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Indocin/Indocin SR—Cont.

HOW SUPPLIED

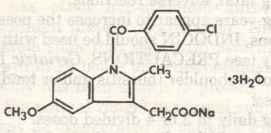
No. 3316—Capsules INDOCIN, 25 mg are opaque blue and white capsules, coded INDOCIN and MSD 25. They are supplied as follows:
NDC 0006-0025-68 bottles of 100
(6505-00-926-2154, 25 mg 100's)
NDC 0006-0025-82 bottles of 1000
(6505-00-931-0680, 25 mg 1000's).
Shown in Product Identification Guide, page 323
No. 3317—Capsules INDOCIN, 50 mg are opaque blue and white capsules, coded INDOCIN and MSD 50. They are supplied as follows:
NDC 0006-0050-68 bottles of 100
(6505-01-049-6811, 50 mg 100's).
Shown in Product Identification Guide, page 323
No. 3376—Oral Suspension INDOCIN, 25 mg per 5 mL, is an off-white suspension with a pineapple coconut mint flavor. It is supplied as follows:
NDC 0006-3376-66 in bottles of 237 mL.
No. 3370—Capsules INDOCIN SR, 75 mg each, are capsules with an opaque blue cap and clear body containing a mixture of blue and white pellets, coded INDOCIN SR and MSD 693. They are supplied as follows:
NDC 0006-0693-31 unit of use bottles of 30
(6505-01-135-7391, 75 mg 30's)
NDC 0006-0693-61 unit of use bottles of 60
(6505-01-137-4629, 75 mg 60's).
Shown in Product Identification Guide, page 323
No. 3354—Suppositories INDOCIN, 50 mg each, are white, opaque, rectal suppositories and are supplied as follows:
NDC 0006-0150-30, boxes of 30
(6505-01-231-7284, 50 mg 30's).
Shown in Product Identification Guide, page 323
Storage
Store Oral Suspension INDOCIN below 30°C (86°F). Avoid temperatures above 50°C (122°F). Protect from freezing.
Store Suppositories INDOCIN below 30°C (86°F). Avoid transient temperatures above 40°C (104°F).

Suppositories INDOCIN are distributed by:
MERCK SHARP & DOHME, Division of Merck & Co., Inc.
West Point, Pa. 19486
Manufactured by:
MERCK SHARP & DOHME
(Italia) S.p.A.
27100—Pavia, Italy
Capsules and Oral Suspension INDOCIN® and Capsules INDOCIN® SR are distributed and manufactured by:
MERCK SHARP & DOHME, Division of Merck & Co., Inc.
West Point, Pa. 19486
7873326 Issued July 1998

INDOCIN® I.V. ℞
(Indomethacin Sodium Trihydrate)

DESCRIPTION

Sterile INDOCIN* I.V. (Indomethacin Sodium Trihydrate) for intravenous administration is lyophilized indomethacin sodium trihydrate. Each vial contains indomethacin sodium trihydrate equivalent to 1 mg indomethacin as a white to yellow lyophilized powder or plug. Variations in the size of the lyophilized plug and the intensity of color have no relationship to the quality or amount of indomethacin present in the vial.
Indomethacin sodium trihydrate is designated chemically as 1-(4-chlorobenzoyl) -5- methoxy-2-methyl-1*H* -indole-3-acetic acid, sodium salt, trihydrate. Its molecular weight is 433.82. Its empirical formula is $C_{19}H_{15}ClNNaO_4 \cdot 3H_2O$ and its structural formula is:



*Registered trademark of MERCK & CO., Inc.

CLINICAL PHARMACOLOGY

Although the exact mechanism of action through which indomethacin causes closure of a patent ductus arteriosus is not known, it is believed to be through inhibition of prostaglandin synthesis. Indomethacin has been shown to be a potent inhibitor of prostaglandin synthesis, both *in vitro* and *in vivo*. In human newborns with certain congenital heart malformations, PGE 1 dilates the ductus arteriosus. In fetal and newborn lambs, E type prostaglandins have also been shown to maintain the patency of the ductus, and as in human newborns, indomethacin causes its constriction.
Studies in healthy young animals and in premature infants with patent ductus arteriosus indicated that, after the first dose of intravenous indomethacin, there was a transient reduction in cerebral blood flow velocity and cerebral blood flow. Similar decreases in mesenteric blood flow and velocity have been observed. The clinical significance of these effects has not been established.
In double-blind placebo-controlled studies of INDOCIN I.V. in 460 small pre-term infants, weighing 1750 g or less, the neonates treated with placebo had a ductus closure rate after 48 hours of 25 to 30 percent, whereas those treated with INDOCIN I.V. had a 75 to 80 percent closure rate. In one of these studies, a multicenter study, involving 405 pre-term *infants, later re-opening of the ductus arteriosus occurred in* 26 percent of neonates treated with INDOCIN I.V., however, 70 percent of these closed subsequently without the need for surgery or additional indomethacin.
Pharmacokinetics and Metabolism
The disposition of indomethacin following intravenous administration (0.2 mg/kg) in pre-term neonates with patent ductus arteriosus has not been extensively evaluated. Even though the plasma half-life of indomethacin was variable among premature infants, it was shown to vary inversely with postnatal age and weight. In one study, of 28 neonates who could be evaluated, the plasma half-life in those less than 7 days old averaged 20 hours (range: 3–60 hours, n = 18). In neonates older than 7 days, the mean plasma half-life of indomethacin was 12 hours (range: 4–38 hours, n = 10). Grouping the neonates by weight, mean plasma half-life in those weighing less than 1000 g was 21 hours (range: 9–60 hours, n = 10); in those neonates weighing more than 1000 g, the mean plasma half-life was 15 hours (range: 3–52 hours, n = 18).
Following intravenous administration in adults, indomethacin is eliminated via renal excretion, metabolism, and biliary excretion. Indomethacin undergoes appreciable enterohepatic circulation. The mean plasma half-life of indomethacin is 4.5 hours. In the absence of enterohepatic circulation, it is 90 minutes. Indomethacin has been found to cross the blood-brain barrier and the placenta.
In adults, about 99 percent of indomethacin is bound to protein in plasma over the expected range of therapeutic plasma concentrations. The percent bound in neonates has not been studied. In controlled trials in premature infants, however, no evidence of bilirubin displacement has been observed as evidenced by increased incidence of bilirubin encephalopathy (kernicterus).

INDICATIONS AND USAGE

INDOCIN I.V. is indicated to close a hemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when after 48 hours usual medical management (e.g., fluid restriction, diuretics, digitalis, respiratory support, etc.) is ineffective. Clear-cut clinical evidence of a hemodynamically significant patent ductus arteriosus should be present, such as respiratory distress, a continuous murmur, a hyperactive precordium, cardiomegaly and pulmonary plethora on chest x-ray.

CONTRAINDICATIONS

INDOCIN I.V. is contraindicated in: neonates with proven or suspected infection that is untreated; neonates who are bleeding, especially those with active intracranial hemorrhage or gastrointestinal bleeding; neonates with thrombocytopenia; neonates with coagulation defects; neonates with or who are suspected of having necrotizing enterocolitis; neonates with significant impairment of renal function; neonates with congenital heart disease in whom patency of the ductus arteriosus is necessary for satisfactory pulmonary or systemic blood flow (e.g., pulmonary atresia, severe tetralogy of Fallot, severe coarctation of the aorta).

WARNINGS

Gastrointestinal Effects:
In the collaborative study, major gastrointestinal bleeding was no more common in those neonates receiving indomethacin than in those neonates on placebo. However, minor gastrointestinal bleeding (i.e., chemical detection of blood in the stool) was more commonly noted in those neonates treated with indomethacin. Severe gastrointestinal effects have been reported in adults with various arthritic disorders treated chronically with oral indomethacin. [For further information, see package circular for Capsules INDOCIN* (Indomethacin)].
Central Nervous System Effects:
Prematurity per se, is associated with an increased incidence of spontaneous intraventricular hemorrhage. Because indomethacin may inhibit platelet aggregation, the potential for intraventricular bleeding may be increased. However, in the large multi-center study of INDOCIN I.V. (see CLINICAL PHARMACOLOGY), the incidence of intraventricular hemorrhage in neonates treated with INDOCIN I.V. was not significantly higher than in the control neonates.
Renal Effects:
INDOCIN I.V. may cause significant reduction in urine output (50 percent or more) with concomitant elevations of blood urea nitrogen and creatinine, and reductions in glomerular filtration rate and creatinine clearance. These effects in most neonates are transient, disappearing with cessation of therapy with INDOCIN I.V. However, because adequate renal function can depend upon renal prostaglandin synthesis, INDOCIN I.V. may precipitate renal insufficiency, including acute renal failure, especially in neonates with other conditions that may adversely affect renal function (e.g., extracellular volume depletion from any cause, congestive heart failure, sepsis, concomitant use of any nephrotoxic drug, hepatic dysfunction). When significant suppression of urine volume occurs after a dose of INDOCIN I.V., no additional dose should be given until the urine output returns to normal levels.
INDOCIN I.V. in pre-term infants may suppress water excretion to a greater extent than sodium excretion. When this occurs, a significant reduction in serum sodium values (i.e., hyponatremia) may result. Neonates should have serum electrolyte determinations done during therapy with *INDOCIN I.V. Renal function and serum electrolytes should* be monitored (see PRECAUTIONS, *Drug Interactions* and DOSAGE AND ADMINISTRATION).

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* Registered trademark of MERCK & CO., Inc.

PRECAUTIONS

General
INDOCIN (Indomethacin) may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the drug with extra care in the presence of existing controlled infection.
Severe hepatic reactions have been reported in adults treated chronically with oral indomethacin for arthritic disorders. [For further information, see package circular for Capsules INDOCIN (Indomethacin)]. If clinical signs and symptoms consistent with liver disease develop in the neonate, or if systemic manifestations occur, INDOCIN I.V. should be discontinued.
INDOCIN I.V. may inhibit platelet aggregation. In one small study, platelet aggregation was grossly abnormal after indomethacin therapy (given orally to premature infants to close the ductus arteriosus). Platelet aggregation returned to normal by the tenth day. Premature infants should be observed for signs of bleeding.
The drug should be administered carefully to avoid extravascular injection or leakage as the solution may be irritating to tissue.
Drug Interactions
Since renal function may be reduced by INDOCIN I.V., consideration should be given to reduction in dosage of those medications that rely on adequate renal function for their elimination. Because the half-life of digitalis (given frequently to pre-term infants with patent ductus arteriosus and associated cardiac failure) may be prolonged when given concomitantly with indomethacin, the neonate should be observed closely; frequent ECGs and serum digitalis levels may be required to prevent or detect digitalis toxicity early. Furthermore, in one study of premature infants treated with INDOCIN I.V. and also receiving either gentamicin or amikacin, both peak and trough levels of these aminoglycosides were significantly elevated.
Therapy with indomethacin may blunt the natriuretic effect of furosemide. This response has been attributed to inhibition of prostaglandin synthesis by non-steroidal anti-inflammatory drugs. In a study of 19 premature infants with patent ductus arteriosus treated with either INDOCIN I.V. alone or a combination of INDOCIN I.V. and furosemide, results showed that neonates receiving both INDOCIN I.V. and furosemide had significantly higher urinary output, higher levels of sodium and chloride excretion, and higher glomerular filtration rates than did those receiving INDOCIN I.V. alone. In this study, the data suggested that therapy with furosemide helped to maintain renal function in the premature infant when INDOCIN I.V. was added to the treatment of patent ductus arteriosus.
Neonatal Effects
In rats and mice, oral indomethacin 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.
Pregnant rats, given 2.0 mg/kg/day and 4.0 mg/kg/day during the last trimester of gestation, delivered offspring whose pulmonary blood vessels were both reduced in number and excessively muscularized. These findings are similar to those observed in the syndrome of persistent pulmonary hypertension of the neonate.

ADVERSE REACTIONS

In a double-blind placebo-controlled trial of 405 premature infants weighing less than or equal to 1750 g with evidence of large ductal shunting, in those neonates treated with indomethacin (n = 206), there was a statistically significantly greater incidence of bleeding problems, including gross or microscopic bleeding into the gastrointestinal tract, oozing from the skin after needle stick, pulmonary hemorrhage, and disseminated intravascular coagulopathy. There was no statistically significant difference between treatment groups with reference to intracranial hemorrhage.
The neonates treated with indomethacin sodium trihydrate also had a significantly higher incidence of transient oliguria and elevations of serum creatinine (greater than or equal to 1.8 mg/dL) than did the neonates treated with placebo.
The incidences of retrolental fibroplasia (grades III and IV) and pneumothorax in neonates treated with INDOCIN I.V.

were no greater than in placebo controls and were statistically significantly lower than in surgically-treated neonates. The following additional adverse reactions in neonates have been reported from the collaborative study, anecdotal case reports, from other studies using rectal, oral, or intravenous indomethacin for treatment of patent ductus arteriosus or in marketed use. The rates are calculated from a database which contains experience of 849 indomethacin-treated neonates reported in the medical literature, regardless of the route of administration. One year follow-up is available on 175 neonates and shows no long-term sequelae which could be attributed to indomethacin. In controlled clinical studies, only electrolyte imbalance and renal dysfunction (of the reactions listed below) occurred statistically significantly more frequently after INDOCIN I.V. than after placebo. Reactions marked with a single asterick (*) occurred in 3–9 percent of indomethacin-treated neonates: those marked with a double asterisk (**) occurred in 3–9 percent of both indomethacin- and placebo-treated neonates. Unmarked reactions occurred in less than 3 percent of neonates.

Renal: renal dysfunction in 41 percent of neonates, including one or more of the following: reduced urinary output; reduced urine sodium, chloride, or potassium urine osmolality, free water clearance, or glomerular filtration, rate; elevated serum creatinine or BUN; uremia.

Cardiovascular: intracranial bleeding**, pulmonary hypertension.

Gastrointestinal: gastrointestinal bleeding*, vomiting, abdominal distention, transient ileus, localized perforation(s) of the small and/or large intestine.

Metabolic: hyponatremia*, elevated serum potassium*, reduction in blood sugar, including hypoglycemia, increased weight gain (fluid retention).

Coagulation: decreased platelet aggregation (see PRECAUTIONS).

The following adverse reactions have also been reported in neonates treated with indomethacin, however, a causal relationship to therapy with INDOCIN I.V. has not been established:

Cardiovascular: bradycardia.

Respiratory: apnea, exacerbation of pre-existing pulmonary infection.

Metabolic: acidosis/alkalosis.

Hematologic: disseminated intravascular coagulation.

Gastrointestinal: necrotizing enterocolitis.

Ophthalmic: retrolental fibroplasia.**

A variety of additional adverse experiences have been reported in adults treated with oral indomethacin for moderate to severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute painful shoulder and acute gouty arthritis (see section ADDITIONAL ADVERSE REACTIONS—ADULTS). Their relevance to the pre-term infant receiving indomethacin for patent ductus arteriosus is unknown, however, the possibility exists that these experiences may be associated with the use of INDOCIN I.V. in pre-term infants.

DOSAGE AND ADMINISTRATION

FOR INTRAVENOUS ADMINISTRATION ONLY.

Dosage recommendations for closure of the ductus arteriosus depends on the age of the infant at the time of therapy. A course of therapy is defined as three intravenous doses of INDOCIN I.V. given at 12–24 hour intervals, with careful attention to urinary output. If anuria or marked oliguria (urinary output < 0.6 mL/kg/hr) is evident at the scheduled time of the second or third dose of INDOCIN I.V., no additional doses should be given until laboratory studies indicate that renal function has returned to normal (see WARNINGS, *Renal Effects*).

Dosage according to age is as follows:

AGE at 1st dose	DOSAGE (mg/kg)		
	1st	2nd	3rd
Less than 48 hours	0.2	0.1	0.1
2–7 days	0.2	0.2	0.2
over 7 days	0.2	0.25	0.25

If the ductus arteriosus closes or is significantly reduced in size after an interval of 48 hours or more from completion of the first course of INDOCIN I.V., no further doses are necessary. If the ductus arteriosus re-opens, a second course of 1–3 doses may be given, each dose separated by a 12–24 hour interval as described above.

If the infant remains unresponsive to therapy with INDOCIN I.V. after 2 courses, surgery may be necessary for closure of the ductus arteriosus. If severe adverse reactions occur, STOP THE DRUG.

Directions for Use

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The solution should be prepared only with 1 to 2 mL of preservative-free sterile Sodium Chloride Injection, 0.9 percent or preservative-free Sterile Water for Injection. Benzyl alcohol as a preservative has been associated with toxicity in neonates. Therefore, all diluents should be preservative-free. If 1 mL of diluent is used, the concentration of indomethacin in the solution will equal approximately 0.1 mg/0.1 mL; if 2 mL of diluent are used, the concentration of the solution will equal approximately 0.05 mg/0.1 mL. Any unused portion of the solution should be discarded because there is no preservative contained in the vial. A fresh solution should be prepared just prior to each administration. Once reconstituted, the indomethacin solution may be injected intravenously. While the optimal rate of injection has not been established, published literature suggests an infusion rate over 20–30 minutes.

Further dilution with intravenous infusion solutions is not recommended. INDOCIN I.V. is not buffered, and reconstitution with solutions at pH values below 6.0 may result in precipitation of the insoluble indomethacin free acid moiety.

HOW SUPPLIED

No. 3406—Sterile INDOCIN I.V. is a lyophilized white to yellow powder or plug supplied as single dose vials containing indomethacin sodium trihydrate, equivalent to 1 mg indomethacin.

NDC 0006-3406-17

(6505-01-209-1192, 3 single dose vials).

Storage

Store below 30°C (86°F). *Protect from light.* Store container in carton until contents have been used.

ADDITIONAL ADVERSE REACTIONS—ADULTS

The following adverse reactions have been reported in adults treated with oral indomethacin for moderate to severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute painful shoulder and acute gouty arthritis. Complaints not of relevance in the treatment of the premature infant, such as anorexia, psychic disturbances, and blurred vision, are not listed.

Incidence 1% to 3%		***Incidence less than 1%***
GASTROINTESTINAL		
diarrhea constipation	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 pre-existing sigmoid lesions development of ulcerative stomatitis toxic hepatitis and jaundice (some fatal cases have been reported) intestinal strictures (diaphragms)
CENTRAL NERVOUS SYSTEM		
none	involuntary muscle movements	aggravation of epilepsy coma peripheral neuropathy convulsions
SPECIAL SENSES		
none	hearing disturbances, deafness	
CARDIOVASCULAR		
none	hypertension hypotension tachycardia	arrhythmia congestive heart failure thrombophlebitis
METABOLIC		
none	edema weight gain flushing	hyperglycemia glycosuria hyperkalemia
INTEGUMENTARY		
none	rash; urticaria petechiae or ecchymosis	exfoliative dermatitis erythema nodosum loss of hair Stevens-Johnson syndrome erythema multiforme toxic epidermal necrolysis
HEMATOLOGIC		
none	leukopenia bone marrow depression anemia secondary to obvious or occult gastrointestinal bleeding	aplastic anemia hemolytic anemia agranulocytosis thrombocytopenic purpura
HYPERSENSITIVITY		
none	acute anaphylaxis acute respiratory distress rapid fall in blood pressure resembling a shock-like state	dyspnea asthma purpura angiitis pulmonary edema
GENITOURINARY		
none	hematuria vaginal bleeding	renal insufficiency, including renal failure
MISCELLANEOUS		
none	epistaxis breast changes, including enlargement and tenderness, or gynecomastia	

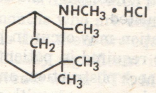
See package circular for Capsules INDOCIN (Indomethacin) for additional information concerning adverse reactions and other cautionary statements.

7414815 Issued June 1998

INVERSINE® Tablets (Mecamylamine HCl), U.S.P. ℞

DESCRIPTION

INVERSINE* (Mecamylamine HCl) is a potent, oral antihypertensive agent and ganglion blocker, and is a secondary amine. It is *N*, 2,3,3-tetramethylbicyclo[2.2.1] heptan-2-amine hydrochloride. Its empirical formula is $C_{11}H_{21}N \cdot HCl$ and its structural formula is:



It is a white, odorless, or practically odorless, crystalline powder, is highly stable, soluble in water and has a molecular weight of 203.75.

INVERSINE is supplied as tablets for oral use, each containing 2.5 mg mecamylamine HCl. Inactive ingredients are acacia, calcium phosphate, D&C Yellow 10, FD&C Yellow 6, lactose, magnesium stearate, starch, and talc.

*Registered trademark of MERCK & CO., INC.

CLINICAL PHARMACOLOGY

Mecamylamine reduces blood pressure in both normotensive and hypertensive individuals. It has a gradual onset of action ($^1/_2$ to 2 hours) and a long-lasting effect (usually 6 to 12 hours or more). A small oral dosage often produces a smooth and predictable reduction of blood pressure. Although this antihypertensive effect is predominantly orthostatic, the supine blood pressure is also significantly reduced.

Pharmacokinetics and Metabolism

Mecamylamine is almost completely absorbed from the gastrointestinal tract, resulting in consistent lowering of blood pressure in most patients with hypertensive cardiovascular disease. Mecamylamine is excreted slowly in the urine in the unchanged form. The rate of its renal elimination is influenced markedly by urinary pH. Alkalinization of the urine reduces, and acidification promotes, renal excretion of mecamylamine.

Mecamylamine crosses the blood-brain and placental barriers.

INDICATIONS AND USAGE

For the management of moderately severe to severe essential hypertension and in uncomplicated cases of malignant hypertension.

CONTRAINDICATIONS

INVERSINE should not be used in mild, moderate, labile hypertension and may prove unsuitable in uncooperative patients. It is contraindicated in coronary insufficiency or recent myocardial infarction.

INVERSINE should be given with great discretion, if at all, when renal insufficiency is manifested by a rising or elevated BUN. The drug is contraindicated in uremia. Patients receiving antibiotics and sulfonamides should generally not be treated with ganglion blockers. Other contraindications are glaucoma, organic pyloric stenosis or hypersensitivity to the product.

WARNINGS

Mecamylamine, a secondary amine, readily penetrates into the brain and thus may produce central nervous sytem effects. Tremor, choreiform movements, mental aberrations, and convulsions may occur rarely. These have occurred most often when large doses of INVERSINE were used, especially in patients with cerebral or renal insufficiency.

When ganglion blockers or other potent antihypertensive drugs are discontinued suddenly, hypertensive levels re-

Continued on next page