565-2015-08

Indomethacin
Extended Release
Capsules, USP
2030725

Indomethacin Extended Release Capsules, USP

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use [see *Warnings and Precautions*].**
- **Indomethacin extended-release capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see *Contraindications and Warnings*].**

Gastrointestinal Risk

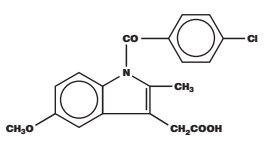
- **NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see WARNINGS).**

DESCRIPTION

Indomethacin cannot be considered a simple analgesic and should not be used in conditions other than those recommended under **INDICATIONS AND USAGE**.

Indomethacin is a non-steroidal anti-inflammatory indole derivative designated chemically as 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid. Indomethacin, USP is practically insoluble in water and sparingly soluble in alcohol. It has a pKa of 4.5 and is stable in neutral or slightly acidic media and decomposes in strong alkali.

The structural formula is:



$C_{19}H_{16}ClNO_4$ M.W. 357.80

Each extended-release capsule, for oral administration contains 75 mg of indomethacin and the following inactive ingredients: sugar spheres, povidone, mannitol, isopropyl alcohol, talc. The hard gelatin shell consists of gelatin, iron oxide yellow, titanium dioxide, sodium lauryl sulfate.

The imprinting ink contains the following: shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, strong ammonia solution, black iron oxide E172 dye and potassium hydroxide.

This product meets USP Drug Release Test 2 Specifications.

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_2 stimulated cerebral blood flow in healthy volunteers following acute oral and intravenous administration. In one study, after one week of treatment with orally administered indomethacin, this effect on basal cerebral blood flow had disappeared. The clinical significance of this effect has not been established.

Indomethacin 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 hour 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.

INDICATIONS AND USAGE

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 (see WARNINGS).

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, USP are 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. (See **PRECAUTIONS, Drug Interactions**).

CONTRAINDICATIONS

Indomethacin extended-release capsules are 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 (see **WARNINGS**: **Anaphylactoid Reactions,** and **PRECAUTIONS: Preexisting Asthma**).

Indomethacin extended-release capsules are contraindicated in the setting of coronary artery bypass graft (CABG) surgery [see Warnings]

WARNINGS

Cardiovascular Effects

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*].

Status 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 to 14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG [*see Contraindications*].

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

Hypertension

NSAIDs, including indomethacin extended-release capsules, can lead to onset of new hypertension or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events. Patients taking thiazides or loop diuretics may have impaired response to these therapies when taking NSAIDs. NSAIDs, including indomethacin extended-release capsules, should be used with caution in patients with hypertension. Blood pressure (BP) should be monitored closely during the initiation of NSAID treatment and throughout the course of therapy.

Heart Failure and Edema

The Coxib and traditional 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*].

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

Gastrointestinal Effects

Risk of Ulceration, Bleeding, and Perforation

NSAIDs, including indomethacin extended-release capsules, can cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the 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. These trends continue with longer duration of use, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

NSAIDs should be prescribed with extreme caution in those with a prior history of ulcer disease or gastrointestinal bleeding. Patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* who use NSAIDs have a greater than 10-fold increased risk for developing a GI bleed compared to patients with neither of these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include concomitant use of oral corticosteroids or anticoagulants, longer duration of NSAID therapy, smoking, use of alcohol, older age, and poor general health status.

Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore, special care should be taken in treating this population.

To minimize the potential risk for an adverse GI event in patients treated with an NSAID, the lowest effective dose should be used for the shortest possible duration. Patients and physicians should remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy and promptly initiate additional evaluation and treatment if a serious GI adverse event is suspected. This should include discontinuation of the NSAID until a serious GI adverse event is ruled out. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

Renal Effects

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 a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

Advanced Renal Disease

No information is available from controlled clinical studies regarding the use of indomethacin extended-release capsules in patients with advanced renal disease. Therefore, treatment with indomethacin extended-release capsules is not recommended in these patients with advanced renal disease. If indomethacin extended-release capsules therapy must be initiated, close monitoring of the patient's renal function is advisable.

Anaphylactoid Reactions

As with other NSAIDs, anaphylactoid reactions may occur in patients without known prior exposure to indomethacin extended-release capsules. Indomethacin extended-release capsules should not be given to patients with the aspirin triad. This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other NSAIDs (see **CONTRAINDICATIONS** and **PRECAUTIONS:(Preexisting Asthma**). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Skin Reactions

NSAIDs, including indomethacin extended-release capsules, can cause serious skin adverse events such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Patients should be informed about the signs and symptoms of serious skin manifestations and use of the drug should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Pregnancy

In late pregnancy, as with other NSAIDs, indomethacin extended-release capsules should be avoided because it may cause premature closure of the ductus arteriosus.

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 severe 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 values has occured, 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 aspirin-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross-reactivity, including bronchospasm, between aspirin and other non-steroidal 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.

Information for Patients

Patients should be informed of the following information before initiating therapy with a NSAID and periodically during the course of ongoing therapy. Patients should also be encouraged to read the NSAID Medication Guide that accompanies each prescription dispensed.

1. **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*].

2. Indomethacin extended-release capsules, like other NSAIDs, can cause GI discomfort and, rarely, serious GI side effects, such as ulcers and bleeding, which may result in hospitalization and even death. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms including epigastric pain, dyspepsia, melena, and hematemesis. Patients should be apprised of the importance of this follow-up (see **WARNINGS,** Gastrointestinal Effects, Risk of Ulceration, Bleeding, and Perforation).

3. Indomethacin extended-release capsules, like other NSAIDs, can cause serious skin side effects such as exfoliative dermatitis, SJS, and TEN, which may result in hospitalization and even death. Although serious skin reactions may occur without warning, patients should be alert for the signs and symptoms of skin rash and blisters, fever, or other signs of hypersensitivity such as itching, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be advised to stop the drug immediately if they develop any type of rash and contact their physicians as soon as possible.

4. **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 healthcare provider if such symptoms occur [*see Warnings*].

5. Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

6. Patients should be informed of the signs of an anaphylactoid reaction (e.g. difficulty breathing, swelling of the face or throat). If these occur, patients should be instructed to seek immediate emergency help (*see* WARNINGS).

7. In late pregnancy, as with other NSAIDs, indomethacin extended-release capsules should be avoided because it will cause premature closure of the ductus arteriosus.

Laboratory Tests

Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding. Patients on long-term treatment with NSAIDs should have their CBC and a chemistry profile checked periodically. If clinical signs and symptoms consistent with liver or renal disease develop, systemic manifestations occur (e.g., eosinophilia, rash, etc.) or if abnormal liver tests persist or worsen, indomethacin extended-release capsules should be discontinued.

Indomethacin Extended-release Capsules, USP

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 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 healthcare 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 a NSAIDs?

Do not take an NSAIDs:

- if you 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 healthcare 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 healthcare provider if you are considering taking NSAIDs during pregnancy. **You should not take NSAIDs after 29 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. 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 healthcare 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.

Size: 250 x 400 mm
Book Folding : 35 x 35 mm
Phema code : F-1856 B-1857
Colour : Pantone Black C
Spec. : Printed on 40 GSM Bible paper, front & backside printing.
Note: Pharma code position and Orientation are tentative, will be change based on folding size

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 extended-release 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. (See 201.57 (f)(4)(N))

Carcinogenesis, Mutagenesis, Impairment of Fertility

Usually only if significant findings have been observed. (See 201.57 (f)(5))

Pregnancy 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 human-milk 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).

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%

GASTROINTESTINAL

nausea[1] with or without vomiting
dyspepsia[1] (including indigestion, heartburn and epigastric pain)
diarrhea
abdominal distress or pain
constipation

CENTRAL NERVOUS SYSTEM

headache (11.7%)
dizziness*
vertigo
somnolence
depression and fatigue (including malaise and listlessness)

SPECIAL SENSES

tinnitus

CARDIOVASCULAR

none

METABOLIC

none

INTEGUMENTARY

none

HEMATOLOGIC

none

HYPERSENSITIVITY

none

GENITOURINARY

none

MISCELLANEOUS

none

Incidence less than 1%

GASTROINTESTINAL

anorexia

bloating (includes 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)

CENTRAL NERVOUS SYSTEM

anxiety (includes 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

dysarthria

SPECIAL SENSES

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

congestive heart failure

hypertension

hypotension

tachycardia

chest pain

arrhythmia; palpitations

METABOLIC

edema

weight gain

fluid retention

flushing or sweating

hyperglycemia

glycosuria

hyperkalemia

INTEGUMENTARY

pruritus

rash; urticaria

petechiae or ecchymosis

exfoliative dermatitis

erythema nodosum

loss of hair

Stevens-Johnson Syndrome

erythema multiforme

toxic epidermal necrolysis

HEMATOLOGIC

leukopenia

bone marrow depression

anemia secondary to obvious or occult gastrointestinal bleeding

aplastic anemia

hemolytic anemia

agranulocytosis

thrombocytopenic purpura

disseminated intravascular coagulation

HYPERSENSITIVITY

acute anaphylaxis

acute respiratory distress

rapid fall in blood pressure resembling a shock-like state

angioedema

dyspnea

asthma

purpura

angiitis

pulmonary edema

fever

GENITOURINARY

hematuria

vaginal bleeding

proteinuria, nephrotic syndrome, interstitial nephritis

BUN elevation

renal insufficiency including renal failure

MISCELLANEOUS

epistaxis

breast changes, including enlargement and tenderness, or gynecomastia

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

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

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

Cardiovascular: Thrombophlebitis

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

Genitourinary: Urinary frequency

OVERDOSAGE

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

Treatment is symptomatic and supportive. The stomach should be emptied as quickly as possible if the ingestion is recent. If vomiting has not occurred spontaneously, the patient should be induced to vomit with syrup of ipecac. If the patient is unable to vomit, gastric lavage should be performed. Once the stomach has been emptied, 25 g 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_{50} of indomethacin in mice and rats (based on 14 day mortality response) was 50 and 12 mg/kg, respectively.

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 (see **WARNINGS**). 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.

Pediatric Use: Indomethacin ordinarily should not be prescribed for children 14 years of age and under **(see** WARNINGS**).**

Adult Use: Dosage Recommendations for Active Stages of the Following**:**

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

The following information is provided as background only and refers to immediate-release indomethacin capsules (25 mg or 50 mg):

Suggested Dosage:

The following recommendations on dosing pertain to immediate-release indomethacin capsules, and provide important information regarding the dosage and administration of indomethacin. The prescriber should be aware of this information when considering and prescribing extended-release indomethacin.

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

In patients who have persistent night pain and/or morning stiffness, the giving of a large portion, up to a maximum of 100 mg, of the total daily dose at bedtime, 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.

The following information refers to Extended-release Indomethacin Capsules (75 mg):

If indomethacin extended-release capsules are used for initiating indomethacin treatment, one capsule daily should be the usual starting dose in order to observe patient tolerance since 75 mg per day is the maximum recommended starting dose for indomethacin (see above). If indomethacin extended-release capsules are used to increase the daily dose, patients should be observed for possible signs and symptoms of intolerance since the daily increment will exceed the daily increment recommended for other dosage forms. For patients who require 150 mg of indomethacin per day and have demonstrated acceptable tolerance, indomethacin extended-release capsules 75 mg may be prescribed as one capsule twice daily.

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

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

Careful instructions to and observations of, the individual patient are essential to the prevention of serious, irreversible, including fatal, adverse reactions.

As advancing years appear to increase the possibility of adverse reactions, indomethacin extended-release capsules should be used with greater care in the aged.

2. Acute painful shoulder (bursitis and/or tendinitis). Initial Dose: 75 mg to 150 mg daily. When 150 mg is prescribed, give as one capsule twice daily.

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 to 14 days.

HOW SUPPLIED

Indomethacin extended-release capsules USP ,75 mg are size '2' hard gelatin capsules, with dark yellow cap imprinted with 'H' and clear transparent body imprinted with '105' containing cream spherical pellets. They are supplied as

Bottles of 30 capsules NDC 31722-565-30
Bottles of 60 capsules NDC 31722-565-60
Bottles of 100 capsules NDC 31722-565-01
Bottles of 500 capsules NDC 31722-565-05
Bottles of 1000 capsules NDC 31722-565-10

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from moisture

CAMBER™ PHARMACEUTICALS, INC.

Manufactured for:
Camber Pharmaceuticals, Inc.
Piscataway, NJ 08854

By: **HETERO™**
Hetero Labs Limited
Jeedimetla, Hyderabad - 500 055, India
Revised: August 2015

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

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

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

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

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare 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 healthcare 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 healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

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

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