

## INDOCID

Multiple Formulations (Indomethacin)

**Cardiovascular Risk**  
NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See PRECAUTIONS.)

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

**Gastrointestinal Risk**  
NSAIDs cause upper gastrointestinal (GI) and lower gastrointestinal adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. (See PRECAUTIONS.)

INDOCID® (indomethacin) 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*. Gastrointestinal effects 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 has not been shown to alter the progressive course of the underlying disease.

INDOCID has been found effective in relieving the fever, 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 dysmenorrhea.

### INDICATIONS

INDOCID is indicated in active stages of:  
Rheumatoid arthritis, medication to severe juvenile rheumatoid arthritis.  
Osteoarthritis, Degenerative joint disease of the hip, Ankylosing spondylitis.  
Acute gouty arthritis.  
It is also indicated for:

Acute musculoskeletal disorders, such as bursitis, tendinitis, synovitis, tenosynovitis, epicondylitis, shoulder, sprain, and strain; Low back pain (commonly referred to as lumbago), Fever, and swelling following dental procedures; Inflammation, pain, erythema and swelling following dental procedures; Inflammation, pain and swelling following orthopedic surgical procedures and non-surgical procedures associated with reduction and immobilization of fractures or dislocations. Pain and associated symptoms of primary dysmenorrhea.

**DOSE AND ADMINISTRATION**

INDOCID is available in the following dosage forms to provide maximum flexibility and interchangeability:

Capsules: 25 mg or 50 mg for oral administration.

Capsules/Retard: 75 mg provide 25 mg of free indomethacin for immediate dissolution and 50 mg of indomethacin coated pellets.

Suppositories: 50 mg and 100 mg.

Injection: 30 mg/2 mL (25 mg/mL), Lyophilized powder to be reconstituted with 2 mL of sterile water to provide a solution of 50 mg (25 mg/mL).

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

Unlike some other potent antiarthritic 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 reduce the risk of side effects.

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 per day.

In treatment of acute gouty arthritis, the recommended daily dosage is 150 mg to 200 mg in divided doses until all symptoms and signs subside. Capsules INDOCID Retard are not recommended for use in acute gouty arthritis.

In primary dysmenorrhea, the recommended dosage is 75 mg daily as a single or

divided dose, starting at the onset of cramps or bleeding and continuing for as long as symptoms persist. In patients with acute joint pain, 50 mg of INDOCID (INTRAMUSCULAR) may be given in a morning and evening. Administration of a NSAID agent may precipitate acute 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 concurrent use of any nephrotoxic drug. Caution should be used when initiating therapy with INDOCID in patients with known or suspected dehydration. It is advisable to hydrate patients first and then start therapy with INDOCID. Caution is also recommended in patients with preexisting 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 pretreatment state.

Increases in serum potassium concentration, including hyperkalemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoadrenergic state associated with the use of these drugs. In patients with renal impairment, since INDOCID is eliminated primarily by the kidneys, patients who 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.

**CONTRAINDICATIONS**

INDOCID should not be used in:

Patients who are hypersensitive to any component of this product.

Patients in whom acute idiopathic thrombocytopenic purpura or thrombocytopenia is suspected or in whom other non-steroidal anti-inflammatory agents.

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

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

**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.

**CARDIOVASCULAR EFFECTS:** Cardiovascular Thrombotic Events: NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs, both COX-2 selective and non-selective, may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. To minimize the potential risk for an adverse cardiovascular event in patients treated with an NSAID, the lowest effective dosage should be used for the shortest duration possible.

**PERIPHERAL EFFECTS:** NSAIDs, including INDOCID, can lead to either a new hypertension or an worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients receiving therapy with a diuretic may have impaired response to these therapies when taking NSAIDs. NSAIDs, including INDOCID, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

**COGNITIVE/HEALTH EFFECTS:** Fluid Retention and Edema: Cognitive/health effects: Fluid retention and peripheral edema have been observed in some patients taking INDOCID. Therefore, as with other NSAIDs, INDOCID should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions predisposing to fluid retention.

**GASTROINTESTINAL EFFECTS:** 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.

Single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small or large intestine have been reported to occur with INDOCID. These events can occur at any time during use and without warning symptoms. 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 ulcers (diverticula, colitis, etc.) have occurred. Increased abdominal pain in ulcerative colitis patients or the development of ulcerative colitis and regional ileitis have been reported to occur rarely.

**RENAL FUNCTION:** As with other NSAIDs, there have been reports of acute interstitial nephritis with hematuria, 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 serious renal injury. In patients with acute renal insufficiency, renal prostaglandin synthesis may maintain or increase renal perfusion. Administration of a NSAID agent may precipitate acute 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 concurrent use of any nephrotoxic drug. Caution should be used when initiating therapy with INDOCID in patients with known or suspected dehydration. It is advisable to hydrate patients first and then start therapy with INDOCID. Caution is also recommended in patients with preexisting 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 pretreatment state.

Increases in serum potassium concentration, including hyperkalemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoadrenergic state associated with the use of these drugs.

Since INDOCID is eliminated primarily by the kidneys, patients who 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.

**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. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued as at the first appearance of skin rash or any other sign of hypersensitivity.

**USE IN PREGNANCY:** INDOCID should be used during the first two trimesters of pregnancy only if the potential benefit justifies the potential risk to the fetus. The known effects of indomethacin and other drugs of this class on the human fetus are unknown. In animal studies, pregnancy includes: constriction of the uterine arteries, premature, and pulmonary hypertension; necrosis of the ductus arteriosus potentially which may result in medical management; myocardial degenerative changes, placental dysfunction with resultant, bleeding, intracranial bleeding, renal dysfunction or failure, renal injury/hypertension which may result in prolonged or permanent renal failure, oligohydramnios, gastrointestinal bleeding, or perforation and increased risk of necrotizing enterocolitis. Use of INDOCID during the third trimester of pregnancy is not recommended.

**LACTATION:** The combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. The coadministration of diflunisal and INDOCID result in an increase of about 300% in indomethacin plasma levels and a concomitant decrease in renal clearance of indomethacin and its conjugates. 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 reduction in the efficacy.

**NURSING MOTHERS:** Administration of INDOCID is not recommended in nursing mothers. Clinical studies have shown that INDOCID did not affect milk quantity or quality, including milk fat content, in patients and in normal subjects. However, when any additional drug, including INDOCID, is added to the treatment of patients on antineoplastic therapy, the patient should be observed closely for alterations of the prothrombin time. In post marketing experience, bleeding has occurred in patients on concomitant treatment with antineoplastic agents and INDOCID. Caution should be exercised when INDOCID and antineoplastic are administered concomitantly.

**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 this effect is desired, which may occur in these circumstances, they should be made cautiously use 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.

**CYCLOSOPORIN:** Administration of NSAID concomitantly with cyclosporin has been associated with an increase in cyclosporin-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporin, and renal function should be monitored carefully.

**LITHIUM:** Indomethacin 50 mg 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 monitored carefully 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.

**DIURETICS:** In some patients, the administration of INDOCID can reduce the

NSAID (ASA?) occurred in controlled clinical trials in less than 1% of patients receiving INDOCID. In a patient with renal insufficiency, acute renal insufficiency, renal prostaglandin synthesis may maintain or increase renal perfusion. Administration of a NSAID agent may precipitate acute 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 concurrent use of any nephrotoxic drug. Caution should be used when initiating therapy with INDOCID in patients with known or suspected dehydration. It is advisable to hydrate patients first and then start therapy with INDOCID. Caution is also recommended in patients with preexisting 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 pretreatment state.

Increases in serum potassium concentration, including hyperkalemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoadrenergic state associated with the use of these drugs.

Since INDOCID is eliminated primarily by the kidneys, patients who 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.

**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. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued as at the first appearance of skin rash or any other sign of hypersensitivity.

**USE IN PREGNANCY:** INDOCID should be used during the first two trimesters of pregnancy only if the potential benefit justifies the potential risk to the fetus. The known effects of indomethacin and other drugs of this class on the human fetus are unknown. In animal studies, pregnancy includes: constriction of the uterine arteries, premature, and pulmonary hypertension; necrosis of the ductus arteriosus potentially which may result in medical management; myocardial degenerative changes, placental dysfunction with resultant, bleeding, intracranial bleeding, renal dysfunction or failure, renal injury/hypertension which may result in prolonged or permanent renal failure, oligohydramnios, gastrointestinal bleeding, or perforation and increased risk of necrotizing enterocolitis. Use of INDOCID during the third trimester of pregnancy is not recommended.

**LACTATION:** The combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. The coadministration of diflunisal and INDOCID result in an increase of about 300% in indomethacin plasma levels and a concomitant decrease in renal clearance of indomethacin and its conjugates. 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 reduction in the efficacy.

**NURSING MOTHERS:** Administration of INDOCID is not recommended in nursing mothers. Clinical studies have shown that INDOCID did not affect milk quantity or quality, including milk fat content, in patients and in normal subjects. However, when any additional drug, including INDOCID, is added to the treatment of patients on antineoplastic therapy, the patient should be observed closely for alterations of the prothrombin time. In post marketing experience, bleeding has occurred in patients on concomitant treatment with antineoplastic agents and INDOCID. Caution should be exercised when INDOCID and antineoplastic are administered concomitantly.

**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 this effect is desired, which may occur in these circumstances, they should be made cautiously use 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.

**CYCLOSOPORIN:** Administration of NSAID concomitantly with cyclosporin has been associated with an increase in cyclosporin-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporin, and renal function should be monitored carefully.

**LITHIUM:** Indomethacin 50 mg 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 monitored carefully 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.

**DIURETICS:** In some patients, the administration of INDOCID can reduce the

NSAID, indomethacin, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when INDOCID and diuretics are used concomitantly, the potential for the observed effects to be altered by the desired effect of the diuretic is obtained.

INDOCID reduces total plasma renal 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 methimazole to a maintenance schedule of INDOCID resulted in reversible acute renal failure in two of four healthy volunteers. INDOCID and thiazimide should not be administered together.

INDOCID and potassium-sparing diuretics such as 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. Concomitant use of these agents with diuretics should be monitored closely.

**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.

**ANTHYPERSENSITIVE REACTIONS:** 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 lisinopril 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, the co-administration of an NSAID and an ACE inhibitor or angiotensin II antagonist may result in further deterioration of renal function.

**ACE INHIBITORS/ANGIOTENSIN II ANTAGONISTS:** In patients with renal impairment, the concomitant use of INDOCID and ACE inhibitor or angiotensin II antagonist may result in further deterioration of renal function.

**PHENYLEPHRINE/ALPHAGOLAMINE:** Hypertensive crises have been reported due to oral phenylephrine alone and rarely to phenylephrine/alpha-galactamine 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 phenylephrine/alpha-galactamine are administered concomitantly.

**OVERDOSSAGE:** The following symptoms may be observed following overdosage: nausea, vomiting, intense headache, dizziness, mental confusion, drowsiness, or lethargy. There have been reports of paresthesias, numbness, and convulsions. Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible if the ingestion is recent. If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac. If the patient is unable to vomit, gastric lavage should be performed. Give activated charcoal (1 g/kg of activated charcoal may be given).

Depending on the condition of the patient, close medical observation and nursing care may be required. The patient should be followed for several days because gastrointestinal ulceration and hemorrhage have been reported as adverse reactions of indomethacin. Use of acetaminophen may be helpful.

**AVAILABILITY:** INDOCID is available in capsules and suppositories. Capsules INDOCID 25 mg are supplied in packages of 30, 100 and 1000 capsules. Suppositories INDOCID 100 mg are supplied in packages of 3 and 10 suppositories.

**Storage/Conditions:** Store in a dry place below 30°C, protected from light. Do not refrigerate.

**This is a medication**

A medication is a product which affects your health, and its consumption contrary to instructions is dangerous for you.

Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold you the medication.

The doctor and the pharmacist are experts in medicine, its benefits and risks.

Do not by yourself interrupt the period of treatment prescribed.

Do not repeat the same prescription without consulting your doctor.

**Do not use after expiry date.**

**Keep Medication out of reach of children.**

Suppositories are Manufactured in Zouk Mosbeh, Lebanon, by

ALGORITHM S.A.L.

Capsules are Packaged in Zouk Mosbeh, Lebanon, by

HEPATIC: Hepatic reactions reported on rare occasions in conjunction with indomethacin therapy are jaundice and hepatitis and some fatal cases have been reported.

**CARDIOVASCULAR-RENAL:** Cardiovascular - renal reactions which may occur infrequently in conjunction with indomethacin therapy include edema, ele-