. Indomethacin 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, indomethacin in intact animals did not affect the size of the adrenals or the thymus, nor did it retard gain in bodyweight; these are sensitive indicators of adrenal activation. The anti-inflammatory activity of combinations of indomethacin and a steroid was that of either drug alone in comparable doses.

Experiments have shown indomethacin to have a favourable effect upon adjuvant induced polyarthritis in rats; it was more active than phenylbutazone or aspirin 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 indomethacin 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 indomethacin to be about 9 times as potent as aminophenazone, 24 times as potent as phenylbutazone, and 43 times as potent as aspirin.

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

Analgesic Activity. Indomethacin 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 noninflamed foot. Qualitatively, indomethacin 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 indomethacin were assayed in the inflamed foot assay, the compound was found to be about 28 times as potent as aspirin and about 14 times as potent as phenylbutazone.

**Pharmacokinetics**

Following single oral doses of indomethacin capsules 25 mg or 50 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of approximately 1 and 2 microgram/mL, respectively, at about two hours. Orally administered indomethacin capsules are virtually 100% bioavailable, with 90% of the dose absorbed within four hours.

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 mg or 50 mg three times a day, the steady-state plasma concentrations of indomethacin average 1.4 times those following the first dose.

Indomethacin 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 indomethacin and its glucuronide), and 33% is recovered in faeces (1.5% as indomethacin). About 90% of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations.

**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.
Contraindications

Patients who are hypersensitive to any component of this product.

Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other NSAIDs.

As with other anti-inflammatory agents, indomethacin may mask the signs and symptoms of peptic ulcer. Because indomethacin 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.

Treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Use in Pregnancy (see Precautions - Use in Pregnancy).

Use in Lactation (see Precautions - Use in Lactation).

Patients with severe heart failure.

Precautions

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

Serious Gastrointestinal Effects

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.

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 3-6 months and in about 2-4% 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 indomethacin. Fatalities have been reported in some instances. Rarely, intestinal ulceration has been associated with stenosis and obstruction.

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.

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 ulceration 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. The gastrointestinal effects may be reduced by giving the oral formulation of the drug immediately after meals, with food, milk or with antacids.

**Cardiovascular Effects**

**Cardiovascular Thrombotic Events**

Observational studies have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of an adverse cardiovascular event in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see Dosage and Administration).

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use. However, the concurrent use of NSAIDs and aspirin 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. Caution is advised when prescribing NSAIDs 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 indomethacin. Therefore, as with other NSAIDs, Arthrexin should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions predisposing to fluid retention.

**Ocular Effects**

Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with indomethacin. 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 indomethacin. 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 lightheadedness, may occur usually early in treatment with indomethacin. Although the severity of these effects rarely requires discontinuing therapy, if headache persists, despite dose reduction, indomethacin 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**

Like other anti-inflammatory analgesic antipyretic drugs, indomethacin 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. Indomethacin should be used with caution in patients with existing, but controlled, infection.

**Platelet Aggregation**

Indomethacin, like other NSAIDs, can inhibit platelet aggregation. This effect is of shorter duration than that seen with aspirin and usually disappears within 24 hours after discontinuation of Arthrexin. Indomethacin 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. Indomethacin 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 indomethacin. Caution should be exercised when indomethacin and anticoagulants are administered concomitantly. Adjustment of dosage for oral anticoagulants may be required.

**Renal Function**

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 indomethacin.

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 indomethacin in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with indomethacin. Caution is also recommended in patients with pre-existing kidney disease. A 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 Precautions - Interactions with Other Medicines).

Since indomethacin 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 indomethacin is not recommended in these patients with advanced renal disease. If indomethacin therapy must be initiated, close monitoring of the patient’s renal function is advisable.

**Severe Skin Reactions**

NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and 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.

**Laboratory Tests**

As with other NSAIDs, borderline elevations of one or more liver tests may occur.

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. 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 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 indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

**Use in Pregnancy (Category C)**

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

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 foetal ductus arteriosus, tricuspid incompetence and pulmonary hypertension, non-closure of ductus arteriosus postnataally 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, gastrointestinal bleeding or perforation, increased risk of necrotising enterocolitis and delayed labour and birth.

*Australian Categorisation Definition of Category C:* Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

**Use in Lactation**

Indomethacin is excreted in breast milk. Therefore, administration of Arthrexin is not recommended during lactation.

**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.

**Interactions with Other Medicines**

**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.

**Aspirin**

The use of Arthrexin in conjunction with aspirin or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of indomethacin and aspirin does not produce any greater therapeutic effect than the use of indomethacin 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/day decreases indomethacin blood levels approximately 20%.

**Diflunisal**

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

See Precautions – Anticoagulants.

Probenecid

When Arthrexin is given to patients receiving probenecid, the plasma levels of indomethacin 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. Indomethacin has been reported to decrease the tubular secretion of methotrexate and to potentiate toxicity.

Cyclosporin

The concomitant administration of non-steroidal anti-inflammatory drugs with cyclosporin has been associated with an increase in cyclosporin-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. In patients taking cyclosporin, NSAIDs should be used with caution and the patients’ renal function monitored carefully.

Lithium

Indomethacin 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 indomethacin and lithium are given concomitantly, the patient should be carefully observed for signs of lithium toxicity. (Refer 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.

Digoxin

Indomethacin 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.

Indomethacin reduces basal plasma renin activity (PRA) as well as those elevations of PRA induced by frusemide 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 indomethacin 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 indomethacin.

**β-Adrenergic Receptor Blocking Agents**

A decrease in the antihypertensive effect of β-adrenergic receptor blocking agents by non-steroidal anti-inflammatory drugs including indomethacin 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.

**Antihypertensive Medications**

The concomitant use of indomethacin and some antihypertensive agents has resulted in an attenuation of the latter's hypotensive effect acutely, due at least in part to indomethacin'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 (e.g. prazosin), an ACE inhibitor (e.g. captopril or lisinopril), a beta-adrenergic blocking agent, a diuretic (see **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.

**Combination Use of ACE inhibitors or Angiotensin ReceptorAntagonists, 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 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 indomethacin. This additive effect is probably due partly to indomethacin's ability to inhibit prostaglandin synthesis. Caution should be exercised when Arthrexin and phenylpropanolamine are administered together.
Adverse Effects

Central Nervous System

Headache, dizziness, lightheadedness, depression, vertigo and fatigue (including malaise and listlessness). Reactions reported infrequently include peripheral neuropathy, mental confusion, syncope, anxiety, drowsiness, convulsions, coma, 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

Most frequently occurring 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 indomethacin include ulcerative colitis and regional ileitis.

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

Hepatic

Reactions reported rarely are jaundice and hepatitis; some fatal cases have been reported.

Cardiovascular/Renal

Reactions which occur infrequently include oedema, elevation of blood pressure, tachycardia, chest pain, arrhythmia, hypotension, palpitations, congestive heart failure, BUN elevation and haematuria.

Hypersensitivity

Reactions reported infrequently are pruritus, urticaria, angiitis, 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.

Haematological

Reactions which occur infrequently 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 indomethacin has not been established. Some patients
may manifest anaemia secondary to obvious or occult gastrointestinal bleeding. Therefore, appropriate blood determinations are recommended.

**Ocular**

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 indomethacin. Similar eye changes have been observed in some patients with this disease who have not received indomethacin.

**Auditory**

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**

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

**Causal Relationship Unknown**

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

**Cardiovascular**

Thrombophlebitis.

**Haematological**

Although there have been several reports of leukopenia, 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 also **Precautions**).

**Dosage and 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.

Unlike some other potent antirheumatic agents, an initial high loading dose of Arthrexin is not necessary. In chronic rheumatic disorders, the initial doses should be low and increased gradually when necessary, continuing for an adequate period (up to one month is recommended). This will produce maximum benefit and minimal side effects.

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

Use with great care in the elderly.

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 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.

**Overdosage**

*Symptoms.* Nausea, vomiting, intense headache, dizziness, mental confusion, disorientation or lethargy may be observed. There have been reports of paraesthesiae, numbness and convulsions.

*Treatment.* Symptomatic and supportive. Therapy with indomethacin 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's progress should be followed for several days, because gastrointestinal ulceration and haemorrhage have been reported as adverse reactions of indomethacin. Use of antacids may be helpful.

Contact the Poisons Information Centre on 131126 (Australia) for advice on management of overdosage.

**Presentation and Storage Conditions**

*Arthrexin*, 25 mg capsule: white, marked IN-25; bottles of 6*, 30*, 50, 90*, 250* and 1000* capsules; blisters* of 30*, 50* and 90* capsules.

* Not marketed in Australia.

Store below 30°C.
Name and Address of the Sponsor

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Poison Schedule of the Medicine

S4 – Prescription Only Medicine

Date of Approval

Approved by the Therapeutic Goods Administration on 16 April 1996.

Date of most recent amendment: 14 October 2011.