

## INDOLIN

## Capsules & Suppositories

### Composition

#### Indolin Capsules

Each capsule contains Indomethacin 25 mg.

#### Indolin Suppositories

Each suppository contains Indomethacin 100 mg.

### Action

Indomethacin has anti-inflammatory and analgesic-antipyretic properties. The anti-inflammatory effects of indomethacin are evident in patients with rheumatoid and other types of arthritis and in acute gout. Although indomethacin is more potent than aspirin, the anti-inflammatory effects of tolerated doses of indomethacin in rheumatoid arthritis are not superior to those of salicylate. Whether indomethacin has analgesic properties distinct from its anti-inflammatory effects remains uncertain. However, in patients with acute post-operative and post-traumatic pain of mild to moderate intensity, single doses of indomethacin provide relief approximately equivalent to that of 600 mg of aspirin. The antipyretic effect of indomethacin has also been readily demonstrated in patients with fever. Single doses of indomethacin are usually adequately tolerated; however, because of its potential toxicity, indomethacin is not recommended as a general analgesic-antipyretic.

Like the salicylates and related anti-inflammatory agents, indomethacin inhibits the biosynthesis of prostaglandins; this action may be the basis of its anti-inflammatory and antipyretic properties and certain of its other effects. Like colchicine, it inhibits motility of polymorphonuclear leucocytes; like salicylate, it uncouples oxidative phosphorylation in cartilaginous and hepatic mitochondria.

### Pharmacokinetics

Indomethacin is rapidly and almost completely absorbed from the gastro-intestinal tract. Peak plasma concentrations is attained within 2 hours in fasting subjects but may be somewhat delayed when taken after meals. Indomethacin is 90% bound to plasma proteins and extensively bound to tissues. The concentration of indomethacin in the cerebrospinal fluid is low.

Indomethacin is largely converted to inactive metabolites. About half of a single oral dose is O-demethylated and about 10% is conjugated with glucuronic acid by the hepatic microsomal enzymes. A portion is also N-deacylated by a non-microsomal system. Some of these metabolites are detectable in plasma, and free and conjugated metabolites are eliminated in the urine, bile, and faeces.

Entero-hepatic cycling of the conjugates takes place. 10 - 20% of the indomethacin is excreted unchanged in the urine, in part by tubular secretion. The plasma half-life is extremely variable and ranges between 2 and 11 hours.

### Indications

Indolin has been found to be effective in active stages of the following:

- moderate to severe rheumatoid arthritis, including acute flares of chronic disease
- moderate to severe ankylosing spondylitis
- moderate to severe osteoarthritis
- acute musculoskeletal disorders such as bursitis, tendinitis, synovitis, tenosynovitis, and in low back pain
- acute gouty arthritis
- pain and associated symptoms of primary dysmenorrhea.

### Contraindications

- Known hypersensitivity to indomethacin.
- Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by acetylsalicylic acid or other NSAID's.

- Indomethacin is not recommended for use in pregnant women and nursing mothers because of the known effect of drugs of this class on the human fetal cardiovascular system (closure of the ductus arteriosus) during the third trimester of pregnancy.
- Indomethacin should not be administered to patients with active gastrointestinal lesions, or with a history of recurrent gastrointestinal lesions. Indomethacin suppositories are contraindicated in patients with a history of proctitis or recent rectal bleeding.

### **Warnings**

Because of the variability of the potential of Indomethacin to cause adverse reactions in the individual patient, the lowest possible effective dosage should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150-200 mg/day, without corresponding improved clinical benefits.

Proper instruction and observation of, the individual patient are essential in the prevention of serious adverse reactions.

As advancing years appear to increase the possibility of adverse reactions, Indolin should be used with particular caution in elderly patients.

### **Gastrointestinal**

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's. Although minor upper gastrointestinal problems, such as dyspepsia, are common and usually develop early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAID's, even in the absence of previous gastrointestinal tract symptoms.

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 (e.g. diverticulum, carcinoma) has occurred. Increased abdominal pain in ulcerative colitis patients, or the development of ulcerative colitis and regional ileitis, has 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 signalling 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.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. With the exception of a prior history of serious gastrointestinal events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism and smoking, 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 do, and most spontaneous reports of fatal gastrointestinal events are in this population.

### **Renal**

As with other NSAID's, 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, and advanced age, extracellular volume depletion from any cause, congestive heart failure, septicaemia, pyelonephritis, or concomitant use of any nephrotoxic drug. Discontinuation of NSAID therapy is typically followed by recovery to the pre-treatment 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.

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

### **Hepatic**

As with other NSAID's, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, remain essentially unchanged, or be transient with continued therapy. The serum glutamic pyruvic transaminase (SGPT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or (serum glutamic oxaloacetic transaminase) (SGOT) occurred in controlled clinical trials in less than 1% of patients.

Patients with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has been reported, should be evaluated for evidence of the development of more severe hepatic reactions while on therapy with Indomethacin. Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with indomethacin, as with other NSAID's. Although such reactions are rare, if abnormal liver tests persist or worsen, or clinical signs and symptoms consistent with liver disease develop, or systemic manifestations occur (e.g. eosinophilia, rash, etc.), Indomethacin should be discontinued.

### **Ocular**

Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who 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**

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. Patients should be warned that their ability to perform potentially hazardous tasks requiring mental alertness or physical coordination, such as driving a vehicle or operating machinery, might be impaired. Indomethacin may also cause headache. Headache that persists despite dosage reduction requires the cessation of Indomethacin therapy.

### **Pregnancy and Breastfeeding**

See Contraindications.

### **Paediatric Use**

Safe conditions for use in children have not been established. Therefore, Indomethacin should not be prescribed for children 14 years of age and under, except in circumstances where lack of efficacy or toxicity associated with other drugs warrant the risk. Such patients should be monitored closely.

### **Adverse Reactions**

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

#### **Incidence Greater than 1%**

##### *Gastrointestinal*

Nausea with or without vomiting, dyspepsia including indigestion, heartburn and epigastric pain, diarrhea, abdominal distress or pain and constipation.

##### *Central Nervous System*

Headache, dizziness, vertigo, somnolence, depression and fatigue (including malaise and listlessness).

##### *Special Senses*

Tinnitus.

#### **Incidence Less than 1%**

##### *Gastrointestinal*

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 (e.g. diverticulum, carcinoma), development of ulcerative colitis and regional ileitis, ulcerative stomatitis, toxic hepatitis and jaundice (some fatal cases have been reported).

##### *Central Nervous System*

Anxiety (including nervousness), muscle weakness, involuntary muscle movements, insomnia, muzziness, psychic disturbances including psychotic episodes, mental confusion, drowsiness, light headedness, syncope, paresthesia, aggravation of epilepsy and parkinsonism, depersonalization, coma, peripheral neuropathy, convulsions and dysarthria.

##### *Special Senses*

Corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with indomethacin; blurred vision, diplopia, hearing disturbances and deafness.

##### *Cardiovascular*

Hypertension, hypotension, tachycardia, chest pain, congestive heart failure, arrhythmia and palpitations.

##### *Metabolic*

Edema, weight gain, fluid retention, flushing or sweating, hyperglycemia, glycosuria and hyperkalemia.

##### *Integumentary*

Pruritus, rash, urticaria, petechiae or ecchymosis, exfoliative dermatitis, erythema nodosum, loss of hair, Stevens-Johnson syndrome, erythema multiforme and toxic epidermal necrolysis.

##### *Hematological*

Leukopenia, bone marrow depression, anemia secondary to obvious or occult gastrointestinal bleeding, aplastic anemia, hemolytic anemia, agranulocytosis, thrombocytopenic purpura and disseminated intravascular coagulation.

### *Hypersensitivity*

Acute anaphylaxis, acute respiratory distress, rapid fall in blood pressure resembling a shock-like state, angioedema, dyspnea, asthma, purpura, angiitis and pulmonary edema.

### *Genitourinary*

Hematuria, vaginal bleeding, proteinuria, nephrotic syndrome, interstitial nephritis, blood urea nitrogen (BUN) elevation and renal insufficiency including renal failure.

### *Miscellaneous*

Epistaxis, breast changes including enlargement and tenderness or gynecomastia.

## **Precautions**

Indomethacin may mask the usual signs and symptoms of infection. Therefore, physicians must be continually on the alert for onset of infection, and should use the drug with extra care in the presence of existing, controlled infection.

Fluid retention and peripheral edema have been reported in some patients taking indomethacin. Therefore, as with other NSAID's, 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 hemodynamic, presumably due to inhibition of prostaglandin-dependent compensatory mechanisms.

Indomethacin, like other NSAID's, can inhibit platelet aggregation. This effect is of shorter duration than that observed with acetylsalicylic acid, 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.

## **Drug Interactions**

### *Indomethacin/ Anticoagulants*

Although indomethacin does not influence the hypoprothrombinemia produced by anticoagulants, the gastrointestinal ulceration or hemorrhage potential of indomethacin may cause increased risk to patients receiving anticoagulant therapy.

### *Indomethacin/ Digoxin*

Concomitant administration 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.

### *Indomethacin/ Probenecid*

Concurrent administration with probenecid may increase the serum levels of indomethacin, possibly enhancing its effectiveness and/or increasing the potential for toxicity.

### *Indomethacin/ Acetylsalicylic Acid*

The use of indomethacin in conjunction with acetylsalicylic acid or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of indomethacin and acetylsalicylic acid does not produce any greater therapeutic effect than the use of indomethacin alone. Furthermore, in one of these clinical studies, the incidence of gastrointestinal side effects was significantly increased with combined therapy. In a study in normal volunteers, it was found that chronic concurrent administration of 3.6 grams of acetylsalicylic acid per day decreases indomethacin blood levels by approximately 20%.

### *Indomethacin/ Diflunisal*

Concurrent use is not recommended, since fatal gastrointestinal hemorrhage has been reported.

#### *Indomethacin/ Lithium*

Concurrent administration may cause elevated plasma lithium levels. Patients should be observed for signs of lithium toxicity.

#### *Indomethacin/ Furosemide/ Thiazide Diuretics*

Concurrent administration may reduce the natriuretic and antihypertensive effect of furosemide and thiazides in some patients.

#### *Indomethacin/ Triamterene/ Potassium-sparing Diuretics*

Concurrent use with triamterene is not recommended, since possible renal toxicity may result. Indomethacin and potassium-sparing diuretics, each by itself, may lead to increased serum potassium levels. Therefore, 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.

#### *Indomethacin/ Antihypertensive Medications*

Co-administration of indomethacin and some antihypertensive agents has resulted in an acute attenuation of the latter's hypotensive effects, due at least in part to indomethacin inhibition of prostaglandin synthesis. The prescriber should, therefore, exercise caution when considering the addition of indomethacin to the regimen of a patient taking one of the following antihypertensive agents: an alpha-adrenergic blocking agent (such as prazosin), an angiotensin converting enzyme inhibitor (such as captopril or lisinopril), a  $\beta$ -adrenergic blocking agent, a diuretic, or hydralazine.

#### *Indomethacin/ Phenylpropanolamine*

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

#### *Indomethacin/ Methotrexate*

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

#### *Indomethacin/ Cyclosporine*

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

### **Diagnostic Interference**

False-negative results in the Dexamethasone suppression test (DST) in patients treated with indomethacin have been reported. Therefore, results of the DST should be interpreted with caution in these patients.

### **Dosage and Administration**

#### **Oral Therapy**

Indolin should always be taken with food, immediately after meals, or with antacids, to reduce gastric irritation.

#### **Rheumatoid Arthritis, Ankylosing Spondylitis and Osteoarthritis**

In moderate to severe conditions of rheumatoid arthritis (including acute flares of chronic disease), ankylosing spondylitis and osteoarthritis, administer 1 Indolin capsule, 2 or 3 times daily.

If this is well tolerated, 25 or 50 mg may increase the daily dosage at weekly intervals, if required by continuing symptoms, 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 administration of a large portion, up to a maximum of 100 mg, of the total daily dose at bedtime, either orally or by rectal suppositories, 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, the dosage should be reduced rapidly to a tolerated dose, and the patient observed closely. If severe adverse reactions occur, the drug should be discontinued. 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 prevent serious, irreversible, and even fatal adverse reactions.

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

#### **Acute Musculoskeletal Disorders**

The recommended initial dosage for the management of acute musculoskeletal disorders such as bursitis, tendinitis, synovitis and tenosynovitis, and for low back pain is 75-150 mg daily, in 3 or 4 divided doses. The drug should be discontinued after the signs and symptoms of inflammation have been controlled for several days. The usual course of therapy is 7-14 days.

#### **Acute Gouty Arthritis**

Suggested dosage is 50 mg 3 times daily, 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 2-4 hours. Tenderness and heat usually subside within 24-36 hours, and swelling gradually disappears within 3-5 days.

#### **Primary Dysmenorrhea**

3 Indolin capsules in divided doses, starting with onset of cramps or bleeding, and continuing for as long as the symptoms usually last.

#### **Rectal Therapy**

In rheumatic and musculoskeletal disorders, Indolin suppositories may be used as an alternative to Indolin capsules. The usual dosage is one suppository, 1-2 times a day. One suppository should be used at bedtime. If another is necessary, it should be used in the morning.

#### **Over Dosage**

##### **Manifestations**

The following symptoms may be observed following oral over dosage: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, or lethargy. There have been reports of paresthesias, numbness and convulsions.

##### **Treatment**

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 grams of activated charcoal may be given.

Depending on the condition of the patient, close medical observation and nursing may be required.

The patient should be followed for several days, because gastrointestinal ulceration and hemorrhage have been reported as adverse reactions of indomethacin. Administration of antacids may be helpful.

**Presentation**

**Indolin Capsules**

Box of 20 capsules

**Indolin Suppositories**

Box of 12 suppositories