

Data Sheet

INDOCID[®] PDA

*Indomethacin sodium trihydrate equivalent to 1 mg indomethacin
Powder for Injection*

Presentation

Off-white to yellow lyophilised powder contained in a clear glass vial with mauve cap. Upon reconstitution with preservative free sterile sodium chloride injection 0.9% or sterile preservative free water for injection a clear slightly yellow solution essentially free of visible particles is formed.

Therapeutic Class

INDOCID PDA is a non steroidal anti-inflammatory agent for closure of Patent Ductus Arteriosus.

Indications

INDOCID PDA is indicated to close patent ductus arteriosus in premature infants when usual medical management is ineffective.

Dosage and Administration

FOR INTRAVENOUS ADMINISTRATION ONLY

After assessing the risk/benefit ratio in each individual patient, the lowest effective dose for the shortest possible duration should be used.

Dosage

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 INDOCID PDA 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 INDOCID PDA no additional doses should be given until laboratory studies indicate that renal function has returned to normal. (See WARNINGS AND PRECAUTIONS).

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 INDOCID PDA 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 condition is unchanged after 2 courses of therapy with INDOCID PDA, surgery may be necessary for closure of the ductus arteriosus. If severe adverse reactions occur, **STOP THE MEDICINE.**

Administration

Reconstitution of INDOCID PDA.

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.

The solution should be prepared only with 1 to 2mL of preservative-free sterile sodium chloride injection 0.9%, or sterile preservative-free water for injection. 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 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.

Benzyl alcohol as a preservative has been associated with toxicity in neonates. Therefore, all diluents should be preservative-free.

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

INDOCID PDA is not buffered. Further dilution with I.V. infusion solutions is not recommended.

Contraindications

INDOCID PDA is contraindicated:

- in neonates with proven or suspected infection that is untreated;
- in neonates who are bleeding, especially those with active intracranial haemorrhage, gastrointestinal bleeding or ulceration, or haemorrhagic diathesis;
- in 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);
- in neonates with thrombocytopenia;
- in neonates with coagulation defects, or those taking anticoagulants;
- in neonates with or who are suspected of having necrotising enterocolitis;

- in neonates with significant impairment of renal function, or on intensive diuretic therapy.

Warnings and Precautions

For additional information, see package circular for INDOCID PDA (indomethacin).

General

INDOCID PDA may mask the usual signs and symptoms of infection. Therefore, the physician must be continually on the alert for this and should use the medicine with extra care in the presence of existing controlled infection.

Severe hepatic reactions have been reported in adults treated for a prolonged period with oral indomethacin for arthritic disorders. If clinical signs and symptoms consistent with liver disease develop in the neonate, or if systemic manifestations occur, INDOCID PDA should be discontinued.

NSAIs should be administered to patients with impaired liver function only in cases of necessity.

The propensity of NSAIs to interact with other medicines may influence the treatment of other conditions.

INDOCID PDA may inhibit platelet aggregation. Premature infants should be observed for signs of bleeding.

The medicine should be administered carefully to avoid extravascular injection or leakage as the solution may be irritating to tissue.

Cardiovascular Thrombotic Events

Observational studies in adults have indicated that non-selective NSAIDs may be associated with an increased risk of serious cardiovascular events, including myocardial infarction and stroke, which may increase with dose or duration of use. Patients with cardiovascular disease or cardiovascular risk factors may also be at greater risk. To minimise the potential risk of adverse cardiovascular events in patients taking an NSAID, especially in those with cardiovascular risk factors, the lowest effective dose should be used for the shortest possible duration (see Dosage and Administration).

There is no consistent evidence that the concurrent use of aspirin mitigates the possible increased risk of serious cardiovascular thrombotic events associated with NSAID use.

Hypertension

Studies in adults have indicated that NSAIDs may lead to the onset of new hypertension or worsening of pre-existing hypertension and patients taking anti-hypertensives with NSAIDs may have an impaired anti-hypertensive response. Caution is advised when prescribing NSAIDs to patients with hypertension. Blood pressure should be monitored closely during initiation of NSAID treatment and at regular intervals thereafter.

Heart Failure

Fluid retention and oedema have been observed in some patients taking NSAIDs, therefore caution is advised in patients with fluid retention or heart failure. This information is based on data in adult patients.

Gastrointestinal Effects

Clinical results indicate that major gastrointestinal bleeding was no more common in those neonates receiving indomethacin than in those on placebo. However, 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 for a prolonged period with oral indomethacin.

Data in adults indicate that all NSAIDs can cause gastrointestinal discomfort and serious, potentially fatal gastrointestinal effects such as ulcers, bleeding and perforation which may increase with dose or duration of use, but can occur at any time without warning. Upper gastrointestinal ulcers, gross bleeding or perforation caused by NSAIDs occur in approximately 1% of patients treated for 3 – 6 months and in about 2 – 4 % of patients treated for one year. These trends continue with longer duration of use, increasing the likelihood of developing a serious gastrointestinal event at some time during the course of therapy. However, even short term therapy is not without risk.

Caution is advised in patients with risk factors for gastrointestinal events who may be at greater risk of developing serious gastrointestinal events, e.g. the elderly, those with a history of serious gastrointestinal events, smoking and alcoholism. When gastrointestinal bleeding or ulcerations occur in patients receiving NSAIDs, the drug should be withdrawn immediately. Doctors should warn patients about the signs and symptoms of serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increases the risk of serious gastrointestinal adverse events.

Severe Skin Reactions

Data in adults indicate that NSAIDs may very rarely cause serious cutaneous adverse events such as exfoliative dermatitis, toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), which can be fatal and occur without warning. These serious adverse events are idiosyncratic and independent of dose or duration of use. Patients should be advised of the signs and symptoms of serious skin reactions and to consult their doctor at the first appearance of a skin rash or any other sign of hypersensitivity.

Central Nervous System Effects

Prematurity per se, is associated with an increased incidence of spontaneous intraventricular haemorrhage. Because indomethacin may inhibit platelet aggregation, the potential for intraventricular bleeding may be increased.

Renal Effects

INDOCID PDA may cause significant reduction in urine output (50% 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 INDOCID PDA.

However, because adequate renal function can depend upon renal prostaglandin synthesis, INDOCID PDA 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 medicine, hepatic dysfunction). When significant suppression of urine volume occurs after a dose of INDOCID PDA, no additional dose should be given until the urine output returns to normal levels.

INDOCID PDA in preterm infants may suppress water excretion to a greater extent than sodium excretion. This may result in hyponatraemia. Renal function and serum electrolytes

should be monitored, and dosage should be minimised in patients with renal impairment (see DOSAGE AND ADMINISTRATION).

Animal Toxicology

In rats and mice, oral indomethacin 4mg/kg/day given during the last three days of gestation caused a decrease in maternal weight gain and some maternal and foetal deaths. An increased incidence of neuronal necrosis in the diencephalon in the live-born foetuses 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 3 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 muscularised. These findings are similar to those observed in the syndrome of persistent pulmonary hypertension of the neonate.

Adverse Effects

In a major collaborative double-blind placebo-controlled trial of 405 premature infants weighing less than or equal to 1750g with evidence of large ductal shunting, there was a statistically significantly greater incidence of bleeding problems (excluding intracranial haemorrhage) in those neonates treated with indomethacin than in those treated with placebo. Specifically, these bleeding disorders included gross or microscopic bleeding into the gastrointestinal tract, oozing from the skin after needle puncture, pulmonary haemorrhage, and disseminated intravascular coagulopathy. There was no statistically significant difference between treatment groups with reference to intracranial (intraventricular) haemorrhage.

The neonates treated with indomethacin sodium trihydrate also had a significantly higher incidence of transient oliguria and hypercreatininaemia (greater than or equal to 1.8mg/dl) than did the neonates treated with placebo.

The incidence of retrolental fibroplasia (grades III and IV) and pneumothorax in neonates treated with INDOCID PDA were not greater than in placebo controls and were statistically significantly lower than in surgically-treated infants.

The following additional adverse effects in neonates have been reported from the collaborative study, anecdotal case reports, and from other studies using rectal, oral, or intravenous indomethacin for treatment of patent ductus arteriosus (849 indomethacin-treated neonates). One year follow-up is available on 175 infants and shows no long term sequelae which could be attributed to indomethacin. In the collaborative study, only electrolyte imbalance and renal dysfunction (of the reactions listed below) occurred statistically significantly more frequently after INDOCID PDA than after placebo.

Renal:

Renal failure and renal dysfunction 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
- uraemia

Gastrointestinal:

Gastrointestinal bleeding, vomiting, abdominal distension, melena, transient ileus, gastric perforation, localised perforation(s) of the small and/or large intestine, necrotizing enterocolitis.

Additional Laboratory Findings:

Hyponatraemia; elevated serum creatinine; elevated serum potassium; elevated BUN; decreased platelet aggregation; and reduction in blood sugar, including hypoglycaemia.

Cardiovascular:

Pulmonary hypertension, intracranial bleeding.

General:

Increased weight gain (fluid retention); exacerbation of infection.

Causal Relationship Unknown

The following adverse effects have also been reported in neonates treated with indomethacin, however, a causal relationship to therapy with INDOCID PDA has not been established:

Cardiovascular:

Bradycardia.

Respiratory:

Apnoea, exacerbation of pre-existing pulmonary infection.

Metabolic:

Acidosis/alkalosis.

Haematologic:

Disseminated intravascular coagulation, thrombocytopenia.

Ophthalmic:

Retrolental fibroplasia.

Interactions

Preterm infants with patent ductus arteriosus and associated cardiac failure are frequently treated with digitalis. The half-life of digitalis in preterm infants may be further prolonged due to reduced renal function during therapy with indomethacin. Where both medicines are used concomitantly, the neonate should be observed closely; frequent ECGs and serum digitalis levels may be required to prevent or to detect digitalis toxicity early. Furthermore, in one study of premature infants treated with INDOCID PDA and also receiving either gentamicin or amikacin both peak and trough levels of these aminoglycosides were significantly elevated.

Indomethacin usually does not influence the hypoprothrombinemia produced by anticoagulants. When indomethacin is added to anticoagulants, prothrombin time should be monitored closely. In post marketing experience, bleeding has been reported in patients on concomitant treatment with anticoagulants and INDOCID PDA. Caution should be exercised when INDOCID PDA and anticoagulants are administered concomitantly.

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 usually reversible.

Therapy with indomethacin may decrease the natriuretic effect of furosemide (see WARNINGS AND PRECAUTIONS).

Overdosage

The following signs and symptoms have occurred in individuals (not necessarily in premature infants) following an overdose of oral indomethacin: nausea, vomiting, intense headache, dizziness, mental confusion, disorientation, lethargy, paresthesias, numbness, and convulsions. There are no specific measures to treat acute overdosage with INDOCID PDA. The patient should be followed for several days because gastrointestinal ulceration and haemorrhage have been reported as adverse reactions of indomethacin.

Actions

INDOCID PDA (indomethacin sodium trihydrate) for intravenous administration is sterile, lyophilised indomethacin sodium equivalent to 1mg indomethacin.

Although the exact mechanism of action through which indomethacin causes closure of a patent ductus arteriosus is not known, the effect 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 foetal and newborn lambs, prostaglandin E has also been shown to maintain the patency of the ductus, and as in human newborns, indomethacin causes its constriction.

INDOCID PDA has been used to close haemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750g when after 48 hours usual medical management (e.g. fluid restriction, diuretics, digitalis, respiratory support) is ineffective. Clearcut clinical evidence of a haemodynamically 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.

Pharmacokinetics

The disposition of indomethacin following intravenous administration (0.2mg/kg) in pre-term infants 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 evaluable neonates, 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 1000g was 21 hours (range: 9-60 hours, n=10); in those neonates weighing more than 1000g, 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 half-life of indomethacin is estimated to be about 4.5 hours. Indomethacin exists in the plasma as the parent medicine 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 medicine and metabolites (32 percent as indomethacin and its glucuronide), and 33 percent is recovered in faeces (1 percent as indomethacin). 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).

Pharmaceutical Precautions

Protect from light.
Store below 25 °C.

Medicine Classification

Prescription Medicine

Package Quantities

INDOCID PDA is available in 3 mL vials each containing 1 mg of indomethacin equivalent.

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