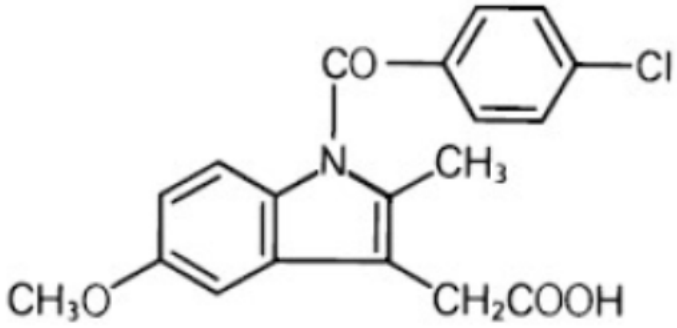
Approved Date: April 9th, 2007
Revision Date: December 1st, 2015

Package Insert of Indomethacin sustained-release Capsules

Please read the package insert carefully and use according to doctor's instructions.

[Drug Name]
Generic Name: Indomethacin sustained-release Capsules
Chinese Pinyin: Yinduomeixin Huanshi Jiaonang

[Active Ingredients]
The active pharmaceutical ingredient (API) of this product is Indomethacin.
Chemical Name of the API: 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid.
Structural Formula:



Molecular Formula: $C_{19}H_{15}ClNO_{46}$
Molecular Weight: 357.80

[Inactive Ingredients]
Starch, Sucrose, Sucrose Stearate, Pharmaceutical Grade Sucrose Pellet, Purified Water, Acrylic Resin, Castor oil, Alcohol.

[Properties]
This product is a capsule containing white, off-white, yellow pellets.

[Indications]
Carefully consider the potential benefits and risks of indomethacin extended-release capsules and other treatment options before deciding to use indomethacin extended-release capsules. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.
Indomethacin extended-release 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).

Indomethacin extended-release capsules is not recommended for the treatment of 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.

[Strength]
75 mg

[Dosage and Administration]
Carefully consider the potential benefits and risks of indomethacin extended-release capsules and other treatment options before deciding to use indomethacin extended-release capsules. Use the lowest effective dose for the shortest duration consistent with individual patient treatment goals.

Indomethacin extended-release capsules 75 mg are available for oral use. Indomethacin extended release capsules can be administered once a day and can be substituted for indomethacin 25 mg capsules t.i.d. However, there will be significant differences between the two dosage regimens in indomethacin blood levels, especially after 12 hours (see CLINICAL PHARMACOLOGY). In addition, indomethacin extended-release capsules 75 mg b.i.d. can be substituted for indomethacin 50 mg capsules t.i.d.

Indomethacin extended-release capsules may be substituted for all the indications of indomethacin capsules except acute gouty arthritis.

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 extended-release capsules 75 mg with food, immediately after meals or with antacids to reduce gastric irritation.

[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. In controlled clinical trials, the incidence of adverse reactions to indomethacin extended-release capsules and equal 24-hour doses of indomethacin capsules were similar.

Incidence greater than 1%	**Incidence less than 1%**	
Gastrointestinal		
Nausea* with or without vomiting Dyspepsia* (including indigestion, heartburn and epigastric pain) Diarrhea Abdominal distress or pain Constipation	Anorexia Bloating (included distention) 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 preexisting 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)
Central Nervous System		
Headache (11.7%) Dizziness*	Anxiety (includes nervousness) Muscle weakness	Light-headedness, Syncope Paresthesia

Vertigo Somnolence Depression and fatigue (including malaise and listlessness)	Involuntary muscle movements Insomnia, Muzziness Psychic disturbances including psychotic episodes Mental confusion Drowsiness	Aggravation of epilepsy and parkinsonism Depersonalization Coma Peripheral neuropathy Convulsions Dysarthria
Special Senses		
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 Diplopia Hearing disturbances, deafness
Cardiovascular		
None	Hypertension Hypotension Tachycardia Chest pain	Congestive heart failure Arrhythmia; palpitations
Metabolic		
None	Edema Weight gain Fluid retention Flushing or sweating	Hyperglycemia Glycosuria Hyperkalemia
Integumentary		
None	Pruritus Rash; urticaria Petechiae or ecchymosis	Exfoliative dermatitis Erythema nodosum Loss of hair Stevens-Johnson Syndrome Erythema mulitforme Toxic epidermal necrolysis
Hematologic		
None	Leukopenia Bone marrow depression Anemia secondary to obvious or occult gastrointestinal bleeding	Aplastic anemia Hemolytic anemia Agranulocytosis Thrombocytopenic purpura Disseminated intravascular coagulation
Hyper sensitivity		
None	Acute anaphylaxis Acute respiratory distress Rapid fall in blood pressure resembling a shock-like state Angioedema	Dyspnea Asthma Purpura Angiitis Pulmonary edema Fever
Genitourinary		
None	Hematuria Vaginal bleeding Proteinuria	BUN elevation Renal insufficiency including renal

	Nephritic syndrome Interstitial nephritis	failure
Miscellaneous		
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 Relations hip 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:
A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A β-hemolytic streptococcus, has been described in persons treated with nonsteroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcome.
Cardiovascular: Thrombophlebitis.
Hematologic: Although there have been several reports of leukemia, the supporting information is weak.
Genitourinary: Urinary frequency.

[Contraindications]
Indomethacin extended-release capsules is contraindicated in patients with known hypersensitivity to indomethacin.
Indomethacin extended-release capsules should not be given to patients who have experienced asthma, urticaria or allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.
Indomethacin extended-release capsules is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

[Precautions]

General
Indomethacin extended-release capsules cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to disease exacerbation. Patients on prolonged corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.
The pharmacological activity of indomethacin extended-release capsules in reducing [fever and] inflammation may diminish the utility of these diagnostic signs in detecting complications of presumed noninfectious, painful conditions.

Hepatic Effects
Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including indomethacin extended-release capsules. These laboratory abnormalities may progress, may remain unchanged or may be transient with continuing therapy. Notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In addition, rare cases of hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure, some of them with fatal outcomes have been reported.

A patient with symptoms and/or signs suggesting liver dysfunction or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with indomethacin extended-release capsules. If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), indomethacin extended-release capsules should be discontinued.

Hematological Effects
Anemia is sometimes seen in patients receiving NSAIDs, including indomethacin extended-release capsules. This may be due to fluid retention, occult or gross GI blood loss or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including indomethacin extended-release capsules, should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia. NSAIDs inhibit platelet aggregation and have been shown to prolong bleeding time in some patients. Unlike aspirin, their effect on platelet function is quantitatively less, of shorter duration and reversible.
Patients receiving indomethacin extended-release capsules who may be adversely affected by alterations in platelet function, such as those with coagulation disorders or patients receiving anticoagulants, should be carefully monitored.

Preexisting Asthma
Patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirinsensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, indomethacin extended-release capsules should not be administered to patients with this form of aspirin sensitivity and should be used with caution in patients with preexisting asthma.

[Use in Pregnant and Lactation]
Teratogenic Effects
Pregnancy Category C
Reproductive studies conducted in rats and rabbits have not demonstrated evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.
Nonteratogenic Effects
Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during pregnancy (particularly late pregnancy) should be avoided.
Labor and Delivery
In rat studies with NSAIDs, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition and decreased pup survival occurred. The effects of indomethacin extended-release capsules on labor and delivery in pregnant women are unknown.
Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in humanmilk and because of the potential for serious adverse reactions in nursing infants from indomethacin extended-release capsules, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

[Pediatric Use]
Safety and effectiveness in pediatric patients below the age of 14 years old have not been established.

[Geriatric Use]
As with any NSAIDs, caution should be exercised in treating the elderly (65 years and older).

[Drug Interactions]

ACE-Inhibitors
Reports suggest that NSAIDs may diminish the antihypertensive effect of ACE-inhibitors. This interaction should be given consideration in patients taking NSAIDs concomitantly with ACE-inhibitors.

Aspirin
When indomethacin extended-release capsules are administered with aspirin, its protein binding is

reduced, although the clearance of free indomethacin extended-release capsules is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of indomethacin and aspirin is not generally recommended because of the potential of increased adverse effects.

Furosemide
Clinical studies, as well as post marketing observations, have shown that indomethacin extendedrelease capsules can reduce the natriuretic effect-of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis. During concomitant therapy with NSAIDs, the patient should be observed closely for signs of renal failure (see WARNINGS, Renal Effects), as well as to assure diuretic efficacy.

Lithium
NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. The mean minimum lithium concentration increased 15% and the renal clearance was decreased by approximately 20%. These effects have been attributed to inhibition of renal prostaglandin synthesis by the NSAID. Thus, when NSAIDs and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate
NSAIDs have been reported to competitively inhibit methotrexate accumulation in rabbit kidney slices. This may indicate that they could enhance the toxicity of methotrexate. Caution should be used when NSAIDs are administered concomitantly with methotrexate.

Warfarin

The effects of warfarin and NSAIDs on GI bleeding are synergistic, such that users of both drugs together have a risk of serious GI bleeding higher than users of either drug alone.

Drug/Laboratory Test Interactions
Only if positive interactions have been observed.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Usually only if significant findings have been observed.

[Over-Dosage]
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 of indomethacin in mice and rats (based on 14 day mortality response) was 50 and 12 mg/kg, respectively.

[Pharmacology and Toxicology]

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 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.

[Pharmacokinetics]

Indomethacin extended-release capsules (75 mg) are designed to release 25 mg of drug initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours). Plasma concentrations of indomethacin fluctuate less and are more sustained following administration of indomethacin extended-release capsules than following administration of 25 mg indomethacin capsules given at 4 to 6 hours intervals. In multiple-dose comparisons, the mean daily steady state plasma level of indomethacin attained with daily administration of indomethacin extended-release capsules 75 mg was indistinguishable from that following indomethacin 25 mg capsules given at 0, 6 and 12 hours daily. However, there was a significant difference in indomethacin plasma levels between the two dosage regimens especially after 12 hours.

Controlled clinical studies of safety and efficacy in patients with osteoarthritis have shown that one capsule of indomethacin extended-release was clinically comparable to one 25 mg indomethacin capsule t.i.d.; and in controlled clinical studies in patients with rheumatoid arthritis, one capsule of indomethacin extended-release taken in the morning and one in the evening were clinically indistinguishable from one 50 mg capsule of indomethacin t.i.d.

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 desmethyldesbenzoyl 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 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.

[Storage]
Seal and store away from direct sunlight.

[Packaging]
Aluminum-plastic blister packaging, 10 tablets/plate, one plate/carton
Aluminum-plastic blister packaging, 10 tablets/plate, two plates/carton

[Shelf-Life]
36 months

[Executive Standard]
Chinese Pharmacopoeia 2015 Edition Second Part

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