HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Indomethacin for Injection safely and effectively. See full prescribing information for Indomethacin for Injection. Indomethacin for Injection Initial U.S. Approval: 1965

INDICATIONS AND USAGE
Indomethacin for Injection is a cardiovascular drug indicated:
• To close a hemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g. (1)

DOSEAGE AND ADMINISTRATION
• Dosage is dependent on the age of the infant at time of therapy. A course of therapy requires intravenous doses of Indomethacin for injection given at 12 to 24 hour intervals.

<table>
<thead>
<tr>
<th>AGE at 1st dose</th>
<th>DOSAGE (mg/kg)</th>
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</thead>
<tbody>
<tr>
<td>Less than 48</td>
<td>1st 2nd 3rd</td>
</tr>
<tr>
<td>hours</td>
<td>0.2 0.1 0.1</td>
</tr>
<tr>
<td>2 to 7 days</td>
<td>0.2</td>
</tr>
<tr>
<td>Over 7 days</td>
<td>0.2 0.25 0.25</td>
</tr>
</tbody>
</table>

• 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 Indomethacin for injection, do not give additional doses until laboratory studies indicate that renal function has returned to normal.

• 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 Indomethacin for injection, no further doses are necessary.

• If the neonate remains unresponsive to therapy with Indomethacin for Injection after 2 courses, surgery may be necessary for closure of the ductus arteriosus. (2.1)

DOSE FORMS AND STRENGTHS
• Single use vials of 1 mg indomethacin as a sterile, lyophilized powder or plug for reconstitution. (3)

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5.5 Central Nervous System Effects
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FULL PRESCRIBING INFORMATION
1 INDICATIONS AND USAGE
Indomethacin for Injection is indicated to close a hemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when 48 hours usual medical management is ineffective. Clear-cut clinical evidence of a hemodynamically significant patent ductus arteriosus should be present, such as respiratory distress, a continuoous murmur, a hyperactive precordium, cromegaly, or pulmonary plethora on chest x-ray.

2 DOSAGE AND ADMINISTRATION
For intravenous administration:
Dosage recommendations for closure of the ductus arteriosus depend on the age of the infant at the time of therapy. A course of therapy is defined as three intravenous doses of Indomethacin for injection given at 12 to 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 Indomethacin for injection, do not give additional doses until laboratory studies indicate that renal function has returned to normal. (see Warnings and Precautions (5.7)).

Dosage according to age is as follows:

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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 Indomethacin for Injection, no further doses are necessary. If the ductus arteriosus re-opens, a second course of 1 to 3 doses may be given, each dose separated by a 12 to 24 hour interval as described above.

If the neonate remains unresponsive to therapy with Indomethacin for Injection after 2 courses, surgery may be necessary for closure of the ductus arteriosus.

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

The reconstituted solution, pH 6.0 to 7.5, is clear, colorless, and as in human newborns, indomethacin causes its constriction.

5.3 Platelet aggregation:
In double-blind, placebo-controlled studies of premature infants treated with Indomethacin for Injection alone or a combination of Indomethacin for Injection and caffeine for the prevention of intraventricular hemorrhage, 70 percent in the Indomethacin group treated with Indomethacin for Injection had a 75 percent or greater 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. (5.3)

5.4 Gastrointestinal Effects:
• Infections, most common adverse reactions are bleeding problems, higher incidence of transient oliguria and elevations of serum creatinine. (6.1)

5.5 Central Nervous System Effects:
• Monitor for hepatic reactions. Indomethacin for Injection may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and other signs of possible infection. (5.5)

5.6 Renal Effects:
• Monitor prothrombin time when indomethacin is added to anticoagulants. (5.6)

5.7. Administration
• When used concomitantly with digoxin, monitor neonates for the development of digoxin toxicity. (7.1)
• Monitor prothrombin time when indomethacin is added to anticoagulants. (7.2)

ADVERSE REACTIONS
Most common adverse reactions are bleeding problems, higher incidence of transient oliguria and elevations of serum creatinine. (6.1)

7 DRUG INTERACTIONS
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7.2 Anticoagulants
7.3 Furosemide
7.4 Aminoglycosides
7.5 Drugs that Act on the Renin-Angiotensin System

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12 CLINICAL PHARMACOLOGY
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*Sections or subsections omitted from the full prescribing information are not listed.

CONTRAINDICATIONS
Indomethacin for Injection is contraindicated in neonates:
• With proven or suspected infection that is untreated
• Who are bleeding, especially those with active intracranial hemorrhage or gastrointestinal bleeding
• With thrombocytopenia or coagulation defects
• With or who are suspected of having necrotizing enterocolitis
• With significant impairment of renal function
• With congenital heart disease in whom patency of the ductus arteriosus is necessary for

WARNINGS AND PRECAUTIONS
• Indomethacin may mask the usual signs of infection. (5.1)
• Monitor for hepatic reactions. Indomethacin for Injection may need to be discontinued. (5.2)
• Indomethacin for Injection may inhibit platelet aggregation. (5.3)
• Gastrointestinal Effects: Monitor neonates for blood in stool. (5.4)
• Central Nervous System Effects: Monitor neonates for intraventricular hemorrhage. (5.5)
• Renal Effects: Monitor renal function and serum electrolytes. (5.6)

REFERENCES

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satisfactory pulmonary or systemic blood flow (e.g., severe tetralogy of Fallot, severe coarctation of the aorta).

5 WARNINGS AND PRECAUTIONS

5.1 Induction

Indomethacin may mask the usual signs and symptoms of infection. Therefore, the physician should be alert for this and should use the drug with extra care in the presence of existing controlled infection.

5.2 Hepatic Reactions

Serious hepatic reactions have been reported in adults treated chronically with oral indomethacin. [For further information, see package insert for oral indomethacin]. If clinical deterioration occurs, consistent with disease in the liver, clinical studies indicate that hepatic disease develop in the neonate, or if systemic manifestations occur, discontinue Indomethacin for Injection.

5.3 Platelet Aggregation

Indomethacin for Injection may inhibit platelet aggregation. In a small study, platelet aggregation was grossly abnormal after indomethacin therapy in premature infants with patent ductus arteriosus (i.e., chemical detection of blood in the stool) was more commonly noted in neonates treated with indomethacin for Injection. Severe gastrointestinal effects have been reported in adults with various arthritides treated chronically with oral indomethacin. [For further information, see package insert for oral indomethacin].

5.5 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 hemorrhaging may be increased. However, in the large multicenter study of Indomethacin for Injection, the incidence of intraventricular hemorrhage in neonates treated with Indomethacin for Injection was not significantly higher than in the control neonates.

5.6 Renal Effects

Indomethacin for Injection may cause significant reductions 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 are transient, disappearing with cessation of therapy with Indomethacin for Injection. However, because adequate renal function can depend upon renal prostaglandin synthesis, Indomethacin for Injection may contribute to renal insufficiency, including acute renal failure, especially in neonates, with or without other conditions that may adversely affect renal function (e.g., extracellulor volume depletion, congestive heart failure, sepsis, concomitant use of any nephrotoxic drug, hepatic dysfunction). When significant suppression of urine output occurs after a dose of Indomethacin for Injection, do not give additional doses until urine output returns to normal levels.

Indomethacin for Injection in pre-term infants may lead to oliguria or anuria, with postnatal weight gain with evidence of large ductal shunting, in those neonates treated with indomethacin (n=206). There was a statistically significantly greater incidence of bleeding problems in the indomethacin group compared to placebo. The incidence of bleeding problems was significantly higher in the group of neonates with patent ductus arteriosus. The incidence of bleeding problems was significantly higher in the neonates treated with Indomethacin for Injection and furosemide than in those treated with Indomethacin for Injection alone. In this study, neonates treated with indomethacin (n=206) had a 75 percent closure rate, whereas neonates treated with placebo had a ductus closure rate of 5 percent. The significance of these effects has not been established for the concomitant use of indomethacin in the treatment of patent ductus arteriosus. In the large multicenter study of Indomethacin for Injection, infants weighing 1750 g or less, the neonates treated with Indomethacin for Injection and furosemide, who had patent ductus arteriosus treated with either Indomethacin for Injection and furosemide, or indomethacin alone, had a closure rate of 80 percent. These effects may be prolonged when given concomitantly with indomethacin, but the neonates receiving concomitant digoxin closely, frequent ECGs and serum digoxin levels may be required to prevent or detect digoxin toxicity early.

5.7 Administration

Administration of Indomethacin for Injection carefully to avoid extravascular injection or leakage as the solution is being at issue.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

In the collaborative study, major gastrointestinal bleeding was not observed in neonates receiving indomethacin than in neonates on placebo. However, various adverse gastrointestinal effects (i.e., chemical detection of blood in the stool) were more commonly noted in neonates treated with indomethacin for Injection. Severe gastrointestinal effects have been reported in adults with various arthritides treated chronically with oral indomethacin. [For further information, see package insert for oral indomethacin].

6.2 Hepatic Reactions

Serious hepatic reactions have been reported in adults treated chronically with oral indomethacin. [For further information, see package insert for oral indomethacin]. If clinical deterioration occurs, consistent with disease in the liver, clinical studies indicate that hepatic disease develop in the neonate, or if systemic manifestations occur, discontinue Indomethacin for Injection.

6.3 Platelet Aggregation

Indomethacin for Injection may inhibit platelet aggregation. In a small study, platelet aggregation was grossly abnormal after indomethacin therapy in premature infants with patent ductus arteriosus (i.e., chemical detection of blood in the stool) was more commonly noted in neonates treated with indomethacin for Injection. Severe gastrointestinal effects have been reported in adults with various arthritides treated chronically with oral indomethacin. [For further information, see package insert for oral indomethacin].

7 DRUG INTERACTIONS

7.1 Digoxin

Because the half-life of digoxin (given frequently to pre-term infants with patent ductus arteriosus and acute renal failure) may be prolonged when given concomitantly with indomethacin, but the neonates receiving concomitant digoxin closely, frequent ECGs and serum digoxin levels may be required to prevent or detect digoxin toxicity early.

7.2 Anticoagulants

Indomethacin usually does not influence the hypoprothrombinemia produced by anticoagulants. When indomethacin is added to anticoagulants, monitoring of the effects is necessary. In post-marketing experience, bleeding has been reported in patients treated with anticoagulants and Indomethacin for Injection.

7.3 Furosemide

Therapy with indomethacin may blunt the natriuretic effect of furosemide. This response has been attributed to inhibition of prostaglandin synthesis by indomethacin, a non-steroidal anti-inflammatory drug. In a study of 19 premature infants with patent ductus arteriosus treated with either Indomethacin for Injection or furosemide, results showed that infants receiving both Indomethacin for Injection and furosemide had significantly higher plasma chloride, sodium, and glucose levels than those receiving Indomethacin for Injection alone. In this study, therapy with furosemide helped to maintain renal function in the premature infant when Indomethacin for Injection was added.

7.4 Aminoacids

In one study of premature infants treated with Indomethacin for Injection and also receiving
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).

13 NONCLINICAL TOXICOLOGY

In rats and mice, oral indomethacin 4 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 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups. Administration of 0.5 or 4 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 mg/kg/day and 4 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Sterile Indomethacin for Injection is a lyophilized white to yellow powder or plug supplied as single dose vials containing indomethacin for injection, equivalent to 1 mg indomethacin.

Product NDC No. No.
605903 63323-659-03 1 mg per vial, Packaged individually.

This container closure is not made with natural rubber latex.

16.2 Storage

Store at 25°C (77°F) with excursions permitted to 15° to 30°C (59° to 86°F). Protect from light. Store container in carton until contents have been used.