Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Indocid PDA 1 mg Powder for Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Indocid' PDA contains 1.25 mg of the active ingredient indometacin sodium trihydrate equivalent to 1.0 mg of Indometacin.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection
A sterile, off-white to yellow lyophilised powder for solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

'Indocid' PDA is indicated for the closure of patent ductus arteriosus in premature babies.

For use in specialised premature baby units of hospitals.

4.2 Posology and method of administration

For intravenous use only.
A course of therapy is defined as three intravenous doses of 'Indocid' PDA given at 12- to 24-hour intervals, with careful attention to urinary output.

If anuria or marked oliguria (urinary output of 0.6 ml/kg/hour) is evident at the time of the scheduled second or third dose, 'Indocid' PDA must not be given until laboratory studies indicate that renal function has returned to normal.

Dosage recommendations depend closely on the age of the infant:

	Dosage (mg/kg)		
Age at 1st dose	*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 is closed or significantly reduced in size 48 hours after the first course of therapy, no further treatment is necessary. If the ductus arteriosus reopens, a second course of therapy may be given.

If the condition is unchanged after the second course of therapy, surgery may then be necessary. If severe adverse reactions occur, stop the treatment.
For instructions for dilution and rate of infusion, see section 6.6.

4.3 Contraindications

'Indocid' PDA is contra-indicated in infants with established or suspected untreated infection; infants who are bleeding, especially with active intracranial haemorrhage or gastro-intestinal bleeding; infants 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); infants with thrombocytopenia; infants with coagulation defects; infants with known or suspected necrotising enterocolitis; infants with significant impairment of renal function.

4.4 Special warnings and precautions for use

General: 'Indocid' may mask the usual signs and symptoms of infection. The drug must therefore be used cautiously in the presence of existing controlled infection.

Because severe hepatic reactions have been reported in adults on prolonged therapy with oral indometacin, 'Indocid' PDA should be discontinued if signs and symptoms consistent with liver disease develop in the neonate.

Indocid' PDA may inhibit platelet aggregation. Premature babies should be observed for signs of bleeding. This should be borne in mind particularly in those infants with spontaneous intraventricular haemorrhage.

Indocid' PDA should be administered carefully to avoid extravasation and resultant irritation to tissues.

Gastro-intestinal effects: Clinical results indicate that major gastro-intestinal bleeding was no more common in those babies receiving indometacin than in those receiving placebo. However, minor gastro-intestinal bleeding (i.e. chemical detection of blood in the stool) was more common in infants treated with indometacin. The risks of continuing therapy in the face of such reactions must be carefully weighed against the possible benefits to the patient. Severe gastro-intestinal effects have been reported in adults treated for prolonged periods with oral indometacin.

CNS reactions: Prematurity *per se* is associated with an increased incidence of spontaneous intraventricular haemorrhage. Because indometacin 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 elevated blood urea and creatinine, and reduced glomerular filtration rate (GFR) and creatinine clearance. In most babies, these effects are transient and disappear when therapy with 'Indocid' PDA is stopped. However, because adequate renal function can depend on renal prostaglandin synthesis, 'Indocid' PDA may precipitate renal insufficiency including acute renal failure. This is most likely in babies with conditions such as extracellular volume depletion from any cause, congestive heart failure (CHF), sepsis, or hepatic dysfunction or who are undergoing therapy with nephrotoxic drugs which may affect renal function. It is mandatory that renal function be monitored closely during use of this product.

Whenever a significant suppression of urine volume occurs with treatment, treatment with 'Indocid' PDA must stop until urine output returns to normal.

Indocid' PDA may suppress water excretion in premature babies to a greater extent than the excretion of sodium. This may result in hyponatraemia. Renal function and plasma electrolytes should be monitored.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions
The half-life of digitalis in premature babies with patent ductus arteriosus and with cardiac failure is often prolonged by indometacin. When both drugs are used concomitantly, frequent monitoring of ECG and serum digitalis may help to prevent or detect digitalis toxicity early.

In a study of premature infants treated with 'Indocid' PDA and also receiving gentamicin or amikacin, both peak and trough levels of these aminoglycosides were significantly elevated.

'Indocid' may reduce the diuretic and antihypertensive effect of furosemide, and when used concurrently such therapy should be reviewed.

Indometacin usually does not influence the hypoprothrombinaemia produced by anticoagulants. When indometacin 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. Caution should be exercised when Indocid and anticoagulants are administered concomitantly.

In some patients with compromised renal function, the co-administration of a non-steroidal anti-inflammatory drug (NSAID) and an angiotensin converting enzyme (ACE) inhibitor or angiotensin II antagonist may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible.

4.6 Fertility, pregnancy and lactation

Not applicable.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Side effects

Haemorrhagic: Gross or microscopic bleeding into the gastro-intestinal tract; oozing from the skin after needle puncture; pulmonary haemorrhage; and disseminated intravascular coagulopathy, intracranial bleeding.

Renal: 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; transient oliguria; and hypercreatinaemia.

Gastro-intestinal: Vomiting; abdominal distension; melaena; transient ileus; gastric perforation; and localised perforations of the small and/or large intestine, necrotising enterocolitis.

Metabolic: Hypersensitivity; hyponatraemia; elevated plasma potassium; elevated blood urea; hypoglycaemia.

Cardiovascular: Pulmonary hypertension.

Coagulation: Decreased platelet aggregation.

General: Weight gain (fluid retention); and exacerbation of infection.

Causal relationship unknown: Although the following reactions have been reported in babies, a definite causal relationship has not been established.

Cardiovascular: Bradycardia.

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

Haematological: Disseminated intravascular coagulation.

Metabolic: Acidosis, alkalosis.

Ophthalmic: Retrolental fibroplasia.

4.9 Overdose

It is recommended that ‘Indocid’ PDA should be administered only in a neonatal intensive-care unit.

Dosage is critical. The following signs and symptoms have occurred in individuals (not necessarily in premature infants) following an overdose of oral indometacin: nausea, vomiting, intense headache, dizziness, mental confusion,

disorientation, lethargy, paraesthesiae, numbness, and convulsions.

There are no specific measures to treat acute overdosage with ‘Indocid’ PDA. The patient should be followed for several days because gastro-intestinal ulceration and haemorrhage have been reported as adverse reactions of indometacin. Any complications occurring in the gastro-intestinal, renal and central nervous systems should be treated symptomatically and supportively.

Plasma half-life of intravenous indometacin was inversely variable to the post-natal age and weight of the baby. In one study, a mean plasma half-life in babies less than a week old averaged 20 hours, while older babies showed a 12 hour average. Grouping the same babies by weight, the mean plasma half-life seen in babies under 1000 g was 21 hours, in heavier babies the half-life was reduced to an average of 15 hours.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Although the exact mechanism of action through which indometacin causes closure of patent ductus arteriosus is not known, it is believed to be through inhibition of prostaglandin synthesis. Indometacin 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, PGE1 dilates the ductus arteriosus. In foetal and newborn lambs, E-type prostaglandins have also been shown to maintain the patency of the ductus, as in human newborns, indometacin causes its constriction.

Studies in healthy young animals and in premature infants with patent ductus arteriosus indicated that, after the first dose of intravenous indometacin, 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.

5.2 Pharmacokinetic properties

The disposition of indometacin following intravenous administration in pre-term neonates with patent ductus arteriosus has not been extensively evaluated. Even though the plasma half-life of indometacin was variable among premature infants, it was shown to vary inversely with post-natal age and weight. In one study of 28 evaluable infants, the plasma half-life in those infants less than 7 days old averaged 20 hours and in infants older than 7 days, the mean plasma half-life was 12 hours. Grouping the infants by weight, the mean plasma half-life in those weighing less than 1000 g was 21 hours, and those weighing more than 1000 g was 15 hours.

5.3 Preclinical safety data

In rats and mice, oral indometacin 4 mg/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 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 muscularised. These findings are similar to those observed in the syndrome of persistent pulmonary hypertension of the newborn.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Indocid PDA does not contain any inactive ingredients.

6.2 Incompatibilities

Further dilution with intravenous infusion solutions is not recommended. Precipitation may occur at pH levels below 6.

Indocid PDA is not buffered and reconstitution at pH levels below 6 may cause precipitation of insoluble indometacin.

6.3 Shelf life

3 years as lyophilised powder. After reconstitution use immediately. Discard any unused content.

6.4 Special precautions for storage

Do not store above 25ºC. Keep the vials in the outer carton.

6.5 Nature and contents of container

Type I flint glass vial with grey butyl lyo-closures and aluminium seals.
Each carton contains 3 vials.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Intravenous solution should be prepared just prior to use and any unused portion remaining in the opened vial should be discarded.
When reconstituted, “Indocid” PDA is acceptable for use only when clear and free from particulate matter.

Directions for use.

The solution should be prepared only with 1 to 2 ml 0.9% Sodium Chloride Injection BP or
Water for Injection Ph. Eur. Preparations containing dextrose must not be used.

Preservatives should be carefully avoided at every stage because of the risk of toxicity in the newborn; any unused portion remaining in the opened vial should be discarded.

A fresh solution should be prepared just prior to each administration according to the dilution table below:

Amount of diluent used for each vial	Concentration achieved
1 ml	0.1mg/0.1ml
2 ml	0.05 mg/0.1ml

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.

7 MARKETING AUTHORISATION HOLDER

Lundbeck Pharmaceuticals Ireland Limited
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8 MARKETING AUTHORISATION NUMBER

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