



7 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	
Clinical Impact:	<ul style="list-style-type: none">Indomethacin and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of indomethacin and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone.Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	Monitor patients receiving concomitant use of indomethacin with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding [see Warnings and Precautions (5.1)].
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of GI adverse reactions as compared to use of the NSAID alone [see Warnings and Precautions (5.2)].
Intervention:	Concomitant use of indomethacin and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding [see Warnings and Precautions (5.1)]. Indomethacin suppository is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta Blockers	
Clinical Impact:	<ul style="list-style-type: none">NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta blockers (including propranolol).In 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.
Intervention:	<ul style="list-style-type: none">During concomitant use of indomethacin and ACE inhibitors, ARBs, or beta blockers, monitor blood pressure to ensure that the desired blood pressure is obtained.During concomitant use of indomethacin and ACE inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function [see Warnings and Precautions (5.6)].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 Impact:	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.
Intervention:	It has been reported that the addition of 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. Both indomethacin suppository and potassium-sparing diuretics may be associated with increased serum potassium levels. The potential effects of indomethacin and potassium-sparing diuretics on potassium levels and renal function should be considered when these agents are administered concurrently. Indomethacin and furosemide should not be administered together. During concomitant use of indomethacin suppository with diuretics, observe patients for signs of worsening renal function, in addition to assessing 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	
Clinical Impact:	The concomitant use of indomethacin with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of indomethacin suppository and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration decreased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of indomethacin suppositories and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of indomethacin suppositories and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of indomethacin and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of indomethacin and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	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)].
Intervention:	Combined 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.
Intervention:	The concomitant use of indomethacin with other NSAIDs or salicylates, especially diflunisal, is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of indomethacin and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity [see the pemetrexed prescribing information].
Intervention:	During concomitant use of indomethacin and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 75 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 pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., rofecoxib, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Probenecid	
Clinical Impact:	When indomethacin is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased.
Intervention:	During the concomitant use of indomethacin and probenecid, a lower total 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 reduces basal plasma renin activity (PRA), as well as those elevations of PRA induced by furosemide administration, or salt or volume depletion. These facts should be considered when evaluating plasma renin activity in hypertensive patients.

False-negative results in the dexamethasone 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, can cause premature closure of the fetal ductus arteriosus and fetal renal dysfunction leading to oligohydramnios and, in some cases, neonatal renal impairment. Because of these risks, limit dose and duration of exposure from about 20 and 30 weeks of gestation, and avoid indomethacin use at about 30 weeks of gestation and later in pregnancy [see Clinical Considerations, Data].

Premature Closure of Fetal Ductus Arteriosus

Use of NSAIDs, including indomethacin, at about 30 weeks gestation or later in pregnancy increases the risk of premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment

Use of NSAIDs at about 20 weeks gestation or later in pregnancy has been associated with cases of fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment.

Data from observational studies regarding other potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In animal reproduction studies retarded fetal ossification was observed with administration of indomethacin to mice 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 rat and mice dams were dosed during the last three days of gestation, indomethacin produced neonatal necrosis 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 endometrial vascular permeability, histocytot implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as indomethacin, resulted in increased pre- and post-implantation loss. Prostaglandins also have been shown to have an important role in fetal kidney development. In published animal studies, prostaglandin synthesis inhibitors have been reported to impair kidney development when administered at clinically relevant doses.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature Closure of Fetal Ductus Arteriosus:

Avoid use of NSAIDs in women at about 30 weeks gestation and later in pregnancy, because NSAIDs, including indomethacin, can cause premature closure of the fetal ductus arteriosus [see Data].

Oligohydramnios/Neonatal Renal Impairment:

If an NSAID is necessary at about 20 weeks gestation or later in pregnancy, limit the use to the lowest effective dose and shortest duration possible. If indomethacin treatment extends beyond 48 hours, consider monitoring with ultrasound for oligohydramnios. If oligohydramnios occurs, discontinue indomethacin and follow-up according to clinical practice [see Data].

Data

Human Data

Premature Closure of Fetal Ductus Arteriosus:

Published literature reports that the use of NSAIDs at about 30 weeks of gestation and later in pregnancy may cause premature closure of the fetal ductus arteriosus.

Oligohydramnios/Neonatal Renal Impairment:

Published studies and postmarketing reports describe maternal NSAID use at about 20 weeks gestation or later in pregnancy associated with fetal renal dysfunction leading to oligohydramnios, and in some cases, neonatal renal impairment. These adverse outcomes are seen, on average, after days to weeks of treatment, although oligohydramnios has been infrequently reported as soon as 48 hours after NSAID initiation. In many cases, but not all, the decrease in amniotic fluid was transient and reversible with cessation of the drug. There have been a limited number of case reports of maternal NSAID use and neonatal renal dysfunction without oligohydramnios, some of which were irreversible. Some cases of neonatal renal dysfunction required treatment with invasive procedures, such as exchange transfusion or dialysis.

Methodological limitations of these postmarketing studies and reports include lack of a control group; limited information regarding dose, duration, and timing of drug exposure; and concomitant use of other medications. These limitations preclude establishing a reliable estimate of the risk of adverse fetal and neonatal outcomes with maternal NSAID use. Because the published safety data on neonatal outcomes involved mostly preterm infants, the generalizability of certain reported risks to the full-term infant exposed to NSAIDs through maternal use is uncertain.

Animal Data

Reproductive studies were conducted in mice and rats at dosages of 0.5, 1.0, 2.0, and 4.0 mg/kg/day. Except for retarded fetal ossification at 4 mg/kg/day (0.1 times [mice] and 0.2 times [rats] the MRHD on a mg/m² basis, respectively) considered secondary to the decreased average fetal weights, no increase in 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/m² basis) have described maternal toxicity and death, increased fetal resorptions, and fetal malformations. Comparable studies in rodents using high doses of aspirin have shown similar maternal and fetal effects.

In rats and mice, maternal indomethacin administration at 4.0 mg/kg/day (0.2 times and 0.1 times the MRHD on a mg/m² basis) during the last 3 days of gestation was associated with an increased incidence of neonatal necrosis in the decapophan in the live born fetuses however no increase in neonatal necrosis 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/m² basis). Administration of 0.5 or 4.0 mg/kg/day to offspring during the first 3 days of life did not cause an increase in neonatal necrosis at either dose level.

8.2 Lactation

Risk Summary

Based on available published clinical data, indomethacin may be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for indomethacin and any potential adverse effects on the breastfed infant from the indomethacin or from the underlying maternal condition.

Data

In one study, levels of indomethacin in breast milk were below the sensitivity of the assay (<20 mcg/L) in 11 of 15 women using doses ranging from 75 mg orally to 200 mg rectally daily (0.34 to 0.29 mg/kg daily) in the postpartum period. Based on these levels, the average concentration present in breast milk was estimated to be 0.27% 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 estimated infant dose of indomethacin from breast milk was less than 20 mcg/day or 4.5 mg/kg/day assuming breast milk intake of 150 mL/kg/day. This is 0.5% of the maternal weight-adjusted dosage or about 3% of the neonatal dose for treatment of pediatric patients.

8.3 Females and Males of Reproductive Potential

Infertility

Female

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including indomethacin, 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 delay 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, 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 suppositories 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 800 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. If indomethacin treatment is initiated, a suggested starting dose is 1 to 2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 3 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 benefits 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 may cause confusion or rarely, psychosis [see Adverse Reactions (8.1)]; 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 to 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

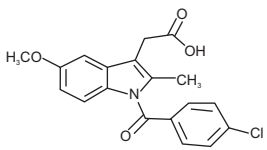
Symptoms following acute NSAID overdosage have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and coma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

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (0.5 to 1.00 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or emetic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (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 overdosage treatment contact a poison control center (1-800-222-1222).

11 DESCRIPTION

Indomethacin Suppositories USP is a nonsteroidal anti-inflammatory drug, available as a suppository containing 50 mg of indomethacin administered for rectal use. The chemical name is 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid. The molecular weight is 357.75. Its molecular formula is C₁₉H₁₅ClNO₃, and it has the following chemical structure.



Indomethacin USP is a white to yellow crystalline powder. It is sparingly soluble in absolute alcohol, chloroform and ether and insoluble in water. It has a pKa of 4.7.

The inactive ingredients in indomethacin suppositories include: Butylated hydroxy anisole, butylated hydroxy toluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000 and sodium chloride. Indomethacin suppositories, 50 mg each, are white to off-white, bullet shaped, rectal suppositories.

FDA approved dissolution test specifications differ from USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Indomethacin has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of indomethacin suppositories, 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.

12.3 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 mcg/mL, respectively, at about 2 hours. Orally administered indomethacin capsules are virtually 100% bioavailable, with 80% of the dose absorbed within 4 hours. With a typical therapeutic regimen of 25 or 50 mg three times a day, the steady-state plasma concentrations of indomethacin are an average 1.4 times those following the first dose.

The rate of absorption is more rapid from the rectal suppository than from indomethacin capsules. Ordinarily, therefore, the total amount absorbed from the suppository would be expected to be at least equivalent to the capsule. In controlled clinical trials, however, the amount of indomethacin absorbed was found to be somewhat less (80 to 90%) than that absorbed from indomethacin capsules. This is probably because some subjects did not retain the material from the suppository for the in vivo study to assure complete absorption. Since the suppository dissolves rather quickly rather than melting slowly, it is seldom recovered in recognizable form if the patient retains the suppository for more than a few minutes.

Distribution

Indomethacin is highly bound to protein in plasma (about 90%) 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-, desbutenyl-, and desmethyldesbutenyl- metabolites, all in the unconjugated form. Appreciable formation of glucuronide conjugates of these metabolites and of indomethacin are formed.

Excretion

Indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. About 80% of an oral dose is recovered in urine as drug and metabolites (20% as indomethacin and its glucuronide), and 33% is recovered in feces (1.5% as indomethacin). The mean half-life of indomethacin is estimated to be about 4.5 hours.

Specific Populations

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

Race: Pharmacokinetic differences due to race have not been identified.

Hepatic Impairment: The pharmacokinetics of indomethacin has not been investigated in patients with hepatic impairment.

Renal Impairment: The pharmacokinetics of indomethacin 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 81-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 62 to 88 weeks) at doses up to 1.5 mg/kg/day (0.04 times [mice] and 0.07 times [rats] the MRHD on a mg/m² basis, respectively).

Mutagenesis

Indomethacin did not have any mutagenic effect in *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 (0.01 times the MRHD on a mg/m² basis) or a two litter reproduction study in rats (0.02 times the MRHD on a mg/m² basis).

14 CLINICAL STUDIES

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, 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 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 suppositories USP, 50 mg each, are white to off-white, bullet shaped suppository packed in Alu/PF molds.

Box of 100 Suppositories
NDC 31722-051-51

Storage

Store at 2° to 8°C (36° to 46°F).

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 suppositories and periodically during the course of ongoing therapy. Indomethacin suppositories are for rectal use only. Advise patients not to use indomethacin suppositories orally or intra-vaginally.

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)].

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, 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 the signs and symptoms of GI bleeding [see Warnings and Precautions (5.2)].

Hepatotoxicity

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 suppositories 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 healthcare provider if such symptoms occur [see Warnings and Precautions (5.5)].

Anaphylactic Reactions

Advise patients to be alert for 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, including DRESS

Advise patients to stop taking indomethacin suppositories immediately if they develop any type of rash or fever and to contact their healthcare provider as soon as possible [see Warnings and Precautions (5.8, 5.10)].

Female Fertility

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

Fetal Toxicity

Inform pregnant women to avoid use of indomethacin suppositories and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus. If treatment with indomethacin suppositories is needed for a pregnant woman between about 20 to 30 weeks gestation, advise her that she may need to be monitored for oligohydramnios. If treatment continues for longer than 48 hours [see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)].

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of indomethacin suppositories with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy [see Warnings and Precautions (5.2) and Drug Interactions (7)].

Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

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



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Revised: 03/2024