PRODUCT MONOGRAPH

INDOCID® 25 mg and 50 mg Capsules
(indomethacin capsules, MSD Std.)

INDOCID® SR 75 mg Capsules (Extended-Release)
(indomethacin extended-release capsules, MSD Std.)

INDOCID® 50 mg and 100 mg Suppositories
(indomethacin suppositories, MSD Std.)

THERAPEUTIC CLASSIFICATION

Non-Steroidal Anti-Inflammatory Drugs

MERCK SHARP & DOHME CANADA
DIVISION OF MERCK FROSST CANADA INC.
KIRKLAND, QUEBEC, CANADA

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Name of Drug

INDOCID® 25 mg and 50 mg Capsules
(indomethacin capsules, MSD Std.)

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THERAPEUTIC CLASSIFICATION

Non-Steroidal Anti-Inflammatory Drugs

ACTION AND CLINICAL PHARMACOLOGY

Indomethacin is a non-steroidal drug that has anti-inflammatory, analgesic, and antipyretic activity. It has a unique chemical structure, which differentiates it from the salicylates, corticosteroids, phenylbutazone-like compounds and colchicine. Unlike corticosteroids, it has no effect on pituitary or adrenal function.

Indomethacin as certain other non-steroidal anti-inflammatory analgesics is an inhibitor of prostaglandin synthesis *in vitro*. Concentrations are reached during therapy which have been demonstrated to have an effect *in vivo* as well.

Although indomethacin does not alter the course of the underlying disease, it has been found effective to relieve pain, reduce fever, swelling and tenderness, and increase mobility in patients with rheumatic disorders of the types listed.

Pharmacokinetics

In man, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 µg/mL at about 2 hours following single oral doses of 25 and 50 mg, respectively. 90 percent of the orally administered indomethacin is absorbed within 4 hours. Indomethacin is eliminated via renal excretion 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 on 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 (1.5 percent as indomethacin).

About 90 percent of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentration.

Capsules INDOCID® SR 75 mg are designed to release 25 mg of the drug initially and the remaining 50 mg over 6 hours or longer. When measured over a 24-hour period, the cumulative amount and time-course of indomethacin absorption from a single capsule INDOCID® SR are similar to those of 3 doses of 25 mg capsules INDOCID® given at 4 to 6 hour intervals. Absorption into the systemic circulation continues over an extended period with 90 percent of the dose absorbed by 12 hours.

INDICATIONS

INDOCID® (indomethacin) is not a simple analgesic, and its use should be limited to those conditions listed below, particularly those cases not responding to conservative measures.

INDOCID® has been found effective in the symptomatic treatment of:

Selected cases of Rheumatoid Arthritis
Ankylosing (Rheumatoid) Spondylitis
Gout
Selected cases of severe Osteoarthritis, including degenerative disease of the hip.

In these conditions INDOCID® may on occasion replace other commonly used agents such as corticosteroids, salicylates, phenylbutazone-like compounds and colchicine.

Capsules INDOCID® SR may be used for all the indications listed for standard INDOCID® capsules except gout. Dose titration should not be attempted with INDOCID® SR. No long term experience is available on INDOCID® SR. Limited clinical studies of six weeks' duration have shown that one capsule INDOCID® SR was clinically similar to one 25 mg capsule INDOCID® t.i.d.; and one capsule INDOCID® SR taken in the morning and evening was clinically similar to one 50 mg capsule INDOCID® t.i.d.

Suppositories INDOCID® are for those patients in whom rectal administration is preferred.

Rheumatoid Arthritis

INDOCID® may be used singly or in combination with other agents. However, it should not be used as a drug of first choice because of the adverse reactions that may occur with its use.

Best results (relief of pain, tenderness, swelling and stiffness) have been obtained in the acute episodes of the disease. However, in many patients with chronic rheumatoid arthritis, INDOCID® produces a significant lessening of pain and stiffness within 48 hours. In other patients, treatment must be continued longer before significant subjective relief or objective evidence of decreased joint swelling and tenderness occur. In some cases of chronic rheumatoid arthritis, it may be necessary to continue treatment for at least a month before concluding that it has not produced significant benefit. Use of INDOCID® may enable reduction of steroid dosage in patients receiving corticosteroids. In such instances, the steroid dosage should be reduced slowly.

Ankylosing (Rheumatoid) Spondylitis

INDOCID® frequently produces marked relief of pain and improved motion of the spine within 3 to 10 days.

Osteoarthritis

INDOCID® should be used in those cases of severe osteoarthritis which do not respond to treatment with such other drugs as the salicylates. In many cases prompt relief of pain is obtained.

Degenerative Joint Disease (Osteoarthritis) of the Hip

INDOCID® has provided relief of pain and increased range of motion in patients with degenerative joint disease of the hip.

Gout

In acute attacks of gout the response to INDOCID® is usually rapid and often dramatic. Marked reduction of pain may be obtained within 2 to 4 hours. Tenderness and heat subside within 24 to 36 hours, and swelling decreases over a 3 to 5 day period.

CONTRAINDICATIONS

As with other anti-inflammatory agents, indomethacin may mask the signs and symptoms of peptic ulcer. Indomethacin itself may cause peptic ulceration or irritation of the gastrointestinal tract. For these reasons, it should not be given to patients with active peptic ulcer, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions.

INDOCID® (indomethacin) is contraindicated in patients who are hypersensitive to any component of this product, and in patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by acetylsalicylic acid (ASA) or other non-steroidal anti-inflammatory agents. Fatal anaphylactoid reactions have occurred in such individuals.

Indomethacin suppositories are contraindicated in subjects with a recent history of rectal bleeding or proctitis.

The drug should not be prescribed for children because safe conditions for use have not been established. In a few cases of severe juvenile rheumatoid arthritis, where INDOCID® was given along with other drugs, severe reactions, including fatalities, were reported.

WARNINGS

Gastrointestinal System

Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with non-steroidal anti-inflammatory drugs (NSAIDs) including INDOCID® (indomethacin).

INDOCID® should be given under close medical supervision to patients prone to gastrointestinal tract irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment.

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from NSAIDs. For such patients, consideration should be given to a starting dose lower than usual, with individual adjustment when necessary and under close supervision. See PRECAUTIONS for further advice.

Central Nervous System

Patients who suffer from dizziness, lightheadedness, or feelings of detachment on indomethacin should be cautioned against operating motor vehicles or other machinery, climbing ladders, etc., if these symptoms are present.

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

Use in Pregnancy

The safety of indomethacin for use in pregnancy has not been established.

Indomethacin has been found to delay parturition in rats. This effect has been described with other non-steroidal anti-inflammatory agents which inhibit prostaglandin synthesis.

In rats, 4.0 mg/kg/day given during the last three days of gestation caused some maternal and fetal deaths. An increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses was observed. At 2.0 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups.

Use in Nursing Mothers

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

PRECAUTIONS

Gastrointestinal System

If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs INDOCID® (indomethacin) should be discontinued, an appropriate treatment instituted and patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of INDOCID® therapy when and if these adverse reactions appear.

Indomethacin, both capsules and suppositories, should be used with caution because of the gastrointestinal reactions which may occur. The incidence of gastrointestinal effects may be decreased by giving the drug immediately after meals, with food or with antacids. The risk of continuing therapy with indomethacin in the face of such symptoms must be weighed against the possible benefits to the individual patient. Indomethacin suppositories should be given with caution to patients with any anal or rectal pathology.

Studies in normal subjects with radioactive chromate-tagged red blood cells indicate that large doses of indomethacin (50 mg four times a day) produce less fecal blood loss than average doses of acetylsalicylic acid (600 mg four times a day). Notwithstanding, indomethacin may cause single or multiple ulceration of the stomach, duodenum, or small and large intestine. There have been reports of severe bleeding and of perforation with a few fatalities. Patients may also develop gastrointestinal bleeding with no obvious ulcer formation. If gastrointestinal bleeding occurs, discontinue using the drug. In many patients with peptic ulceration, a history of a previous ulcer was present or they were on concomitant steroids, salicylates or phenylbutazone. A possible potentiation of the ulcerogenic effect of these drugs cannot be ruled out at present. In some patients there was no history of a previous ulcer and other drugs were not being given. As a result of obvious or occult gastrointestinal bleeding some patients may manifest anemia. For this reason appropriate blood determinations are recommended periodically.

Renal Function

As with other non-steroidal anti-inflammatory drugs, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome in patients receiving long-term administration of indomethacin.

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. 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 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-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.

Hepatic Function

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 (ALAT) or SGOT (ASAT) 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 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.

During long-term therapy, liver function tests should be monitored periodically. If this drug is to be used in the presence of impaired liver function, it must be done under strict observation.

Fluid and Electrolyte Balance

Fluid retention and peripheral edema 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.

Serum electrolytes should be monitored periodically during long-term therapy, especially in those patients at risk.

Hematology

Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when INDOCID® is administered.

Blood dyscrasias associated with the use of non-steroidal anti-inflammatory drugs are rare, but could have severe consequences.

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 hemostatic defects, INDOCID® should be used with caution in persons with coagulation defects.

Infection

In common with other drugs which have anti-inflammatory, analgesic and antipyretic properties, indomethacin possesses the potential of masking the signs and symptoms which ordinarily accompany infectious disease. The physician must 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, infections.

Ophthalmology

Corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients with rheumatoid arthritis on prolonged therapy with indomethacin. Similar eye changes have been observed in some patients with this disease who have not received indomethacin. Nevertheless, where therapy is prolonged, it is desirable to perform ophthalmological examinations at periodic intervals.

Central Nervous System

Headache may occur, usually early in treatment with indomethacin. If headache persists despite dosage reduction therapy with indomethacin shoud be discontinued. (Also, see WARNINGS).

Hypersensitivity Reactions

Patients should be followed carefully to detect unusual manifestations of drug sensitivity, and since advancing years appear to increase the possibility of adverse reactions, indomethacin should be used with greater care in the elderly.

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 hemorrhage. The coadministration of diflunisal and INDOCID® results in a 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.

Anticoagulants

Controlled clinical studies have shown that INDOCID® did not influence the hypoprothrombinemia produced by the use of anticoagulants in patients and in normal subjects. However, when any additional drug, including INDOCID®, is added to the treatment of patients on anticoagulant therapy, the patient should be observed closely for alterations of the prothrombin time.

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®.

Beta-adrenergic Receptor Blocking Agents

A decrease in the antihypertensive 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.

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.

Lithium

Indomethacin 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 the Product Monograph for lithium preparation 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.

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 therapeutic effect. When increases in the dose of INDOCID® are made under these circumstances, they should be made cautiously and in small increments.

Clinical Lab Tests

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.

ADVERSE REACTIONS

The most common adverse reactions encountered with NSAIDs are gastrointestinal, of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion, particularly in the elderly.

The adverse reactions for INDOCID® (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 INDOCID® and these adverse reactions, some of which have been reported only rarely.

In controlled clinical trials, the incidence of adverse reactions to INDOCID® SR Capsules and equal 24-hour doses of Capsules INDOCID® were similar.

The adverse reactions reported with INDOCID® Capsules may occur with use of the suppositories. In addition, rectal irritation and tenesmus have been reported in patients who have received the suppositories.

Incidence >1%	Incidence <1%	
GASTROINTESTINAL		
Nausea[X] with or without vomiting	Anorexia	Gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum,) carcinoma, etc.) development of ulcerative colitis and regional ileitis
Dyspepsia[X] (including indigestion, heartburn and epigastric pain)	Bloating (includes distention)	Ulcerative stomatitis
Diarrhea	Flatulence	Toxic hepatitis and jaundice (some fatal cases have been reported)
Abdominal distress or pain	Peptic ulcer	
Constipation	Gastroenteritis	
	Rectal bleeding	
	Proctitis	
	Single and multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestines	
	Intestinal ulceration associated with stenosis and obstruction	

X Reactions occurring in 3% to 9% of patients treated with INDOCID® (Those reactions occurring in less than 3% of the patients are unmarked.)

Incidence >1%	Incidence <1%	
CENTRAL NERVOUS SYSTEM		
Headache	Anxiety (includes nervousness)	Lightheadedness
Dizziness[X]	Muscle weakness	Syncope
Vertigo	Involuntary muscle movements	Paresthesia
Somnolence	Insomnia	Aggravation of epilepsy and parkinsonism
Depression and fatigue (including malaise and listlessness)	Muzziness	Depersonalization
	Psychic disturbances including psychotic episode	Coma
	Mental confusion	Peripheral neuropathy
	Drowsiness	Convulsions
		Dysarthria
DERMATOLOGIC		
None	Pruritus	Exfoliative dermatitis
	Rash: urticaria	Erythema nodosum
	Petechiae or ecchymosis	Loss of hair
		Stevens-Johnson syndrome
		Erythema multiforme
		Toxic epidermal necrolysis
CARDIOVASCULAR		
None	Hypertension	Congestive heart failure
	Hypotension	Arrhythmia; palpitations
	Tachycardia	
	Chest pain	

[X] Reactions occurring in 3% to 9% of patients treated with INDOCID® (Those reactions occurring in less than 3% of the patients are unmarked.)

Incidence >1%	Incidence <1%	
SPECIAL SENSES		
Tinnitus	Ocular - corneal deposits and retinal disturbances including those of the macula, have been reported in some patients on prolonged therapy with INDOCID®	Blurred vision, diplopia Hearing disturbances, deafness
HEMATOLOGIC		
None	Leukopenia Bone marrow depression Anemia secondary to obvious or occult gastrointestinal bleeding	Aplastic anemia Hemolytic anemia Agranulocytosis Thrombocytopenic purpura Disseminated intravascular coagulation
GENITOURINARY		
None	Hematuria Vaginal bleeding Proteinuria Nephrotic syndrome Interstitial nephritis	BUN elevation Renal insufficiency, including renal failure
HYPERSENSITIVITY		
None	Acute anaphylaxis Acute respiratory distress Rapid fall in blood pressure resembling a shock-like state Angioedema	Dyspnea Asthma Purpura Angiitis Pulmonary edema

Incidence >1%	Incidence <1%	
METABOLIC		
None	Edema	Hyperglycemia
	Weight gain	Glycosuria
	Fluid retention	Hyperkalemia
	Flushing or sweating	
MISCELLANEOUS		
None	Epistaxis	
	Breast changes, including enlargement and tenderness, or gynecomastia	

The following local adverse reactions have been associated with the use of suppositories INDOCID®:

- tenesmus
- proctitis
- rectal bleeding
- burning
- pain
- discomfort
- itching

ADVERSE REACTIONS - CAUSAL RELATIONSHIP UNKNOWN

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

Cardiovascular
Thrombophlebitis

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

Genitourinary
Urinary frequency

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Relatively little experience is available recording overdosage with indomethacin. Nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy might be observed. There have been reports of paresthesias, numbness, and convulsions. Signs of gastrointestinal hemorrhage could appear but have not been reported following the acute ingestion of large amounts of indomethacin accidentally or intentionally.

Treatment of overdosage: 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.

DOSAGE AND ADMINISTRATION

INDOCID® (indomethacin) is available in the following dosage forms:

Capsules: 25 mg or 50 mg as standard capsules
75 mg as extended-release capsules (pelletized form).

Rectal suppositories: each containing 50 mg or 100 mg of indomethacin.

In chronic disorders, treatment should be started with a dosage of 25 mg two or three times a day. By starting therapy with low dosage, increased gradually when necessary, maximum benefit will be produced with fewer adverse reactions. Always give INDOCID® with food immediately after meals or with antacids to reduce gastric irritation.

As with all drugs, the lowest possible effective dose should be utilized for each individual patient.

The drug should not be prescribed for children because safe conditions for use have not been established.

Since advancing years appear to increase the possibility of adverse reactions, INDOCID® should be used with greater care in the elderly.

Adult Dosage Recommendations

1. Rheumatoid arthritis and ankylosing (Rheumatoid) spondylitis.

   Initial Dosage: 25 mg two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg at about weekly intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg a day is reached.

   If a satisfactory response is not obtained with 200 mg a day, larger doses probably will not be effective.

If adverse reactions develop as the dosage is increased, reduce the dosage to a tolerated level and maintain this for 3 to 4 weeks. If an adequate response has not been obtained, gradually increase the daily dosage by 25 mg at about weekly intervals to 150 mg to 200 mg a day.

For patients with acute rheumatoid arthritis or with acute flares of chronic rheumatoid arthritis, increase the dosage daily by 25 mg until a satisfactory response is obtained or a total daily dosage of 150 to 200 mg is reached. If adverse effects develop as the dosage is increased, the dosage should be reduced to a tolerated level for 2 or 3 days, and then gradually increased by 25 mg every few days as tolerated. After the acute phase is under control, it is often possible to reduce the daily dosage gradually to 75 to 100 mg.

Reduction of Steroid Dosage: Use of indomethacin often will permit a gradual reduction of steroid dosage by 25 to 50 percent. In some patients steroids can be slowly discontinued over a period of several weeks or months. The usual precautions should be observed in withdrawing steroids.

2. Severe Osteoarthritis and Degenerative Joint Disease of the Hip.

   Initial Dosage: 25 mg two or three times a day. If the response is not adequate, increase the daily dosage by 25 mg at about weekly intervals until a satisfactory response is obtained or a dosage of 150 to 200 mg a day is reached. If a satisfactory response is not obtained with 200 mg a day, larger doses will probably not be effective.

If adverse reactions develop as the dosage is increased, reduce the dosage to a tolerated level and maintain this for 3 to 4 weeks. If an adequate response has not then been obtained, gradually increase the daily dosage by 25 mg at about weekly intervals to 150 to 200 mg a day.

3. Gout.

   To Control Acute Attacks: 50 mg three times a day until all signs and symptoms subside. 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.

Use of Alternate Dosage Forms

INDOCID® SR 75 mg capsule

INDOCID® SR may be tried after the daily dose has been established using the standard capsules and found to fall within 75-150 mg range. Patients stabilized on 25 mg three times daily should be tried on one SR capsule once daily and those stabilized on 50 mg three times daily should be tried on one SR capsule twice daily.

Suppositories INDOCID®

The recommended dosage of INDOCID Suppositories is 100 to 200 mg daily and should be individually adjusted to the patient's response and tolerance. Daily dose of 100 mg can be given as 50 mg twice daily or as 100 mg at night. Doses higher than 100 mg must be given on a twice daily schedule.

Combined Administration

One 50 mg or 100 mg suppository at bedtime, supplemented the following day by 25 mg capsules as needed up to a total of 150 mg to 200 mg of indomethacin. The total daily dose of INDOCID® (capsules and suppositories) should not exceed 200 mg.

AVAILABILITY

Capsules INDOCID® for oral administration contain either 25 mg or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, gelatin, lactose, lecithin, magnesium stearate. The gelatin capsule contains FD & C Blue 1, FD & C Red 3, and titanium dioxide.

Capsules INDOCID® SR for extended-release oral administration contain 75 mg of indomethacin and the following inactive ingredients: cellulose, confectioner's sugar, FD & C Blue 2, gelatin, hydroxypropyl methylcellulose, magnesium stearate, polyvinyl acetate-crotonic acid copolymer, starch; the gelatin capsule contains FD & C Yellow 6, FD & C Yellow 10, and titanium dioxide. The product conforms to the requirements of the USP Drug Release Test No. 1.

Suppositories INDOCID® for rectal use contain either 50 mg or 100 mg of indomethacin and the following inactive ingredients: butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000 and sodium chloride for 50 mg only.

They are supplied as follows:

Ca 8662 - INDOCID® Capsules, 25 mg each, are opaque blue and white, imprinted with the MSD trademark in black and potency, and are supplied in bottles of 100 and 1,000.

Ca 8663 - INDOCID® Capsules, 50 mg each, are opaque blue and white, imprinted with the MSD trademark in black and potency, and are supplied in bottles of 100 and 500.

Ca 8863X - INDOCID® SR Capsules, 75 mg each, are opaque with yellow cap and clear body, containing a mixture of blue and white pellets, imprinted with the MSD trademark in black and "693". They are supplied in blisters of 30 and in bottles of 30 and 250.

Ca 8760 - INDOCID® Suppositories, 50 mg each are white opaque suppositories supplied in boxes of 30.

Ca 8711 - INDOCID® Suppositories, 100 mg each, are white opaque suppositories supplied in boxes of 30.

INFORMATION TO THE PATIENT

(Detailed information is provided to physicians and pharmacists)

NAME

INDOCID® is the proprietary name of Merck Sharp & Dohme for indomethacin.

PURPOSE OF THIS MEDICINE

INDOCID® which has been prescribed to you by your physician, is one of a large group of non-steroidal anti-inflammatory drugs (NSAIDs) and is used to treat the symptoms of certain types of arthritis, including gout. It helps to relieve joint pain, swelling, stiffness and fever by reducing the production of certain substances (prostaglandins) and helping to control inflammation and other body reactions.

IMPORTANT NOTICE

ADVISE YOUR PHYSICIAN

- If you ever had an allergic reaction (especially difficulty breathing, a runny nose, skin rashes or hives)

    . to INDOCID®
    . to acetylsalicylic acid (ASA) (ASA is the active ingredient of many pain and fever preparations that can be sold without prescription).
    . to any other anti-inflammatory medication used in the treatment of arthritis such as acetylsalicylic acid, diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, mefenamic acid, piroxicam, sulindac, tiaprofenic acid or tolmetin;

A previous allergic reaction to one of these could increase the risk of an allergic reaction to INDOCID®.

- If you ever had an ulcer, with or without bleeding, of the stomach, duodenum, or any part of the digestive tract, liver or kidney diseases or any other medical problems.

- If you are taking other medications (non-prescription or prescription drugs), particularly medications to thin the blood (anticoagulants) or medications to lower the level of sugar in the blood (hypoglycemic agents).

IF SUCH IS THE CASE, YOUR PHYSICIAN WILL ADVISE YOU ON THE APPROPRIATE COURSE OF ACTION.

Note also that INDOCID® is not recommended for use during pregnancy and that breast-feeding should not be undertaken while on INDOCID®.

AVAILABILITY

INDOCID® is supplied in three dosage forms.

Capsules INDOCID® for oral administration contain either 25 mg or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, gelatin, lactose, lecithin, magnesium stearate. The gelatin capsule contains FD & C Blue 1, FD & C Red 3, and titanium dioxide.

Capsules INDOCID® SR for extended-release oral administration contain 75 mg of indomethacin and the following inactive ingredients: cellulose, confectioner's sugar, FD & C Blue 2, gelatin, hydroxypropyl methylcellulose, magnesium stearate, polyvinyl acetate-crotonic acid copolymer, starch; the gelatin capsules contains FD & C Yellow 6, FD & C Yellow 10, and titanium dioxide. The product conforms to the requirements of the USP Drug Release Test No. 1.

Suppositories INDOCID® for rectal use contain either 50 mg or 100 mg of indomethacin and the following inactive ingredients: butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000 and sodium chloride for 50 mg only.

HOW TO USE THIS MEDICINE

To lessen stomach upset, take this medicine immediately after a meal or with food or milk. If stomach upset (indigestion, nausea, vomiting, stomach pain or diarrhea) occurs and continues, contact your physician.

PLEASE ADHERE TO THE DOSAGE AND ADMINISTRATION INSTRUCTIONS WHICH YOUR PHYSICIAN HAS GIVEN YOU

- Do not take more of it, do not take it more often, and do not take it for a longer period of time than your physician prescribed

- If you are taking INDOCID® to relieve arthritis, you must take it regularly as prescribed by your physician. In some types of arthritis, up to 2 weeks may pass before you begin to feel better and up to 1 month may pass before you feel the full effects of this medicine.

IF YOU MISS A DOSE...

If you miss a dose of INDOCID® and remember within an hour or so, take it right away. Then go back to your regular dosing schedule.

But if you do not remember until later, do not take the missed dose at all and do not double the next one. Instead, go back to your regular dosing schedule.

Do not take ASA (acetylsalicylic acid), ASA-containing compounds or other drugs used to relieve symptoms of arthritis while taking INDOCID® unless directed to do so by your physician.

If you are prescribed this medication for use over a long period of time, your physician will check your health during regular visits to assess your progress and to ensure that this medication is not causing unwanted effects.

Along with its beneficial effects, INDOCID® like other NSAID drugs, may cause some undesirable reactions. Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects. Although not all of these side effects are common, when they do occur they may require medical attention. Check with your physician immediately if any of the following are noted:

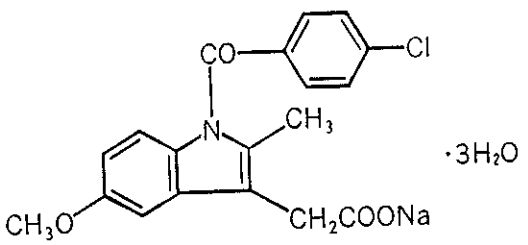
bloody or black tarry stools;
shortness of breath, wheezing, any trouble in breathing or tightness in the chest;
skin rash, swelling, hives or itching;
indigestion, nausea, vomiting, stomach pain or diarrhea;
yellow discolouration of the skin or eyes, with or without fatigue;
any changes in the amount or colour of your urine (such as dark; red or brown);
swelling of the feet or lower legs;
blurred vision or any visual disturbance;
mental confusion, depression, dizziness, lightheadedness; hearing problems.

While taking this medication:

- tell any other physician, dentist or pharmacist that you consult or see, that you are taking this medication;
- be cautious about driving or participating in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication;
- check with your physician if you are not getting any relief or if any problems develop;
- report any untoward reactions to your physician. This is very important as it will aid in the early detection and prevention of potential complications.
- your regular medical checkups are essential;
- if you require more information on this drug, consult your physician or pharmacist.
- keep this medication, and all others, out of the reach of children.

CHEMISTRY

The chemical name for indomethacin is 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. The empirical formula is $C_{19}H_{16}ClNO_4$ (molecular weight 357.80). It has the following structural formula:



Indomethacin occurs as a yellowish-white powder with a melting point of about 156° 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.

PHARMACOLOGY

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 edema induced by subplantar injection of carrageenin in rats. The latter appears to correlate well with anti-rheumatic activity in man. Assays of relative potency indicated that indomethacin was more potent than acetylsalicylic acid, phenylbutazone or hydrocortisone, the potency ratios varied with the test employed. Good anti-inflammatory effect is exhibited in rats at 1/20th of the average human dose.

The inhibition of carrageenin-induced edema by indomethacin is specific; the compound failed to inhibit edema induced by a variety of agents other than carrageenin, nor did it reduce edema if the drug was administered after the edema 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 given to 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 greater than that of either drug alone in comparable doses.

Recent experiments have shown indomethacin to have a favorable 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 anti-arthritic activity.

Antipyretic Activity

The antipyretic activity of indomethacin has been demonstrated in rabbits and rats injected with bacterial pyrogen, and in the classical yeast-induced fever assay in rats. A direct comparison of peak antipyretic activity in the yeast fever test showed indomethacin to be about 9 times as potent as 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 observations in patients with a variety of febrile conditions. However, indomethacin should not be used as an antipyretic agent.

Analgesic Activity

Laboratory tests designed to detect mild analgesic activity indicate that indomethacin is more potent than acetylsalicylic acid or aminopyrine. However, indomethacin should not be given as a simple analgesic.

ANIMAL TOXICOLOGY

Indomethacin had been given to nine species of animals in short and long term studies. However, with the exception of pigs and chickens, the human dose is not tolerated. The main toxic signs exhibited are inflammation and/or ulceration of the gastrointestinal mucosa and diarrhea.

Reproduction and teratogenic studies in mice, rats and rabbits showed no effect on fetal development or the reproduction cycle. There was some decrease in fetal viability and some delay in the onset of parturition in the rat, as has been observed with other non-steroid anti-inflammatory agents. A similar delay in the onset of parturition was not observed in the rabbit. Studies in mice demonstrated that indomethacin crosses the placental barrier.

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