

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

The 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.