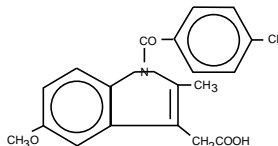




**INDOMETHACIN CAPSULES USP**  
**Rx only**

**DESCRIPTION**

Indomethacin cannot be considered a simple analgesic and should not be used in conditions other than those recommended under **INDICATIONS AND USAGE**. Indomethacin is available in 25 mg and 50 mg capsules for oral administration. Inactive ingredients include: corn starch, D&C Red No. 7 calcium lake, D&C Yellow No. 10, FD&C Green No. 3, FD&C Blue No. 1 aluminum lake, FD&C Blue No. 2 aluminum lake, gelatin, lactose monohydrate, lecithin, silicon dioxide, sodium lauryl sulfate, stearic acid, synthetic black iron oxide and titanium dioxide. Indomethacin is a nonsteroidal anti-inflammatory indole derivative designated chemically as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. Indomethacin is practically insoluble in water and sparingly soluble in alcohol. It has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali. The structural formula is:



C<sub>19</sub>H<sub>16</sub>ClNO<sub>4</sub>

M.W.357.79

**CLINICAL PHARMACOLOGY**

Indomethacin is a nonsteroidal drug with anti-inflammatory, antipyretic and analgesic properties. Its mode of action, like that of other anti-inflammatory drugs, is not known. However, its therapeutic action is not due to pituitary-adrenal stimulation.

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. Prostaglandins sensitize 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, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

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 suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with indomethacin for rheumatoid arthritis has been demonstrated by a reduction in joint swelling, average number of joints involved, and morning stiffness; by increased mobility as demonstrated by a decrease in walking time; and by improved functional capability as demonstrated by an increase in grip strength.

Indomethacin has been reported to diminish basal and CO<sub>2</sub> 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.

Indomethacin capsules have been found effective in relieving the pain, reducing the fever, swelling, redness and tenderness of acute gouty arthritis (See **INDICATIONS**). Following single oral doses of indomethacin 25 mg or 50 mg, the drug is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mcg/mL, respectively, at about 2 hours. Orally administered indomethacin capsules are virtually 100% bioavailable, with 90% of the dose absorbed within 4 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 50 mg t.i.d., the steady-state plasma concentrations of indomethacin are an 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 percent of an oral dosage is recovered in urine as drug and metabolites (26 percent as indomethacin and its glucuronide), and 33 percent is recovered in feces (1.6 percent as indomethacin).

About 99% of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta. In a gastrosopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group receiving Capsules indomethacin than in the group taking Suppositories indomethacin 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 indomethacin was comparable. The incidence of lower gastrointestinal adverse effects was greater in the suppository group.

**INDICATIONS AND USAGE**

Indomethacin capsules have been found effective in active stages of the following:

1. Moderate to severe rheumatoid arthritis including acute flares of chronic disease.
2. Moderate to severe ankylosing spondylitis.
3. Moderate to severe osteoarthritis.
4. Acute painful shoulder (bursitis and/or tendinitis).
5. Acute gouty arthritis.

Indomethacin may enable the reduction of steroid dosage in patients receiving steroids for the more severe forms of rheumatoid arthritis. In such instances the steroid dosage should be reduced slowly and the patients followed very closely for any possible adverse effects.

The use of indomethacin 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 (See **DRUG INTERACTIONS**).

**CONTRAINDICATIONS**

Indomethacin should not be used in:  
—Patients who are hypersensitive to this product.  
—Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other nonsteroidal anti-inflammatory agents.

**WARNINGS**

**General**

Because of the variability of the potential of indomethacin to cause adverse reactions in the individual patient, the following are strongly recommended:

1. The lowest possible effective dose for the individual patient should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150-200 mg/day, without corresponding increase in clinical benefits.
2. Careful instructions to, and observations of, the individual patient are essential to the prevention of serious adverse reactions. As advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the elderly.
3. Effectiveness of indomethacin in pediatric patients has not been established. Indomethacin should not be prescribed for pediatric patients 14 years of age and younger unless toxicity or lack of efficacy associated with other drugs warrants the risk.

In experience with more than 900 pediatric patients reported in the literature or to the manufacturer who were treated with indomethacin capsules, side effects in pediatric patients were comparable to those reported in adults. Experience in pediatric patients has been confined to the use of indomethacin capsules.

If a decision is made to use indomethacin for pediatric patients two years of age or older, such patients should be monitored closely and periodic assessment of liver function is recommended. There have been cases of hepatotoxicity reported in pediatric patients with juvenile rheumatoid arthritis, including fatalities.

If indomethacin treatment is instituted, a suggested starting dose is 2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 4 mg/kg/day or 150-200 mg/day, whichever is less. As symptoms subside, the total daily dosage should be reduced to the lowest level required to control symptoms, or the drug should be discontinued.

**Gastrointestinal Effects**

Single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and 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 colitis and regional ileitis have been reported to occur rarely.

Because of the occurrence, and at times severity, of gastrointestinal reactions to indomethacin, the prescribing physician must be continuously alert for any sign or symptom signaling a possible gastrointestinal reaction. The risks of continuing therapy with indomethacin in the face of such symptoms must be weighed against the possible benefits to the individual patient.

Indomethacin should not be given to patients with active gastrointestinal lesions or with a history of recurrent gastrointestinal lesions except under circumstances which warrant the very high risk and where patients can be monitored very closely.

The gastrointestinal effects may be reduced by giving indomethacin capsules immediately after meals, with food, or with antacids.

**Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy**

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

**Renal Effects**

As with other nonsteroidal anti-inflammatory drugs, long-term administration of indomethacin to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal and renal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with conditions such as renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion from any cause, congestive heart failure, septicemia, pyelonephritis, or concomitant use of any nephrotoxic drug. Indomethacin or other NSAIDs should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of NSAID therapy is typically 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 hyporenemic-hypoadosteronism state (see **PRECAUTIONS, Drug Interactions**).

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

**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 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**

Indomethacin may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions. If severe CNS adverse reactions develop, indomethacin should be discontinued.

Indomethacin may cause drowsiness; therefore, patients should be cautioned about engaging in activities requiring mental alertness and motor coordination, such as driving a car. Indomethacin may also cause headache. Headache which persists, despite dosage reduction, requires cessation of therapy with indomethacin.

**Use in Pregnancy and the Neonatal Period**

Indomethacin is not recommended for use in pregnant women, since safety for use has not been established.

The known effects of indomethacin and other drugs of this class on the human fetus during the third trimester of pregnancy include: constriction of the ductus arteriosus prenatally, tricuspid incompetence, and pulmonary hypertension; non-closure of the 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, oliguria/anuria, gastrointestinal bleeding or perforation, and increased risk of necrotizing enterocolitis. Teratogenic studies were conducted in mice and rats at dosages of 0.5, 1, 2, and 4 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day considered secondary to the decreased average fetal weights, no increase in fetal malformations was observed as compared with control groups. Other studies in mice reported in the literature using higher doses (5 to 15 mg/kg/day) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. Comparable studies in rodents using high doses of aspirin have shown similar maternal and fetal effects.

As with other nonsteroidal anti-inflammatory agents which inhibit prostaglandin synthesis, indomethacin has been found to delay parturition in rats.

In rats and mice, 4 mg/kg/day given during the last three days of gestation caused a decrease in maternal weight gain and some maternal and fetal deaths. An increased incidence of neuronal necrosis in the diencéphalon in the live-born fetuses was observed. At 2 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups. Administration of 0.5 or 4 mg/kg/day during the first three days of life did not cause an increase in neuronal necrosis at either dose level.

**Use in Nursing Mothers**

Indomethacin is excreted in the milk of lactating mothers. Indomethacin is not recommended for use in nursing mothers.

**PRECAUTIONS**

**General**

Non-steroidal anti-inflammatory drugs, including indomethacin, may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing infection.

Fluid retention and peripheral edema have been observed in some patients taking indomethacin. Therefore, as with other nonsteroidal anti-inflammatory drugs, indomethacin should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions predisposing to fluid retention.

In a study of patients with severe heart failure and hyponatremia, indomethacin was associated with significant deterioration of circulatory hemodynamics, presumably due to inhibition of prostaglandin dependent compensatory mechanisms.

Indomethacin, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation. This effect is of shorter duration than that seen with aspirin and usually disappears within 24 hours after discontinuation of indomethacin. 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 hemostatic defects, indomethacin should be used with caution in persons with coagulation defects.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. 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 more severe hepatic reaction while on therapy with indomethacin. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with indomethacin as with other non-steroidal anti-inflammatory drugs. Although such reactions are rare, 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.) indomethacin should be discontinued.

**Information for Patients**

Indomethacin, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

NSAIDs (Nonsteroidal Anti-inflammatory Drugs) are often essential agents in the management of arthritis; but they may be commonly employed for conditions which are less serious or conditions which are self-limiting. Physicians may wish to discuss with their patients the potential risks (see **WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS**) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

**Laboratory Tests**

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (See **WARNINGS, Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy**).

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

In an 8-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day, indomethacin had no tumorigenic effect.

Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73-110 weeks) and the mouse (dosing period 62-88 weeks) at doses up to 1.5 mg/kg/day.



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Indomethacin did not have any mutagenic effect in *in vitro* bacterial tests (Ames test and *E. Coli* with or without metabolic activation) and a series of *in vivo* tests including the host-mediated assay, sex-linked recessive lethals in *Drosophila*, and the micronucleus test in mice.

Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study or a two litter reproduction study in rats.

**Drug Interactions**

In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin. In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, diflunisal and indomethacin should not be used concomitantly.

In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 g of aspirin per day decreases indomethacin blood levels approximately 20%.

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

Clinical studies have shown that indomethacin does not influence the hypoprothrombinemia produced by anticoagulants. However, when any additional drug, including indomethacin, is added to the treatment of patients on anticoagulant therapy, the patient should be observed for alterations of the prothrombin time. When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, a lower total daily dosage of indomethacin may produce a satisfactory therapeutic effect. When increases in the dose of indomethacin are made, they should be made carefully and in small increments. Caution should be used if indomethacin is administered simultaneously with methotrexate. Indomethacin has been reported to decrease the tubular secretion of methotrexate and to potentiate its toxicity.

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 carefully monitored.

Indomethacin capsules, 50 mg 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 concentration should be increased at the outset of such combination drug treatment.

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

In some patients, the administration of indomethacin can reduce the diuretic, natriuretic, and antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when indomethacin 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 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 indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and triamterene should not be administered together.

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

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by nonsteroidal anti-inflammatory drugs including indomethacin has been reported. Therefore, when using these blocking agents to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained. There are reports that indomethacin can reduce the antihypertensive effect of captopril in some patients.

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.

**Pediatric Use**

Effectiveness in pediatric patients 14 years of age and younger has not been established. (See **WARNINGS**).

**Geriatric Use**

As with any NSAID, caution should be exercised in treating the elderly (65 years and older) since advancing age appears to increase the possibility of adverse reactions (see **WARNINGS, General**, and **DOSE AND ADMINISTRATION**). Elderly patients seem to tolerate ulceration or bleeding less well than other individuals and many spontaneous reports of fatal GI events are in this population (see **WARNINGS, Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy**).

Indomethacin may cause confusion or, rarely, psychosis (see **ADVERSE REACTIONS**); physicians should remain alert to the possibility of such adverse effects in the elderly.

This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be increased in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function (see **WARNINGS, Renal Effects**).

**ADVERSE REACTIONS**

The adverse reactions for indomethacin capsules listed in the following table have been arranged into two groups: (1) incidence greater than 1%; and (2) incidence less than 1%. The incidence for group (1) was obtained from 33 double-blind controlled clinical trials reported in the literature (1,092 patients). The incidence for group (2) was based on reports in clinical trials, in the literature, and on voluntary reports since marketing. The probability of a causal relationship exists between indomethacin and these adverse reactions, some of which have been reported only rarely.

	Incidence greater than 1%	Incidence less than 1%
<b>GASTROINTESTINAL</b>	nausea* with or without vomiting, dyspepsia* (including indigestion, heartburn and epigastric pain), diarrhea, abdominal distress or pain, constipation.	anorexia, bloating, (includes distension), flatulence, peptic ulcer, gastroenteritis, rectal bleeding, proctitis, single or multiple ulcerations; including perforation and hemorrhage of the esophagus, stomach, duodenum, or small and large intestines, intestinal ulceration associated with stenosis and obstruction, gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.), development of ulcerative colitis and regional ileitis, ulcerative stomatitis, toxic hepatitis and jaundice (some fatal cases have been reported), intestinal strictures (diaphragms).
<b>CENTRAL NERVOUS SYSTEM</b>	headache (11.7%), dizziness*, vertigo, somnolence, depression and fatigue (including malaise and listlessness).	anxiety (includes nervousness), muscle weakness, involuntary muscle movements, insomnia, muzziness, psychic disturbances including psychotic episodes, mental confusion, drowsiness, light-headedness, syncope, paralysis, aggravation of epilepsy and parkinsonism, depersonalization, coma, peripheral neuropathy, convulsion, dysarthria.
<b>SPECIAL SENSES</b>	tinnitus	ocular - corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with indomethacin, blurred vision, hearing disturbances, deafness, diplopia.
<b>CARDIOVASCULAR</b>	none	hypertension, hypotension, tachycardia, chest pain, congestive heart failure, arrhythmia; palpitations.

<b>METABOLIC</b>	none	edema, weight gain, fluid retention, flushing or sweating, hyperglycemia, glycosuria, hyperkalemia.
<b>INTEGUMENTARY</b>	none	pruritus, rash; urticaria, petechiae or ecchymosis, exfoliative dermatitis, erythema nodosum; loss of hair, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis.
<b>HEMATOLOGIC</b>	none	leukopenia, bone marrow depression, anemia secondary to obvious or occult gastrointestinal bleeding, aplastic anemia, hemolytic anemia, agranulocytosis, thrombocytopenic purpura, disseminated intravascular coagulation.
<b>HYPERSENSITIVITY</b>	none	acute anaphylaxis, acute respiratory distress, rapid fall in blood pressure resembling a shock-like state, angioedema, dyspnea, asthma, purpura, angitis, pulmonary edema, fever.
<b>GENITOURINARY</b>	none	hematuria, vaginal bleeding, proteinuria, nephrotic syndrome, interstitial nephritis, BUN elevation, renal insufficiency, including renal failure.
<b>MISCELLANEOUS</b>	none	epistaxis; breast changes including enlargement and tenderness, or gynecomastia.

\*Reactions occurring in 3% to 9% of patients treated with indomethacin. (Those reactions occurring in less than 3% of the patients are unmarked).

**Causal Relationship Unknown**

Other reactions have been reported but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility cannot be excluded. Therefore, these observations are being listed to serve as alerting information to physicians:

**Cardiovascular**

**Thrombophlebitis**

Although there has been several reports of leukemia, the supporting information is weak.

**Genitourinary**

**Urinary frequency.**

A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A  $\beta$  hemolytic streptococcus, has been described in persons treated with non-steroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcome (see also **PRECAUTIONS, General**).

**OVERDOSAGE**

The following symptoms may be observed following overdosage: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation 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. Once the stomach has been emptied, 25 or 50 g 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 antacids may be helpful.

The oral LD<sub>50</sub> of indomethacin in mice and rats (based on 14 day mortality response) was 50 and 12 mg/kg, respectively.

**DOSE AND ADMINISTRATION**

Indomethacin is available as 25 and 50 mg capsules for oral use.

Adverse reactions appear to correlate with the size of the dose of indomethacin in most patients but not all. Therefore, every effort should be made to determine the smallest effective dosage for the individual patient.

Always give indomethacin capsules with food, immediately after meals, or with antacids to reduce gastric irritation.

**Pediatric Use**

Indomethacin ordinarily should not be prescribed for pediatric patients 14 years of age and under (see **WARNINGS**).

**Adult Use**

**Dosage Recommendations for Active Stages of the Following**

1. Moderate to severe rheumatoid arthritis including acute flares of chronic disease; moderate to severe ankylosing spondylitis; and moderate to severe osteoarthritis.

Suggested Dosage: Indomethacin capsules 25 mg b.i.d. or t.i.d. If this is well tolerated, increase the daily dosage by 25 or by 50 mg, if required by continuing symptoms, at weekly intervals until a satisfactory response is obtained or until a total daily dose of 150-200 mg is reached. **DOSES ABOVE THIS AMOUNT GENERALLY DO NOT INCREASE THE EFFECTIVENESS OF THE DRUG.**

In patients who have persistent night pain and/or morning stiffness, the giving of a large portion, up to a maximum of 100 mg of the total daily dose at bedtime may be helpful in affording relief. The total daily dose should not exceed 200 mg. In acute flares of chronic rheumatoid arthritis, it may be necessary to increase the dosage by 25 mg or, if required, by 50 mg daily.

If minor adverse effects develop as the dosage is increased, reduce the dosage rapidly to a tolerated dose and **OBSERVE THE PATIENT CLOSELY.**

If severe adverse reactions occur, **STOP THE DRUG.** After the acute phase of the disease is under control, an attempt to reduce the daily dose should be made repeatedly until the patient is receiving the smallest effective dose or the drug is discontinued.

Careful instructions to, and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions. As advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the elderly (See **PRECAUTIONS, Geriatric Use**).

2. Acute painful shoulder (bursitis and/or tendinitis).

Initial Dose:

75-150 mg daily in 3 or 4 divided doses. The drug should be discontinued after the signs and symptoms of inflammation were controlled for several days. The usual course of therapy is 7-14 days.

3. Acute gouty arthritis.

Suggested Dosage:

Indomethacin capsules 50 mg t.i.d. until pain is tolerable. The dose should then be rapidly reduced to complete cessation of the drug. Definite relief of pain has been reported within 2 to 4 hours. Tenderness and heat usually subside in 24 to 36 hours, and swelling gradually disappears in 3 to 5 days.

**HOW SUPPLIED**

Indomethacin Capsules USP are available as green capsules, imprinted 4029, containing 25 mg of indomethacin USP, packaged in bottles of 30, 50, 100, 500, 1000 and unit-dose boxes of 100 capsules; and as green capsules imprinted 4030, containing 50 mg of indomethacin USP, packaged in bottles of 100, 500 and unit-dose boxes of 100 capsules.

**PHARMACIST:** Dispense in a well-closed container as defined in the USP. Use child-resistant closure (as required). Store at controlled room temperature 15°-30° C (59°-86°F) (See USP).

MANUFACTURED BY  
IVAX PHARMACEUTICALS, INC.  
MIAMI, FL 33137

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