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 g and 1750 g (1) • DOSE 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 hours</td>
<td>1st 0.2 2nd 0.1 3rd 0.1</td>
</tr>
<tr>
<td>2 to 7 days</td>
<td>0.2 0.2 0.2</td>
</tr>
<tr>
<td>Over 7 days</td>
<td>0.2 0.25 0.25</td>
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• If anuria or marked oliguria (urinary output <0.6 mL/kg/hr) is evident at 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)

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.

• 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 satisfactory pulmonary or systemic blood flow. (4)

WARNINGS AND PRECAUTIONS

• Indomethacin may mask the usual signs of infection. (5.1)

• Monitor for signs of 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 intracranial hemorrhage. (5.5)

• Renal Effects: Monitor renal function and serum electrolytes. (5.6)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact APP Pharmaceuticals, LLC, Medical Information and Safety Department at 1-800-651-7712 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

• 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)

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5 WARNINGS AND PRECAUTIONS

5.1 Infection
Indomethacin may mask the usual signs and symptoms of infection. Therefore, the patient must be constantly on the alert for the occurrence of new infection.

5.2 Hepatic Reactions
Severe hepatic reactions have been reported in adults treated with oral indomethacin for arthritis. [For further information, see section 5.3.] If clinical signs and symptoms consistent with liver 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 one small study, platelet aggregation studies were performed in 38 males with abnormal platelet aggregation. The mean percent platelet aggregation returned to normal by the tenth day. Observe premature infants for signs of bleeding.

5.4 Gastrointestinal Effects
In the collaborative study, major gastrointestinal bleeding was no more common in neonates receiving indomethacin than in neonates on placebo. However, minor gastrointestinal bleeding (i.e., chemical detection of blood in the stool) was more commonly noted in 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 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 bleeding may be increased. However, in the 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 reduction in urine output (50 percent or more) in the infant, and consequent 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 Indomethacin for Injection. However, because adequate renal function can depend upon renal prostaglandin synthesis, Indomethacin for Injection 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, sepsis, hypotension, dehydration, septicemia, and hypovolemic shock). 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, osteitis deformans, and ankylosing spondylitis. Acute painful shoulder and acute gouty arthritis (see package insert for oral indomethacin for additional information concerning adverse reactions and other cautionary statements). Their relevance to the preterm infant receiving indomethacin for patent ductus arteriosus is unknown, however, the literature suggests an increased frequency of these experiences may be associated with the use of Indomethacin for Injection in preterm infants.

5.7 Administration
Administer Indomethacin for Injection carefully to avoid extravasation injection or leakage as the solution may be irritating to tissues.

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
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 for Injection (n = 200), there was a statistically significantly greater incidence of bleeding problems, including significant gross or microscopic bleeding into the gastrointestinal tract, oozing from the skin after needle stick, pulmonary hemorrhage, and disseminated intravascular coagulopathy. There was a statistically significant difference in the number of groups treated in clinical trials in which indomethacin is eliminated via renal excretion, than in studies of neonates treated with indomethacin.

In one study of premature infants treated with Indomethacin for Injection and also receiving either gentamicin or amikacin, both peak and trough levels of these aminoglycosides were significantly elevated.

7.5 Drugs that Act on the Renin-Angiotensin System
In some patients with compromised renal function, the co-administration of an NSAID and an ACE inhibitor or angiotensin II antagonist may result in further deterioration of renal function, including possible acute renal failure, which is a potentially irreversible event.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
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.

12.2 Pharmacodynamics
Indomethacin has been shown to be a potent inhibitor of prostaglandin synthase, both in vitro and in vivo. In human newborns with certain congenital heart malformations, PGE1 dilates the ductus arteriosus. In fetal and newborn goats, E type prostaglandins have also been shown to maintain the patency of the ductus, and in human newborns, indomethacin causes its constriction.

Studies in healthy young animals and in premature infants treated with prostaglandin E2 have shown that after the first dose of 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 indomethacin for injection in 460 small preterm 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 indomethacin had a 75 to 80 percent closure rate. In one of these studies, of 28 neonates who could be evaluated, 26 percent of neonates treated with indomethacin for Injection had a ductus closure rate of 10 percent of these closed subsequently without the need for surgery or additional indomethacin.

12.3 Pharmacokinetics
The disposition of indomethacin following intravenous administration (0.2 mg/kg) in premature neonates with patent ductus arteriosus has not been extensively evaluated. Even though the plasma half-life of indomethacin in premature infants, including those 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 10 days averaged 20 hours (range: 3 to 60 hours, n = 18). In infants older than 10 days, the mean plasma half-life of indomethacin was 12 hours (range: 4 to 38 hours, n = 10). Grouping the neonates by weight, mean plasma half-life in those less than 1000 g was 21 hours (range: 9 to 60 hours, n = 10). In those between 1000 and 2000 g, the mean plasma half-life was 15 hours (range: 3 to 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 (kemicterus).

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 Packaged individually.

Vial stoppers do not contain 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.