

PRODUCT INFORMATION

Capsules/Suppositories

INDOCID*
(indomethacin, MSD)

INDOCID* (indomethacin, MSD) is a highly effective non-steroidal anti-inflammatory drug with marked analgesic and antipyretic properties.

Indomethacin 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.

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

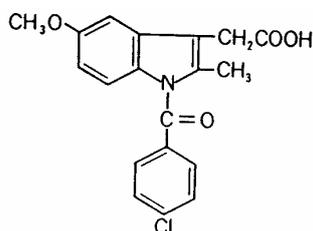
Indomethacin affords relief of symptoms; it does not alter the progressive course of the underlying disease.

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

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

DESCRIPTION

Generic Name:	Indomethacin, MSD
Chemical Name:	1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid.
Empirical Formula:	C ₁₉ H ₁₆ NO ₄ Cl (molecular weight: 357.78)
Structural Formula:	



*Registered Trademark of Merck & Co. Inc., Whitehouse Station, N.J., U.S.A.

Indomethacin occurs as a yellowish-white powder with a melting point of about 156°C to 160°C. It is insoluble in water and in hydrocarbons, but is soluble in alcohols, acetone, ethylene dichloride, and acetonitrile. Stable crystalline solvates are formed with alcohols. Indomethacin is soluble but unstable in alkaline solution. Both the solid and the solutions must be protected from sunlight. In the dry state, the sodium salt is reasonably stable.

Each INDOCID capsule contains 25mg of indomethacin and the following non-medicinal ingredients: lactose, lecithin, silica-colloidal anhydrous, magnesium stearate, gelatin, titanium dioxide, iron oxide Yellow CI77492 and Opacode monogramming ink S-1-27794 BLACK or TEKPrint SW-9008 Black printing ink. Each suppository contains 100mg of indomethacin and the following non-medicinal ingredients: butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerol, macrogol 3350 and macrogol 8000.

CLINICAL PHARMACOLOGY

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.

Following single oral doses of Capsules INDOCID 25mg or 50mg, indomethacin is readily absorbed, attaining peak plasma concentrations of approximately 1 and 2µg/mL, respectively, at about two hours. Orally administered Capsules INDOCID 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 or 50mg t.i.d., the steady-state plasma concentrations of indomethacin average 1.4 times those following the first dose.

The rate of absorption is more rapid from the rectal suppository than from Capsules INDOCID. Ordinarily, therefore, the total amount absorbed from the suppository would be expected to be at least equivalent to the capsule. In controlled clinical trials, however, the amount of indomethacin absorbed was found to be somewhat less (80-90%) than that absorbed from Capsules INDOCID. This is probably because some subjects did not retain the material from the suppository for the one hour necessary to assure complete absorption. 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.

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.

IDC-MF-022006Sv2

In a gastroscopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group receiving Capsules INDOCID than in the group taking Suppositories INDOCID or placebo.

In a double-blind comparative clinical study involving 175 patients with rheumatoid arthritis, however, the incidence of upper gastrointestinal adverse effects with Suppositories or Capsules INDOCID was comparable. The incidence of lower gastrointestinal adverse effects was greater in the suppository group.

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 body weight; 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 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 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 nine times as potent as aminopyrine, 24 times as potent as phenylbutazone, and 43 times as potent as acetylsalicylic acid.

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 non-inflamed 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 acetylsalicylic acid and about 14 times as potent as phenylbutazone.

INDICATIONS

INDOCID 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

INDOCID 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 or other non-steroidal anti-inflammatory agents.

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.

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

INDOCID suppositories are contraindicated in patients with a history of proctitis or recent rectal bleeding.

IDC-MF-022006Sv2

Use in Pregnancy and in Nursing Mothers

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

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, gastrointestinal bleeding or perforation, increased risk of necrotizing enterocolitis, and delayed labour and birth.

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

PRECAUTIONS

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

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

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.

Cardiovascular Effects

Cardiovascular Thrombotic Events

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

There is no evidence to suggest that concurrent use of aspirin mitigates the increased risk of serious CV events associated with NSAID use. However, the concurrent use of NSAIDs and aspirin does increase the risk of serious GI events.

Hypertension

NSAIDs can lead to onset of new hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking antihypertensives along with NSAIDs may have 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 the initiation of NSAID treatment and at regular intervals thereafter.

IDC-MF-022006Sv2

Congestive Heart Failure, Fluid Retention and Oedema

Congestive heart failure, fluid retention and peripheral oedema have been observed in some patients taking INDOCID. Therefore, as with other non-steroidal anti-inflammatory drugs, INDOCID 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 3–6 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 time therapy is not without risk.

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 GI events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur 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 increases the risk of serious gastrointestinal adverse events.

Because of the occurrence and at times severity of gastrointestinal reactions the risks of continuing therapy with INDOCID 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.

Severe Skin Reactions

NSAIDs, including INDOCID, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), 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 informed about the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of skin rash or any other sign of hypersensitivity.

Platelet Aggregation

INDOCID, like other non-steroidal anti-inflammatory agents, 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 INDOCID. INDOCID 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, INDOCID 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. INDOCID 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 INDOCID. Caution should be exercised when INDOCID and anticoagulants are administered concomitantly. Adjustment of dosage for oral anticoagulants may be required.

Suppository

Tenesmus and irritation of the rectal mucosa have been reported occasionally with the use of INDOCID Suppositories.

Ocular Effects

Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with INDOCID. The prescribing physician should be alert to the possible association between the changes noted and INDOCID; 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 where therapy is prolonged.

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 dosage 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.

Indomethacin 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, indomethacin possesses the potential for masking the signs and symptoms which ordinarily accompany infectious disease. 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.

Renal Function

As with other non-steroidal anti-inflammatory drugs, 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 non-steroidal anti-inflammatory agent 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 INDOCID in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with INDOCID. Caution is also recommended in patients with preexisting kidney disease. A non-steroidal anti-inflammatory drug 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 pretreatment 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 DRUG INTERACTIONS).

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

Laboratory Tests

As with other non-steroidal anti-inflammatory drugs, 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 non-steroidal anti-inflammatory drugs. 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 INDOCID.

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

DRUG INTERACTIONS

Acetylsalicylic Acid

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

Diflunisal

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

Other NSAIDs

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

Probenecid

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

Methotrexate

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

Cyclosporine

Administration of non-steroidal anti-inflammatory drugs concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporine, and renal function should be monitored carefully.

Lithium

Indomethacin 50mg t.i.d. 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. (Read circulars 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

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

Diuretics

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

INDOCID 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 INDOCID resulted in reversible acute renal failure in two of four healthy volunteers. INDOCID and triamterene should not be administered together.

INDOCID and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of INDOCID 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 INDOCID.

Antihypertensive Medications

Co-administration of INDOCID 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. The prescriber should, therefore, exercise caution when considering the addition of INDOCID to the regimen of a patient taking one 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 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.

IDC-MF-022006Sv2

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 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.

Beta-Adrenergic Receptor Blocking Agents

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

Phenylpropanolamine

Hypertensive crises have been reported due to oral phenylpropanolamine alone and rarely (< 1/1000) to phenylpropanolamine given with INDOCID. This additive effect is probably due at least in part to indomethacin's inhibition of prostaglandin synthesis. Caution should be exercised when INDOCID and phenylpropanolamine are administered concomitantly.

ADVERSE 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, paraesthesias, dysarthria, aggravation of epilepsy and parkinsonism. These are often transient and disappear frequently with continued treatment or with a reduction of 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 indomethacin include ulcerative colitis and regional ileitis.

Studies in man with radioactive chromate tagged red blood cells indicate that the highest recommended oral dosage of indomethacin (50mg, 4 times a day) produces less faecal blood loss than average doses of acetylsalicylic acid (600mg, 4 times a day).

IDC-MF-022006Sv2

Hepatic

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-life state, acute anaphylaxis, angioneurotic oedema, sudden dyspnoea, asthma and pulmonary oedema.

Haematological

Haematological reactions which may develop infrequently in conjunction with indomethacin therapy are leucopenia, petechiae or ecchymosis, purpura, aplastic and haemolytic anaemia and 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.

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

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.

IDC-MF-022006Sv2

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.

The following local adverse reactions have been associated with use of INDOCID Suppositories: tenesmus; proctitis; rectal bleeding, burning, pain, discomfort and itching.

ADVERSE EFFECTS - CAUSAL RELATIONSHIP UNKNOWN

The following additional adverse effects have been reported; however a causal relationship to therapy with INDOCID has not been established:

Cardiovascular

Thrombophlebitis.

Haematologic

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

Genitourinary

Urinary frequency.

Miscellaneous

Rare occurrences of fulminant necrotizing fasciitis, particular in association with Group A β -haemolytic streptococcus, has been described in persons treated with non-steroidal anti-inflammatory agents, sometimes with fatal outcome (See also PRECAUTIONS).

DOSAGE AND ADMINISTRATION

INDOCID is available for oral administration as a 25mg capsule and as a rectal suppository containing 100mg of indomethacin.

The recommended dosage of INDOCID is 50mg to 200mg daily in divided doses and should be individually adjusted to the 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 INDOCID is not necessary. In chronic rheumatic disorders, initiating therapy with low doses, increasing gradually when necessary, and continuing for an adequate period (up to one month is recommended) will produce maximum benefit and minimise adverse reactions.

In patients with persistent night pain and/or morning stiffness, a dose of up to 100mg at bedtime may be helpful in affording relief. It is rarely necessary to exceed a dosage of 200mg per day.

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

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

IDC-MF-022006Sv2

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

OVERDOSAGE

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 INDOCID. Treatment is symptomatic and supportive. Therapy with INDOCID 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 indomethacin. Use of antacids may be helpful.

Contact the Poisons Information Centre for advice on overdose management.

AVAILABILITY

INDOCID* 25mg, white powder in an opaque ivory capsule. Marked with "25" and "MSD" on capsule in black. Supplied in blister pack of 50.

INDOCID* suppositories, 100mg, white opaque with yellowish cast. Supplied in 20's, foil pack.

SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
54-68 Ferndell St., Granville, NSW 2142

POISONS SCHEDULE – S4

Approved by the Therapeutic Goods Administration on 27 May 1996
Date of last amendment 20 March 2008