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Hyzaar—Cont.

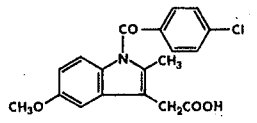
tients with a history of hepatic impairment (see WARNINGS, *Impaired Hepatic Function*). Losartan can be administered once or twice daily at total daily doses of 25 to 100 mg. If the antihypertensive effect measured at trough using once-a-day dosing is inadequate, a twice-a-day regimen at the same total daily dose or an increase in dose may give a more satisfactory response.
Hydrochlorothiazide is effective in doses of 12.5 to 50 mg once daily and can be given at doses of 12.5 to 25 mg as HYZAAR.
To minimize dose-independent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.
The side effects (see WARNINGS) of losartan are generally rare and apparently independent of dose; those of hydrochlorothiazide are a mixture of dose-dependent (primarily hypokalemia) and dose-independent phenomena (e.g., pancreatitis), the former much more common than the latter. Therapy with any combination of losartan and hydrochlorothiazide will be associated with both sets of dose-independent side effects.
Replacement Therapy: The combination may be subtituted for the titrated components.
Dose Titration by Clinical Effect: A patient whose blood pressure is not adequately controlled with losartan monotherapy (see above) may be switched to HYZAAR 50-12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily. If blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to two tablets of HYZAAR 50-12.5 once daily or one tablet of HYZAAR 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily.
A patient whose blood pressure is inadequately controlled by 25 mg once daily of hydrochlorothiazide, or is controlled but who experiences hypokalemia with this regimen, may be switched to HYZAAR 50-12.5 (losartan 50 mg/hydrochlorothiazide 12.5 mg) once daily, reducing the dose of hydrochlorothiazide without reducing the overall expected antihypertensive response. The clinical response to HYZAAR 50-12.5 should be subsequently evaluated and if blood pressure remains uncontrolled after about 3 weeks of therapy, the dose may be increased to two tablets of HYZAAR 50-12.5 once daily or one tablet of HYZAAR 100-25 (losartan 100 mg/hydrochlorothiazide 25 mg) once daily.
The usual dose of HYZAAR is one tablet of HYZAAR 50-12.5 once daily. More than two tablets of HYZAAR 50-12.5 once daily or more than one tablet of HYZAAR 100-25 once daily is not recommended. The maximal antihypertensive effect is attained about 3 weeks after initiation of therapy.
Use in Patients with Renal Impairment: The usual regimens of therapy with HYZAAR may be followed as long as the patient's creatinine clearance is >30 mL/min. In patients with more severe renal impairment, loop diuretics are preferred to thiazides, so HYZAAR is not recommended.
Patients with Hepatic Impairment: HYZAAR is not recommended for titration in patients with hepatic impairment (see WARNINGS, *Impaired Hepatic Function*) because the appropriate 25 mg starting dose of losartan cannot be given. HYZAAR may be administered with other antihypertensive agents.
HYZAAR may be administered with or without food.

HOW SUPPLIED

No. 3502—Tablets HYZAAR, 50-12.5 are yellow, teardrop shaped, film-coated tablets, coded MRK 717 on one side and HYZAAR on the other. Each tablet contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. They are supplied as follows:
NDC 0006-0717-31 unit of use bottles of 30
NDC 0006-0717-54 unit of use bottles of 90
NDC 0006-0717-58 unit of use bottles of 100.
NDC 0006-0717-28 unit dose packages of 100
NDC 0006-0717-82 unit of use bottles of 1,000.
Shown in Product Identification Guide, page 323
No. 3793—Tablets HYZAAR 100-25 are light yellow, teardrop shaped, film-coated tablets, coded MRK 747 on one side and HYZAAR on the other. Each tablet contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide. They are supplied as follows:
NDC 0006-0747-31 unit of use bottles of 30
NDC 0006-0747-58 unit of use bottles of 100
NDC 0006-0747-28 unit dose packages of 100.
Shown in Product Identification Guide, page 323
Storage
Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Keep container tightly closed. Protect from light.
Manufactured for:
MERCK & CO., INC., West Point, PA 19486, USA
by:
DuPont Pharma, Wilmington, DE 19880 USA
7892813 Issued December 1999

INDOCIN® Capsules, Oral Suspension and Suppositories (Indomethacin) ℞

INDOCIN is supplied in three dosage forms. Capsules INDOCIN for oral administration contain either 25 mg or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, FD & C Blue 1, FD & C Red 3, gelatin, lactose, lecithin, magnesium stearate, and titanium dioxide. Suspension INDOCIN for oral use contains 25 mg of indomethacin per 5 mL, alcohol 1%, and sorbic acid 0.1% added as a preservative and the following inactive ingredients: antifoam AF emulsion, flavors, purified water, sodium hydroxide or hydrochloric acid to adjust pH, sorbitol solution, tragacanth. Suppositories INDOCIN for rectal use contain 50 mg of indomethacin and the following inactive ingredients: butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000 and sodium chloride. 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 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 suspension has a pH of 4.0–5.0. The structural formula is:



*Registered trademark of MERCK & CO., Inc.

CLINICAL PHARMACOLOGY

INDOCIN is a non-steroidal 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.
INDOCIN 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.
INDOCIN has been shown to be an effective anti-inflammatory agent, appropriate for long-term use in rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.
INDOCIN affords relief of symptoms; it does not alter the progressive course of the underlying disease.
INDOCIN suppresses inflammation in rheumatoid arthritis as demonstrated by relief of pain, and reduction of fever, swelling and tenderness. Improvement in patients treated with INDOCIN 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.
Capsules INDOCIN have been found effective in relieving the pain, reducing the fever, swelling, redness, and tenderness of acute gouty arthritis—see INDICATIONS.
Following single oral doses of Capsules INDOCIN 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 Capsules INDOCIN are virtually 100% bioavailable, with 90% of the dose absorbed within 4 hours. A single 50 mg dose of Oral Suspension INDOCIN was found to be bioequivalent to a 50 mg INDOCIN capsule when each was administered with food.
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.
The rate of absorption is more rapid from the rectal suppository than from Capsules INDOCIN. 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 (80–90%) than that absorbed from Capsules INDOCIN. This is probably because some subjects did not retain the material from the
Indomethacin exists in the plasma as the parent drug and its desmethyl, desbenzoyl, and desmethyl-desbenzoyl 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.
In a gastroscopic study in 45 healthy subjects, the number of gastric mucosal abnormalities was significantly higher in the group receiving Capsules INDOCIN than in the group taking Suppositories INDOCIN or placebo.
In a double-blind comparative clinical study involving 175 patients with rheumatoid arthritis, however, the incidence of upper gastrointestinal adverse effects with Suppositories or Capsules INDOCIN was comparable. The incidence of lower gastrointestinal adverse effects was greater in the suppository group.

INDICATIONS

Indomethacin has 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).
5. Acute gouty arthritis.

INDOCIN 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 INDOCIN in conjunction with aspirin or other salicylates is not recommended. Controlled clinical studies have shown that the combined use of INDOCIN and aspirin does not produce any greater therapeutic effect than the use of INDOCIN alone. Furthermore, in one of these clinical studies, the incidence of gastrointestinal side effects was significantly increased with combined therapy (see DRUG INTERACTIONS).

CONTRAINDICATIONS

INDOCIN should not be used in:
Patients who are hypersensitive to this product.
Patients in whom acute asthmatic attacks, urticaria, or rhinitis are precipitated by aspirin or other non-steroidal anti-inflammatory agents.
Suppositories INDOCIN are contraindicated in patients with a history of proctitis or recent rectal bleeding.

WARNINGS

General:
Because of the variability of the potential of INDOCIN to cause adverse reactions in the individual patient, the following are strongly recommended:
1. The lowest possible effective dose for the individual patient should be prescribed. Increased dosage tends to increase adverse effects, particularly in doses over 150–200 mg/day, without corresponding increase in clinical benefits.
2. Careful instructions to, and observations of, the individual patient are essential to the prevention of serious adverse reactions. As advancing years appear to increase the possibility of adverse reactions, INDOCIN should be used with greater care in the elderly.
3. Effectiveness of INDOCIN in pediatric patients has not been established. INDOCIN 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 Capsules INDOCIN, side effects in pediatric patients were comparable to those reported in adults. Experience in pediatric patients has been confined to the use of Capsules INDOCIN.
   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 instituted, a suggested starting dose is 2 mg/kg/day given in divided doses. Maximum daily dosage should not exceed 4 mg/kg/day or 150–200 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.

Gastrointestinal Effects:
Single or multiple ulcerations, including perforation and hemorrhage of the esophagus, stomach, duodenum or small and large intestine, have been reported to occur with INDOCIN. Fatalities have been reported in some instances.

pain in ulcerative colitis patients or the development of ulcerative colitis and regional ileitis have been reported to occur rarely.

Because of the occurrence, and at times severity, of gastrointestinal reactions to INDOCIN, the prescribing physician must be continuously alert for any sign or symptom signaling a possible gastrointestinal reaction. The risks of continuing therapy with INDOCIN in the face of such symptoms must be weighed against the possible benefits to the individual patient.

INDOCIN should not be given to patients with active gastrointestinal lesions or with a history of recurrent gastrointestinal lesions except under circumstances which warrant the very high risk and where patients can be monitored very closely.

The gastrointestinal effects may be reduced by giving Capsules INDOCIN immediately after meals, with food, or with antacids.

Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3–6 months, and in about 2–4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Renal Effects:

As with other non-steroidal anti-inflammatory drugs, long term administration of indomethacin to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there have been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome.

A second form of renal toxicity has been seen in patients with prerenal and renal conditions leading to a reduction in renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients administration of an NSAID may cause a dose dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with conditions such as renal or hepatic dysfunction, diabetes mellitus, advanced age, extracellular volume depletion from any cause, congestive heart failure, septicemia, pyelonephritis, or concomitant use of any nephrotoxic drug. INDOCIN or other NSAIDs should be given with caution and renal function should be monitored in any patient who may have reduced renal reserve. Discontinuation of NSAID therapy is typically followed by recovery to the pretreatment state.

Increases in serum potassium concentration, including hyperkalemia, have been reported, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state (see PRECAUTIONS, *Drug Interactions*).

Since INDOCIN is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored; a lower daily dosage should be anticipated to avoid excessive drug accumulation.

Ocular Effects:

Corneal deposits and retinal disturbances, including those of the macula, have been observed in some patients who had received prolonged therapy with INDOCIN. The prescribing physician should be alert to the possible association between the changes noted and INDOCIN. It is advisable to discontinue therapy if such changes are observed. Blurred vision may be a significant symptom and warrants a thorough ophthalmological examination. Since these changes may be asymptomatic, ophthalmologic examination at periodic intervals is desirable in patients where therapy is prolonged.

Central Nervous System Effects:

INDOCIN may aggravate depression or other psychiatric disturbances, epilepsy, and parkinsonism, and should be

Incidence greater than 1%	*Incidence less than 1%*	
GASTROINTESTINAL		
nausea* with or without vomiting	anorexia	gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions (diverticulum, carcinoma, etc.)
dyspepsia* (including indigestion, heartburn and epigastric pain)	bloating (includes distention)	development of ulcerative colitis and regional ileitis
diarrhea	flatulence	ulcerative stomatitis
abdominal distress or pain	peptic ulcer	toxic hepatitis and jaundice (some fatal cases have been reported)
constipation	gastroenteritis	intestinal strictures (diaphragms)
	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	
CENTRAL NERVOUS SYSTEM		
headache (11.7%)	anxiety (includes nervousness)	light-headedness
dizziness*	muscle weakness	syncope
vertigo	involuntary muscle movements	paresthesia
somnolence	insomnia	aggravation of epilepsy and parkinsonism
depression and fatigue (including malaise and listlessness)	muzziness	depersonalization
	psychic disturbances including psychotic episodes	coma
	mental confusion	peripheral neuropathy
	drowsiness	convulsions
		dysarthria
SPECIAL SENSES		
tinnitus	ocular—corneal deposits and retinal disturbances, including those of the macula, have been reported in some patients on prolonged therapy with INDOCIN	blurred vision
		diplopia
		hearing disturbances, deafness

DOCIN may also cause headache. Headache which persists despite dosage reduction requires cessation of therapy with INDOCIN.

Use in Pregnancy and the Neonatal Period

INDOCIN is not recommended for use in pregnant women, since safety for use has not been established. The known effects of indomethacin and other drugs of this class on the human fetus during the third trimester of pregnancy include: constriction of the ductus arteriosus prenatally, tricuspid incompetence, and pulmonary hypertension; nonclosure of the ductus arteriosus postnatally which may be resistant to medical management; myocardial degenerative changes, platelet dysfunction with resultant bleeding, intracranial bleeding, renal dysfunction or failure, renal injury/dysgenesis which may result in prolonged or permanent renal failure, oligohydramnios, gastrointestinal bleeding or perforation, and increased risk of necrotizing enterocolitis. Teratogenic 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 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) 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.

As with other non-steroidal anti-inflammatory agents which inhibit prostaglandin synthesis, indomethacin has been found to delay parturition in rats.

In rats and mice, 4.0 mg/kg/day given during the last three days of gestation caused a decrease in maternal weight gain and some maternal and fetal deaths. An increased incidence of neuronal necrosis in the diencephalon in the live-born fetuses was observed. At 2.0 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups. Administration of 0.5 or 4.0 mg/kg/day during the first three days of life did not cause an increase in neuronal necrosis at either dose level.

Use in Nursing Mothers

INDOCIN is excreted in the milk of lactating mothers. INDOCIN is not recommended for use in nursing mothers.

PRECAUTIONS

General

Non-steroidal anti-inflammatory drugs, including INDOCIN, may mask the usual signs and symptoms of infection.

non-steroidal anti-inflammatory drugs, INDOCIN should be used with caution in patients with cardiac dysfunction, hypertension, or other conditions predisposing to fluid retention.

In a study of patients with severe heart failure and hyponatremia, INDOCIN was associated with significant deterioration of circulatory hemodynamics, presumably due to inhibition of prostaglandin dependent compensatory mechanisms.

INDOCIN, like other non-steroidal anti-inflammatory agents, can inhibit platelet aggregation. This effect is of shorter duration than that seen with aspirin and usually disappears within 24 hours after discontinuation of INDOCIN. INDOCIN has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this effect may be exaggerated in patients with underlying hemostatic defects, INDOCIN should be used with caution in persons with coagulation defects.

As with other non-steroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with INDOCIN. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with INDOCIN as with other non-steroidal anti-inflammatory drugs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), INDOCIN should be discontinued.

Information for Patients

INDOCIN, like other drugs of its class, is not free of side effects. The side effects of these drugs can cause discomfort and, rarely, there are more serious side effects such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes.

Continued on next page

Indocin—Cont.

NSAIDs (Non-steroidal Anti-inflammatory Drugs) are often essential agents in the management of arthritis; but they also may be commonly employed for conditions which are less serious.

Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS) and likely benefits of NSAID treatment, particularly when the drugs are used for less serious conditions where treatment without NSAIDs may represent an acceptable alternative to both the patient and physician.

Laboratory Tests

Because serious GI tract ulceration and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulceration and bleeding and should inform them of the importance of this follow-up (see WARNINGS, *Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy*).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In an 81-week chronic oral toxicity study in the rat at doses up to 1 mg/kg/day, indomethacin had no tumorigenic effect. Indomethacin produced no neoplastic or hyperplastic changes related to treatment in carcinogenic studies in the rat (dosing period 73–110 weeks) and the mouse (dosing period 62–88 weeks) at doses up to 1.5 mg/kg/day.

Indomethacin did not have any mutagenic effect in *in vitro* bacterial tests (Ames test and *E. coli* with or without metabolic activation) and a series of *in vivo* tests including the host-mediated assay, sex-linked recessive lethals in *Drosophila*, and the micronucleus test in mice.

Indomethacin at dosage levels up to 0.5 mg/kg/day had no effect on fertility in mice in a two generation reproduction study or a two litter reproduction study in rats.

Drug Interactions

In normal volunteers receiving indomethacin, the administration of diflunisal decreased the renal clearance and significantly increased the plasma levels of indomethacin. In some patients, combined use of INDOCIN and diflunisal has been associated with fatal gastrointestinal hemorrhage. Therefore, diflunisal and INDOCIN should not be used concomitantly.

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%.

The concomitant use of INDOCIN with other NSAIDs is not recommended due to the increased possibility of gastrointestinal toxicity, with little or no increase in efficacy.

Clinical studies have shown that INDOCIN does not influence the hypoprothrombinemia produced by anticoagulants. However, when any additional drug, including INDOCIN, is added to the treatment of patients on anticoagulant therapy, the patients should be observed for alterations of the prothrombin time.

When INDOCIN is given to patients receiving probenecid, the plasma levels of indomethacin are likely to be increased. Therefore, a lower total daily dosage of INDOCIN may produce a satisfactory therapeutic effect. When increases in the dose of INDOCIN are made, they should be made carefully and in small increments.

Caution should be used if INDOCIN is administered simultaneously with methotrexate. INDOCIN has been reported to decrease the tubular secretion of methotrexate and to potentiate its toxicity.

Administration of non-steroidal anti-inflammatory drugs concomitantly with cyclosporine has been associated with an increase in cyclosporine-induced toxicity, possibly due to decreased synthesis of renal prostacyclin. NSAIDs should be used with caution in patients taking cyclosporine, and renal function should be monitored.

Capsules INDOCIN 50 mg t.i.d. produced a clinically relevant elevation of plasma lithium and reduction in renal lithium clearance in psychiatric patients and normal subjects with steady state plasma lithium concentrations. This effect has been attributed to inhibition of prostaglandin synthesis. As a consequence, when INDOCIN and lithium are given concomitantly, the patient should be carefully observed for signs of lithium toxicity. (Read circulars for lithium preparations before use of such concomitant therapy.) In addition, the frequency of monitoring serum lithium concentration should be increased at the outset of such combination drug treatment.

INDOCIN given concomitantly with digoxin has been reported to increase the serum concentration and prolong the half-life of digoxin. Therefore, when INDOCIN and digoxin are used concomitantly, serum digoxin levels should be closely monitored.

In some patients, the administration of INDOCIN can reduce the diuretic, natriuretic, and, antihypertensive effects of loop, potassium-sparing, and thiazide diuretics. Therefore, when INDOCIN and diuretics are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

INDOCIN 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 hy-

Incidence greater than 1%	*Incidence less than 1%*	
CARDIOVASCULAR		
none	hypertension	congestive heart failure
	hypotension	arrhythmia;
	tachycardia	palpitations
	chest pain	
METABOLIC		
none	edema	hyperglycemia
	weight gain	glycosuria
	fluid retention	hyperkalemia
	flushing or sweating	
INTEGUMENTARY		
none	pruritus	exfoliative dermatitis
	rash; urticaria	erythema nodosum
	petechiae or ecchymosis	loss of hair
		Stevens-Johnson syndrome
		erythema multiforme
		toxic epidermal necrolysis
HEMATOLOGIC		
none	leukopenia	aplastic anemia
	bone marrow depression	hemolytic anemia
	anemia secondary to obvious or occult gastrointestinal bleeding	agranulocytosis
		thrombocytopenic purpura
		disseminated intravascular coagulation
HYPERSENSITIVITY		
none	acute anaphylaxis	dyspnea
	acute respiratory distress	asthma
		purpura
	rapid fall in blood pressure resembling a shock-like state	angiitis
		pulmonary edema
		fever
	angioedema	
GENITOURINARY		
none	hematuria	BUN elevation
	vaginal bleeding	renal insufficiency, including renal failure
	proteinuria	
	nephrotic syndrome	
	interstitial nephritis	
MISCELLANEOUS		
none	epistaxis	
	breast changes, including enlargement and tenderness, or gynecomastia	

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

INDOCIN and potassium-sparing diuretics each may be associated with increased serum potassium levels. The potential effects of INDOCIN and potassium-sparing diuretics on potassium kinetics and renal function should be considered when these agents are administered concurrently.

Most of the above effects concerning diuretics have been attributed, at least in part, to mechanisms involving inhibition of prostaglandin synthesis by INDOCIN.

Blunting of the antihypertensive effect of beta-adrenoceptor blocking agents by non-steroidal anti-inflammatory drugs including INDOCIN has been reported. Therefore, when using these blocking agents to treat hypertension, patients should be observed carefully in order to confirm that the desired therapeutic effect has been obtained. There are reports that INDOCIN can reduce the antihypertensive effect of captopril in some patients.

False-negative results in the dexamethasone suppression test (DST) in patients being treated with INDOCIN have been reported. Thus, results of the DST should be interpreted with caution in these patients.

Pediatric Use

Effectiveness in pediatric patients 14 years of age and younger has not been established (see WARNINGS).

Geriatric Use

As with any NSAID, caution should be exercised in treating the elderly (65 years and older) since advancing age appears to increase the possibility of adverse reactions (see WARNINGS, *General*; and DOSAGE AND ADMINISTRATION).

Elderly patients seem to tolerate ulceration or bleeding less well than other individuals and many spontaneous reports of fatal GI events are in this population (see WARNINGS, *Risk of GI Ulcerations, Bleeding and Perforation with NSAID Therapy*).

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

This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function (see WARNINGS, *Renal*

cidence 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 INDOCIN and these adverse reactions, some of which have been reported only rarely.

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

The adverse reactions reported with Capsules INDOCIN may also occur with use of the suspension.

[See table at top of previous page]

[See table above]

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: Thrombophlebitis

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

Genitourinary: Urinary frequency.

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

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

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