

Indomethacin capsules are contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to indomethacin or any component of the drug product [see Warnings and Precautions (5.7,5.9)]
- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients [see Warnings and Precautions (5.7,5.8)]
- In the setting of coronary artery bypass graft (CABG) surgery [see Warnings and Precautions (5.1)]

5 WARNINGS AND PRECAUTIONS

5.1 Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as indomethacin, increases the risk of serious gastrointestinal (GI) events [see Warnings and Precautions (5.2)].

Stent Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [see Contraindications (4)].

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at an increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID-treated patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of indomethacin capsules in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If indomethacin capsules are used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

5.2 Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including indomethacin, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 to 6 months, and in about 2% to 4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk of GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most gastrointestinal events of fatal GI bleeding occur in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue indomethacin capsules until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding [see Drug Interactions (7)].

5.3 Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs including indomethacin.

Infants/pediatric of the warning signs and symptoms of hepatotoxicity (e.g., anorexia, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue indomethacin capsules immediately, and perform a complete evaluation of the patient.

5.4 Hypertension

NSAIDs, including indomethacin capsules, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs [see Drug Interactions (7)]. Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

5.5 Heart Failure and Edema

The Cardio and additional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of indomethacin may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]) [see Drug Interactions (7)].

Avoid the use of indomethacin capsules in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If indomethacin capsules are used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

5.6 Renal Toxicity and Hypokalemia

Renal Toxicity

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate acute renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery if the pretreatment state.

No information is available from controlled clinical studies regarding the use of indomethacin capsules in patients with advanced renal disease. The renal effects of indomethacin capsules may lessen the progression of renal dysfunction in patients with preexisting renal disease.

Concurrent volume status in dehydrated or hypovolemic patients prior to initiating indomethacin capsules. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of indomethacin capsules [see Drug Interactions (7)]. Avoid the use of indomethacin capsules in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If indomethacin capsules are used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

It has been reported that the addition of the potassium-sparing diuretic, furosemide, to a maintenance schedule of indomethacin resulted in reversible acute renal failure in two of four healthy volunteers. Indomethacin and furosemide should not be administered together.

Hypokalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hypovolemic/hypoadrenalism state.

Both indomethacin and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin on potassium-sparing diuretics or potassium levels and renal function should be considered where these agents are administered concurrently.

5.7 Anaphylactic Reactions

Indomethacin has been associated with anaphylactic reactions in patients with and without known hypersensitivity to indomethacin and in patients with aspirin-sensitive asthma [see Contraindications (4) and Warnings and Precautions (5.8)].

Seek emergency help if an anaphylactic reaction occurs.

5.8 Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps, severe, potentially fatal bronchospasm, and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, indomethacin capsules are contraindicated in patients with the formal aspirin sensitivity [see Contraindications (4)]. When indomethacin capsules are used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

5.9 Serious Skin Reactions

NSAIDs, including indomethacin, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and fatal epidermal necrolysis (EIN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of indomethacin capsules at the first appearance of skin rash or any other signs of hypersensitivity.

Indomethacin capsules are contraindicated in patients with previous serious skin reactions to NSAIDs [see Contraindications (4)].

5.10 Premature Closure of Fetal Ductus Arteriosus

Indomethacin may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including indomethacin capsules, in pregnant women starting at 30 weeks of gestation (third trimester) [see Use in Specific Populations (8.1)].

5.11 Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an idiosyncratic drug effect on erythropoiesis. If a patient treated with indomethacin capsules have any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

NSAIDs, including indomethacin capsules, may increase the risk of bleeding event. Co-morbid conditions, such as coagulation disorders, or concurrent use of warfarin, other anti-coagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs), and serotonin reuptake inhibitors (NRIs) may increase this risk. Monitor these patients for signs of bleeding [see Drug Interactions (7)].

5.12 Masking of Inflammation and Fever

The pharmacological activity of indomethacin capsules in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

5.13 Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically [see Warnings and Precautions (5.2, 5.3, 5.5)].

5.14 Central Nervous System Effects

Indomethacin capsules may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be used with considerable caution in patients with these conditions.

Discontinue indomethacin capsules if severe CNS adverse reaction develops.

Indomethacin capsules may cause drowsiness; therefore, caution patients 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 capsules.

5.15 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 capsules. Be alert to the possible association between the changes noted and indomethacin capsules. It is advisable to discontinue therapy if such changes are observed. If such changes are observed, a significant ophthalmologic examination should be performed at termination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients receiving prolonged therapy. Indomethacin capsules are not indicated for long-term treatment.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Cardiovascular Thrombotic Events [see Warnings and Precautions (5.1)]
- GI Bleeding, Ulceration and Perforation [see Warnings and Precautions (5.2)]
- Hepatotoxicity [see Warnings and Precautions (5.3)]
- Hypertension [see Warnings and Precautions (5.4)]
- Heart Failure and Edema [see Warnings and Precautions (5.5)]
- Renal Toxicity and Hypokalemia [see Warnings and Precautions (5.6)]

- Anaphylactic Reaction (see Warnings and Precautions (5.7))
- Serious Skin Reaction (see Warnings and Precautions (5.9))
- Hematologic Toxicity (see Warnings and Precautions (5.11))

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In a gastroscopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group receiving indomethacin capsules than in the group taking indomethacin suspension as placebo.

In a double-blind comparative clinical study involving 175 patients with rheumatoid arthritis, however, the incidence of upper gastrointestinal adverse effects with indomethacin capsules or suspension was comparable. The incidence of lower gastrointestinal adverse effects was greater in the suspension group.

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 20 double-blind controlled clinical trials reported in the literature (1,082 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 capsules and these adverse reactions, some of which have been reported only rarely.

The adverse reactions reported with indomethacin capsules may occur with use of the suspension. In addition, local irritation and trauma have been reported in patients who have received the capsules.

Table Summary of Adverse Reactions for Indomethacin Capsules

Incidence greater than 1%	Incidence less than 1%	
CENTRAL NERVOUS SYSTEM		
ataxia* with or without vertigo	dizziness	intermittent bleeding, without obvious ulcer formation and perforation of preexisting sigmoid lesions (diverticulum, carcinoma, etc.) development of ulcerative colitis and
diarrhea* (including indigestion, heartburn and epigastric pain)	nausea	
Barre-Lieou abdominal distress or pain constipation	flatulence (includes distention) flatulence	
	pruritic, itchy gastroenteritis	
	local irritation	
	proctitis	regional ileitis ulcerative stomatitis toxic hepatitis and jaundice (some fatal cases have been reported) intestinal strictures (diaphragm)
	ulcer or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestine intestinal ulceration associated with stenosis and obstruction	
CENTRAL NERVOUS SYSTEM		
headache (10-15% incidence)*	asthenia (includes nervousness)	high-healedness
vertigo	muscle weakness	syncope
lassitude	postural muscle movements (tremor)	parosmia
depression and fatigue (including malaise and listlessness)	neuritis	aggravation of epilepsy and parkinsonism
	psychic disturbances including psychotic episodes	epileptiform convulsions
	partial confusion	swims
	parosmia	peripheral neuropathy
		convulsion
		parosmia
SPECIAL SENSES		
vision	ocular - corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with indomethacin capsules	blurred vision
		diplopia
		tearing, disturbances, dryness
CARDIOVASCULAR		
None	hypertension	dispositive heart failure arrhythmias, palpitation
	hypotension	
	thrombocytopenia	
	thrombocytopenia	
	thrombocytopenia	
METABOLIC		
None	edema	hyperglycemia glycosuria hyperkalemia
	weight gain	
	fluid retention	
	fluid retention	
	fluid retention	
INTEGUMENTARY		
None	pruritus	folliculitis dermatitis
	skin eruptions	erythema nodosum
	itching or eczematous	loss of hair
		Stevens-Johnson syndrome erythema multiforme
		toxic epidermal necrolysis
HEMATOLOGIC		
None	thrombocytopenia	thrombotic anemia
	bone marrow depression anemia secondary to obstruction or occult gastrointestinal bleeding	thrombotic purpura disseminated intravascular coagulation
HYPERSENSITIVITY		
None	skin eruptions	pruritus
	acute respiratory distress	swims
	fall in hemoglobin	parosmia
	fall in hemoglobin	angitis pulmonary edema
	shock-like state	fever
	angioedema	
GENITOURINARY		
None	hematuria	BUN elevation
	vaginal bleeding	renal insufficiency,
	proteinuria	including renal failure
	urinary syndrome	
	hematuria	
MISCELLANEOUS		
None	edema	
	weight changes, including enlargement of lymph nodes or adenoids	

*Reactions occurring in 3% to 9% of patients treated with indomethacin capsules. (These 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
- Thrombocytopenia
- Hematologic

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

Concomitant use

A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group AB streptococcal sepsis, has been described in patients treated with nonsteroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcome.

DRUG INTERACTIONS

See Table 2 for clinically significant drug interactions with indomethacin.

Table 2 Clinically Significant Drug Interactions with Indomethacin Drugs That Interfere with Hemostasis

Indomethacin	Indomethacin and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of indomethacin and anticoagulants has increased risk of serious bleeding compared to the use of either drug alone.
Aspirin	Concomitant use of indomethacin and aspirin increases the risk of bleeding more than the NSAID alone.
Aspirin	Concomitant use of indomethacin and aspirin increases the risk of bleeding more than the NSAID alone.
Aspirin	Concomitant use of indomethacin and aspirin increases the risk of bleeding more than the NSAID alone.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or beta-blockers (including propranolol). Patients who are elderly, volume-depleted (including those on diuretic therapy) or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. During concomitant use of indomethacin capsules and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis. It has been reported that concomitant use of indomethacin capsules and ACE inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. Both indomethacin capsules and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin capsules and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently. Indomethacin and potassium-sparing diuretics should not be administered together. During concomitant use of indomethacin capsules with diuretics, observe patients for signs of worsening renal function. In addition, monitor diuretic efficacy including antihypertensive effects. Be aware that indomethacin and potassium-sparing diuretics may both be associated with increased serum potassium levels (see Warnings and Precautions (5.6)).
Digoxin	The concomitant use of indomethacin with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Lithium	During concomitant use of indomethacin capsules and digoxin, monitor serum digoxin levels.
Lithium	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Methotrexate	During concomitant use of indomethacin capsules and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Cyclosporine	During concomitant use of indomethacin capsules and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	Concomitant use of indomethacin capsules and cyclosporine may increase cyclosporine's nephrotoxicity.
Cyclosporine	During concomitant use of indomethacin capsules and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	Concomitant use of indomethacin with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy (see Warnings and Precautions (5.2)). Concomitant use with diflunisal may be particularly hazardous because diflunisal causes significantly higher plasma levels of indomethacin (see Clinical Pharmacology (12.3)). In some patients, combined use of indomethacin and diflunisal has been associated with fatal gastrointestinal hemorrhage.
Penicillins	The concomitant use of indomethacin with other NSAIDs or salicylates, especially diflunisal, is not recommended.
Penicillins	Concomitant use of indomethacin capsules and penicillins may increase the risk of penicillin-associated myelosuppression, renal, and GI toxicity (see the penicillin prescribing information).
Probenecid	During concomitant use of indomethacin capsules and probenecid, the patient with renal impairment whose creatinine clearance ranges from 45 to 70 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of probenecid.
Probenecid	The absence of renal impairment or renal effects has been reported in patients receiving probenecid and NSAIDs, with longer half-lives (e.g., indomethacin, ibuprofen), a pattern which these NSAIDs should increase drug time at least five days before the day of, and two days following probenecid administration.
Probenecid	When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased.
Probenecid	During the concomitant use of indomethacin capsules and probenecid, a lower oral 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.

Effects on Laboratory Tests

Indomethacin capsules reduce 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.

Falsely-negative results in the deaminohydroxylation 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Use of NSAIDs, including indomethacin capsules, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including indomethacin capsules, in pregnant women starting at 30 weeks.

There are no adequate and well-controlled studies of indomethacin capsules in pregnant women. Data from observational studies regarding potential prenatal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. In animal reproduction studies extended feed-oscillation was observed with administration of indomethacin at oral doses and rats during organogenesis at doses 0.1 and 0.2 times, respectively, the maximum recommended human dose (MRHD), 200 mg. In published studies in pregnant mice, indomethacin produced maternal toxicity and death, increased fetal resorptions, and fetal malformations at 0.1 times the MRHD. When oral and intracerebral doses were dosed during the last three days of gestation, indomethacin produced neonatal resorptions in the offspring at 0.1 and 0.05 times the MRHD, respectively (see Data). Based on animal data, prostaglandins have been shown to have an important role in the embryonic vasculature permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthase inhibitors such as indomethacin, resulted in increased pre- and post-implantation loss.

Clinical Considerations

Labor or Delivery

There are no studies on the effects of indomethacin capsules during labor or delivery. In animal studies, NSAIDs, including indomethacin, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth.

Data

Animal data

Reproductive studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day (0.1 times [rat] and 0.2 times [rat] the MRHD on a mg/kg basis, respectively) considered secondary to the decreased average fetal weights, no increased 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, 0.1 to 0.4 times MRHD on a mg/kg basis) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations.

In rat and mice, repeated indomethacin administration of 0.0 mg/kg/day (0.2 times and 0.1 times the MRHD on a mg/kg basis) during the last 3 days of gestation was associated with an increased incidence of neonatal resorptions in the offspring in the first three fetuses born to the dams. Indomethacin resorptions was observed at 2.0 mg/kg/day as compared to the control groups (0.1 times and 0.05 times the MRHD on a mg/kg basis). Administration of 0.1 to 0.4 times the MRHD on a mg/kg basis during the first 3 days of gestation did not cause an increase in neonatal resorptions at either dose level.

8.2 Lactation

Risk Summary

Based on available published clinical data, indomethacin may be present in human milk. The

development and health benefits of breastfeeding should be considered along with the mother's clinical need for indomethacin capsules and any potential adverse effects on the breastfed infant from the indomethacin capsules or from the underlying maternal condition.

Dose

In one study, levels of indomethacin in breast milk were below the sensitivity of the assay (<20 ng/mL) in 11 of 15 women using doses ranging from 75 mg orally to 300 mg orally daily (3.4 to 4.2 mg/kg daily) in the postpartum period. Based on these levels, the average concentration present in breast milk is estimated to be 27% of the maternal weight-adjusted dose. In another study, indomethacin levels were measured in breast milk of eight postpartum women using doses of 75 mg daily and the results were used to calculate an estimated infant daily dose. The volume of breast milk of indomethacin from breast milk was less than 30 mg/day or 4.5 mg/kg/day assuming breast milk intake of 150 mL/kg/day. This is 0.2% of the maternal weight-adjusted dosage or about 7% of the neonatal dose for treatment of pediatric rheumatism.

8.3 Females and Males of Reproductive Potential

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including indomethacin capsules, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including indomethacin capsules, in women who have difficulties conceiving or who are undergoing investigation of infertility.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients 14 years of age and younger has not been established.

Indomethacin capsules 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, in indomethacin treatment. In addition, a suggested starting dose is 1 to 2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 1 mg/kg/day or 150 to 200 mg/day, whichever is less. Limited data are available to support the use of a maximum daily dosage of 4 mg/kg/day or 150 to 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.

8.5 Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects (see Warnings and Precautions (5.1, 5.2, 5.3, 5.6, 5.13)).

Indomethacin in the cause confusion or rarely, psychosis (see Adverse Reactions (6.1)); physicians should remain alert to the possibility of such adverse effects in the elderly.

Indomethacin and its metabolites are known to be substantially excreted by the kidneys, and the risk of adverse reactions in this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, use caution in this patient population, and it may be useful to monitor renal function (see Clinical Pharmacology (12.3)).

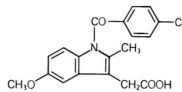
10 OVERDOSAGE

Symptoms following acute NSAID overdosage have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma have occurred, but over care (see Warnings and Precautions (5.1, 5.2, 5.4, 5.6)).

Manage patients with symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Consider gastric and/or activated charcoal (up to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or emesis. Cardiac in symptomatic patients seen within four hours of ingestion in patients with a large overdose (5 to 10 times the recommended dosage) forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding. For additional information about overdose treatment contact a poison control center (1-800-222-1222).

11 DESCRIPTION

Indomethacin capsules, USP for oral administration are provided in two dosage strengths which contain either 25 mg or 50 mg of indomethacin. Indomethacin is a non-steroidal anti-inflammatory imidole derivative designated chemically as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-imidazole-3-acetic acid. The structural formula is:



C₁₇H₁₅ClNO₄ M.W. 357.79

Indomethacin, USP is white to yellowish crystalline powder, having not more than a slight odor. It is sensitive to light, melts at about 192°C and exhibits polymorphism. It 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.

Each indomethacin capsule, USP intended for oral administration contains 25mg or 50 mg of indomethacin. In addition, each capsule also contains the following inactive ingredients: colloidal silicon dioxide, gelatin, FD&C Blue #1, FD&C Yellow #5, magnesium stearate, microcrystalline cellulose, powdered cellulose, sodium lauryl sulphate, sodium starch glycolate and titanium dioxide. The capsules are printed with black pharmaceutical ink which contains black iron oxide as coloring agent.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Indomethacin has analgesic, anti-inflammatory, and antipyretic properties. The mechanism of action of indomethacin capsules, like that of other NSAIDs, is not completely understood but involves inhibition of cyclooxygenase (COX-1 and COX-2).

Indomethacin is a potent inhibitor of prostaglandin synthesis *in vitro*. Indomethacin concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

12.2 Pharmacokinetics

Absorption

Following single oral doses of indomethacin capsules, 25 mg or 50 mg, indomethacin is readily absorbed, attaining peak plasma concentrations of about 1 and 2 mg/mL, respectively, at about 2 hours. Orally administered indomethacin capsules are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours. A single 50 mg dose of indomethacin oral suspension was found to be bioequivalent to 50 mg indomethacin capsules when each was administered with food. With a typical therapeutic regimen of 25 or 50 mg three times a day, the steady-state plasma concentration of indomethacin are an average 1.4 times those following the first dose.

Distribution

Indomethacin is highly bound to protein in plasma (about 99%) over the expected range of therapeutic plasma concentrations. Indomethacin has been found to cross the blood-brain barrier and the placenta, and appears in breast milk.

Elimination

Metabolism

Indomethacin exists in the plasma as the parent drug and its desmethyl-, desbenzyl-, and desmethyl-desbenzyl metabolites, all in the unconjugated form. Appreciable formation of glucuronide conjugates of each metabolite and of indomethacin are formed.

Excretion

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. About 60% of an oral dose is recovered in urine as drug and metabolites (29% as indomethacin and its glucuronides), and 33% is recovered in feces (15% as indomethacin). The mean half-life of indomethacin is estimated to be about 4.5 hours.

Specific Populations

Pediatric

The pharmacokinetics of indomethacin capsules has not been investigated in pediatric patients.

Race

Pharmacokinetic differences due to race have not been identified.

Hepatic Impairment

The pharmacokinetics of indomethacin capsules has not been investigated in patients with hepatic impairment.

Renal Impairment

The pharmacokinetics of indomethacin capsules has not been investigated in patients with renal impairment (see Warnings and Precautions (5.6)).

Drug Interaction Studies

Aspirin

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% (see Drug Interactions (7)). When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 2 for clinically significant drug interactions of NSAIDs with aspirin (see Drug Interactions (7)).

Diflunisal

In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin (see Drug Interactions (7)).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In an 18-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day (0.05 times the MRHD on a mg/m² basis), indomethacin had no tumorigenic effect. Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73 to 110 weeks) and the mouse (dosing period 82 to 98 weeks at doses up to 1.5 mg/kg/day (0.4 times [mice] and 0.07 times [rats] the MRHD on a mg/m² basis), respectively).

Mutagenesis

Indomethacin did not have any mutagenic effect *in vitro* bacterial tests and a series of *in vivo* tests including the host-mediated assay, sex-linked recessive lethals in *Drosophila*, and the micronucleus test in mice.

Impairment of Fertility

Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study (0.1 times the MRHD on a mg/m² basis) or a two time reproduction study in rats (0.02 times the MRHD on a mg/m² basis).

14 CLINICAL STUDIES

Indomethacin capsules have been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, osteoarthritis, spondylitis, and osteoarthritis. Indomethacin capsules afforded relief of symptoms; it does not alter the progressive course of the underlying disease.

Indomethacin capsules suppress inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with indomethacin capsules 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 capacity as demonstrated by an increase in grip strength. Indomethacin capsules 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.

16 HOW SUPPLIED- STORAGE AND HANDLING

Indomethacin Capsules USP, 50 mg are off-white to light yellow, free flowing granular powder filled in size "V" hard plastic capsules with green colored cap printed with "50" in black ink and green colored body imprinted with "50 mg" in black ink and are supplied as follows:

NDC 42708-030-020 in bottle of 20 capsules

Storage

Store at 20° to 25°C (68° to 77°F) (See USP Controlled Room Temperature). Protect from light.

Dispense in a light, light-resistant container using a child-resistant closure.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with indomethacin capsules and periodically during the course of ongoing therapy:

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately [see Warnings and Precautions (5.1)].

Concomitant Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, nausea, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding [see Warnings and Precautions (5.2)].

Hepatoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and “flu-like” symptoms). If these occur, instruct patients to stop indomethacin capsules and seek immediate medical therapy [see Warnings and Precautions (5.3)].

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their health care provider if such symptoms occur [see Warnings and Precautions (5.5)].

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur [see Contraindications (4) and Warnings and Precautions (5.7)].

Serious Skin Reactions

Advise patients to stop indomethacin capsules immediately if they develop any type of rash and to contact their health care provider as soon as possible [see Warnings and Precautions (5.9)].

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including indomethacin capsules, may be associated with a reversible delay in ovulation [see Use in Specific Populations (8.3)].

Fetal Fertility

Inform pregnant women to avoid use of indomethacin capsules and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus [see Warnings and Precautions (5.10) and Use in Specific Populations (8.1)].

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of indomethacin capsules with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and life or life-threatening events [see Warnings and Precautions (5.2) and Drug Interactions (7)]. Advise patients that NSAIDs may be present in “over the counter” medications for treatment of colds, fever, or influenza.

Use of NSAIDs and Low-Dose Aspirin

Inform patients not to use low-dose aspirin concomitantly with indomethacin capsules until they talk to their health care provider [see Drug Interactions (7)].

Manufactured by:

Cardia Healthcare Ltd.

Almudaina, India

Distributed by:

Zydus Pharmaceuticals USA Inc.

Princeton, NJ 08534

Rev: 05/16

Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death.** This risk may happen early in treatment and may increase:
 - with increasing doses of NSAIDs
 - with longer use of NSAIDs

Do not take NSAIDs right before or after a heart surgery called a “coronary artery bypass graft (CABG).”

Avoid taking NSAIDs after a recent heart attack, unless your health care provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.

- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
 - anytime during use
 - without warning symptoms
 - that may cause death

The risk of getting an ulcer or bleeding increases with:

- past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
- taking medicines called “corticosteroids,” “anticoagulants,” “SSRIs,” or “SNRIs”
- increasing doses of NSAIDs
- longer use of NSAIDs
- smoking
- drinking alcohol
- older age
- poor health
- advanced liver disease
- bleeding problems

NSAIDs should only be used:

- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:

- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your health care provider about all of your medical conditions, including if you:

- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your health care provider if you are considering taking NSAIDs during pregnancy. You should not take NSAIDs after 20 weeks of pregnancy, are breastfeeding or plan to breast feed.

Tell your health care provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplement, NSAIDs, and some other medicines can interact with each other and cause serious side effects. Do not start taking any new medicine without talking to your health care provider first.

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See “What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?”

- new or worse high blood pressure
- heart failure
- liver problems including liver failure
- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your health care provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rashes or hives with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your health care provider or get medical help right away. There are not all the possible side effects of NSAIDs. For more information, ask your health care provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your health care provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your health care provider. You can ask your pharmacist or health care provider for information about NSAIDs that is written for health professionals.

Please address medical inquiries to, Medical Affairs@zydususa.com | Tel.: 1-877-993-4779.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:

Cardia Healthcare Ltd.

Almudaina, India

Distributed by:

Zydus Pharmaceuticals USA Inc.

Princeton, NJ 08534

Rev: 05/16

PACKAGE LABEL-PRINCIPAL DISPLAY PANEL

NDC 42788-630-620

Indomethacin capsules USP, 50 mg

20 Capsules

Rx only

OPARMS

MedStart Sample - Not for sale

Indomethacin Capsules USP, 50mg 20 Capsules

Take ___ cap(s) ___ times(s) daily or every ___ hour(s) for ___ day(s)

Div. By: OPARMS, Inc. Keep container tightly closed. Rx Only
Cedar Knolls, NJ 07007 Keep out of reach of children

STORAGE: CONTROLLED ROOM TEMPERATURE

INDOMETHACIN

