



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Indomethacin

Proprietary Product Name: Indocid PDA

Sponsor: Invida Australia Pty Ltd

April 2011

TGA Health Safety
Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	Major Variation (Change in dosage and patient population)
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	18 March 2011
<i>Active ingredient(s):</i>	Indomethacin
<i>Product Name(s):</i>	Indocid PDA
<i>Sponsor's Name and Address:</i>	Invida Australia Pty Ltd Level 8, 67 Albert Avenue, Chatswood NSW 2067
<i>Dose form(s):</i>	Powder or plug for reconstitution and injection
<i>Strength(s):</i>	1 mg
<i>Container(s):</i>	vial
<i>Pack size(s):</i>	3's (single dose vials).
<i>Approved Therapeutic use:</i>	For the closure of patent ductus arteriosus in premature babies. Clear-cut 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. Indocid P.D.A. should only be used in a hospital under supervision of a specialist neonatologist.
<i>Route(s) of administration:</i>	Intravenous (IV)
<i>Dosage:</i>	Slow infusions over 20-30 minutes rather than bolus injections over 5-10 seconds.
<i>ARTG Number (s)</i>	10482

Product Background

The current Australian application seeks to modify the dosing instructions for Indocid PDA, essentially change the recommendation from bolus injections over 5-10 seconds to slow infusions over 20-30 minutes.

Current indications:

Indocid PDA is indicated to close a haemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when after 48 hours (h) usual medical management (for example, fluid restriction, diuretics, digitalis, respiratory support, etc.) is ineffective. Clear-cut 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. The drug should only be used in a hospital under supervision of a specialist neonatologist.

Proposed indications:

Indocid PDA is indicated for the closure of patent ductus arteriosus in premature babies. Clear-cut 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. Indocid PDA should only be used in a hospital under supervision of a specialist neonatologist.

There are other revisions proposed to the Dosage and Administration section of the Australian Product Information (PI) document, including advice on the incorporation of colour Doppler echocardiography as a guide for the dosage strategy.

There is also a change proposed to the wording of the indications which will in effect result in the widening of the patient population. Currently, the first sentence of the indications reads as follows: “*PDA is indicated to close a haemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when after 48 h usual medical management (for example, fluid restriction, diuretics, digitalis, respiratory support etc.) is ineffective.*” Instead the first sentence of the indications is proposed to be, “*Indocid PDA is indicated for the closure of patent ductus arteriosus in premature babies.*” The restriction to haemodynamically significant PDA is maintained in the second sentence of the indications. However, both the weight range restriction and the restriction to second-line treatment following a trial of 48 h of usual medical management have been removed. Interestingly, dosage recommendations for the first 48 h of life, where clearly a prior 48 h of usual medical management would not have been possible, are already tabulated under Dosage in the Dosage and Administration section of the currently approved PI.

There are also revisions proposed to the Clinical Pharmacology and Clinical Trials sections of the Australian PI, as well as amendments to the Warnings, Precautions & Interactions with other Medicines sections of this document.

There has been a shortage of the Australian-registered product of injectable indomethacin since early 2010. The delay has been caused by a change in the manufacturing site in the USA with a consequent delay in the validation of the new site. There are no other manufacturing sites of Indocid PDA or of an equivalent indomethacin product in the world, so the present shortage is global. The sponsor is the only supplier of injectable indomethacin for patent ductus arteriosus (PDA) in Australia.

Although the exact mechanism of action through which indomethacin causes closure of a patent ductus arteriosus is not known, it is believed to be via the 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, prostaglandin E1 (PGE 1) dilates the ductus arteriosus. In fetal and newborn lambs, E type prostaglandins have also been shown to maintain the patency of the ductus whereas indomethacin causes its constriction, similar to what happens in human newborns.

At its 133rd meeting on 25-26 February 1988, the Australian Drug Evaluation Committee (ADEC which has now been succeeded by ACPM) resolved that there should be no objections to the marketing of Indocid PDA in vials containing sterile, lyophilised indomethacin sodium equivalent to 1 mg of indomethacin for use in hospitals only to close a haemodynamically significant patent ductus arteriosus in premature infants weighing between 500 and 1750 g when, after 48 h, usual medical management (such as fluid restriction, diuretics, digitalis and respiratory support) is ineffective. The associated AUST R number is 10482.

The sponsor has not conducted any formal trials on the proposed application for Indocid PDA and the current Australian application is a literature-based submission. An overview of the literature indicated that there was a growing body of international evidence in the form of a large repository of randomised, controlled trials (RCTs), prospective and retrospective studies

already published. The sponsor comments that it was therefore logical that the available data to support the regulatory submission would rely predominantly on published references data.

There are no specific guidelines for the management of patent ductus arteriosus in infants. The following is a list of guidelines (which can be found on the TGA website) relevant to this submission:

TGA Guidelines:

Literature-based submissions - points to consider

EU Guidelines:

CHMP/EWP/147013/2004

Guideline on the role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population (corregendum)

Published: TGA Internet site

Effective: 24 August 2009

EMA/CHMP/PEG/194810/2005

Reflection Paper: Formulations of Choice for the Paediatric Population

Published: TGA Internet site

Effective: 29 June 2009

CPMP/ICH/2711/99

Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population

Published: TGA Internet site

Effective: 19 April 2001

EMA/CHMP/PhVWP/235910/2005

Guideline on Conduct of Pharmacovigilance for Medicines Used by the Pediatric Population

Published: TGA Internet site

Effective: 16 March 2009

Regulatory Status

Indocid PDA is currently registered in Canada (since 20 June 1984), Japan (Indocin IV since October 1994), New Zealand (Indocin IV since 1 June 1983), Singapore (Indocin IV for Injection since 19 February 1991), the United Kingdom (since 14 January 1986) and the USA (Indocin IV since 30 January 1985).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

There were no new quality data submitted with this application.

III. Nonclinical Findings

There were no new nonclinical data submitted with this application.

IV. Clinical Findings

Introduction

Five published studies relating to pharmacokinetics (PK) were included in the submission. With respect to pharmacodynamics (PD) of this product, the current Australian submission

contained data from studies examining the relationship between plasma indomethacin concentrations and effect and also data examining the effects of indomethacin on cerebral, mesenteric and renal blood supply.

The efficacy data comparing bolus with slow infusion administration were summarised in a meta-analysis which was provided as a report in the sponsor's Clinical Overview. The meta-analysis did not examine dosing regimens other than bolus and slow infusion, although some studies that employed alternative regimens (such as continuous infusion) were provided in the submission. In addition, there were efficacy data for indomethacin in comparison with placebo and in comparison with active comparator contained in the submission.

Indomethacin use in pre-term neonates is well documented and there are a large number of published studies included in the submission. However, there was a paucity of post-marketing studies conducted by the sponsor and no Periodic Safety Update Reports were included in the submission.

GCP aspects

The submission was literature based and statements of Good Clinical Practice (GCP) compliance were not provided. It is unlikely the studies were performed to GCP standards, but the majority of the citations had undergone review by institutional ethics committees.

Pharmacokinetics

Bhat R *et al* 1980: mean (SE) protein binding in preterm neonates was 99.3 (0.1) % and in full term neonates was 98.7 (0.2) %. The volume of distribution in preterm neonates was 0.33 to 0.4 L/kg. Clearance was 25% of reported adult values at 9.6 to 25 mL/kg/h. However there were limited numbers of very low birth weight (VLBW) infants in the study and gestational ages (GA) were ≥ 28 weeks. Bioavailability was low as indicated by area under the curve (AUC)/dose of 8.5 for oral and 66 for intravenous administration.

Brash AR 1981: reported considerable variability in pharmacokinetics in a neonatal population ranging from 26 to 34 weeks GA, with volume of distribution ranging from 200 to 600 mL/kg, half-life from 5 to 200 h, plasma concentration at 6 h ranged from 235 to 1100 ng/mL, and plasma clearance ranged from 2 to 40 mL/kg/min.

Mrongovius R *et al* 1982: reported a high degree of variability in trough indomethacin plasma concentrations by either the oral or IV routes.

Petersen S *et al* 1981: reported the plasma half-life of indomethacin to range from 9 to 49 h in neonates with a GA of 29 to 34 weeks.

Vert P *et al* 1980: reports a pharmacokinetic pharmacodynamic observational study conducted in 18 neonates. Pharmacokinetic parameters (half-life, volume of distribution and clearance) were similar for enteral (rectal) and IV administration.

Evaluator's overall conclusions on pharmacokinetics

There is considerable variability in the pharmacokinetics of indomethacin in premature neonates. There is therefore scope for further evaluation of the pharmacokinetics of indomethacin in neonates, possibly using population pharmacokinetic methods. The sponsor might consider sponsoring such studies. The sponsor might also consider updating the Pharmacokinetics section of the Australian PI to include information on volume of distribution, clearance and bioavailability.

Drug Interactions

No new data were submitted under this heading. Some drug-interaction findings are reported under *Safety* below.

Pharmacodynamics

Pharmacokinetic/Pharmacodynamic Data

Brash AR 1981: reported that unsuccessful treatment courses were associated with lower plasma levels, shorter half life and faster clearance ($p < 0.05$).

Smith IJ *et al* 1984: also reported lower mean plasma levels of indomethacin at 6 and 24 h post dose in unsuccessful courses of treatment.

Vert P *et al* 1980: reported that indomethacin plasma AUC was higher in neonates with successful PDA closure compared with those where treatment was not successful.

Shaffer CL *et al* 2002: reported a PK/PD study that used individualized dosing according to the trough indomethacin level. The treatment regimen was: indomethacin 0.25 mg/kg, IV over 30 minutes followed by furosemide 1 mg/kg. Subsequent dosing was individualized to obtain an increase in the 2 hour predose serum indomethacin concentration in the range 0.3 to 0.5 mg/L. PDA closure was successful in 127 (91%) neonates. Closure occurred in 50% by a cumulative dose of 0.6 mg/kg and 85% closed by a cumulative dose of 1.75 mg/kg. Closure occurred in 50% at an indomethacin serum concentration of 1.5 mg/L and in 90% at 4 mg/L. There was renal toxicity in 5% at a cumulative dose of 0.6 mg/kg and 10% at a cumulative dose of 1.75 mg/kg.

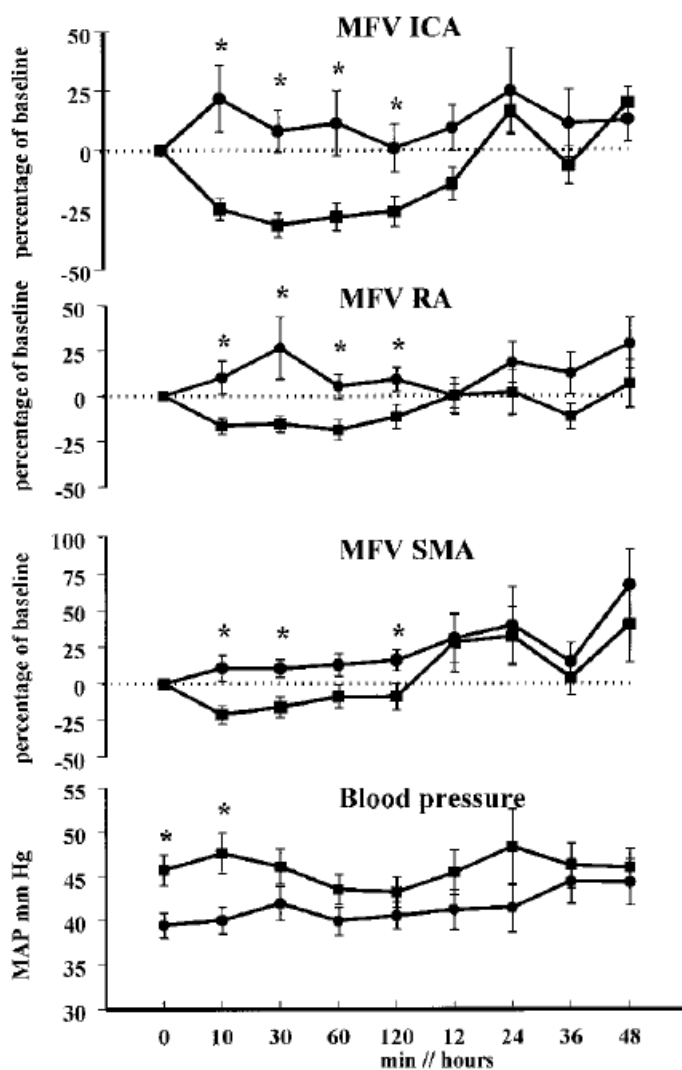
Seyberth HW *et al* 1982: reported that urinary PGE excretion was increased in preterm neonates with PDA, decreased with indomethacin and increased again with reopening of the ductus.

Studies of Organ Blood Flow

Following intravenous indomethacin there are decreases in intracranial, mesenteric and renal blood flow.

- Christmann V *et al* 2002: reported a study of indomethacin given as three bolus injections or as continuous infusion over a 36 hour time period. The dose was 2mg/1mg/1mg for bolus and 4mg for the infusion and was stated to be the same total dose for both groups. The study was conducted as a randomised, open clinical trial and the treatment groups had similar demographic characteristics. In the bolus group there was a significant decrease in flow velocity in the cerebral, renal and mesenteric arteries (Figure 1). There was no change in flow velocities in the continuous infusion group.

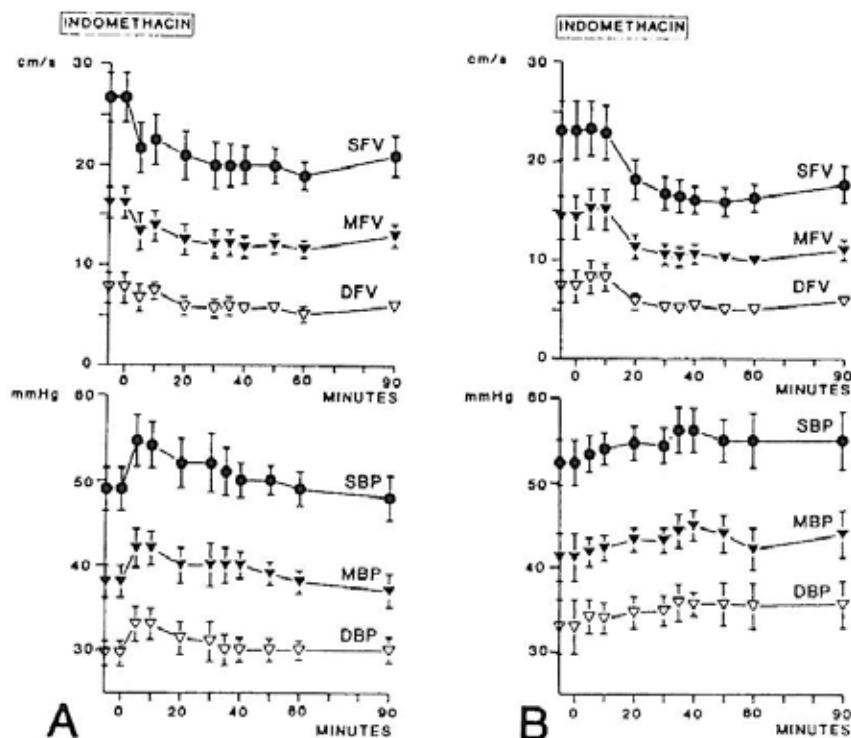
Figure 1 Changes in blood flow velocities and blood pressure



. Changes in blood flow velocities and blood pressure. Changes in blood flow velocities are presented as mean \pm SEM percentage of change from the baseline measurement. MFV: mean flow velocity; ICA: internal carotid artery; RA: renal artery; SMA: superior mesenteric artery. Significant changes between the two groups, expressed as * ($p < 0.05$), were seen during the first 2 h after starting indomethacin treatment. Blood pressure, presented as means \pm SEM mmHg, was significantly lower, expressed as * ($p < 0.05$), in the CONT group at baseline (= 0 min) and 10 min after starting indomethacin treatment. No significant changes occurred within the two groups during the treatment. —●— CONT group. —■— BOLUS group.

- Hammerman C *et al* 1995: was a randomised controlled trial comparing rapid bolus with infusion conducted in 18 neonates. There was no difference in efficacy between bolus and infusion (eight of nine neonates in each group responded). In the bolus group there was a drop in middle cerebral artery (MCA) blood flow to mean (standard deviation (SD)) of 70 (\pm 8) % of baseline by 4 minutes. There was no observed drop in the continuous infusion group ($p < 0.005$). Following subsequent bolus injections MCA blood flow decreased by 10 to 47% from baseline, with no significant changes in the continuous infusion group ($p < 0.005$). Serum creatinine levels were higher in the bolus group at 48 h: 1.4 (6) mg/dL compared with 1.1 (0.2) mg/dL, $p = 0.054$.
- Simko A *et al* 1994: reported a randomised controlled trial conducted in 19 neonates: ten received indomethacin 0.2 mg/kg by rapid intravenous bolus and nine received indomethacin 0.2 mg/kg by intravenous infusion over 30 minutes. Cerebral blood flow velocities were significantly lower by 5 minutes in the rapid infusion group and 30 minutes in the slow infusion group (Figure 2). Hence, both administration regimens resulted in significant decreases in cerebral blood flow velocities.

Figure 2. Changes in cerebral blood flow velocities and arterial blood pressures when indomethacin is infused by rapid bolus (A) or by infusion over 30 minutes (B)



Changes in blood flow velocities and in arterial blood pressures when indomethacin was administered either by rapid infusion (A) or by a 30-minute infusion (B). SFV and the MFV were significantly lower 5 minutes after rapid infusion ($p < 0.05$). These blood flow velocities remained lowered for at least 90 minutes. Rapid infusion caused a significant increase in arterial blood pressures (SBP, MBP, and DBP) at 5 and 10 minutes after indomethacin administration ($p < 0.05$); 30-minute infusion caused gradual decreases in SFV and MFV, which were significantly lower by 20 minutes ($p < 0.05$). These blood flow velocities remained lowered for at least 90 minutes; 30-minute infusion did not cause any significant change in arterial blood pressures. Values are mean \pm 1 SE. SFV, mean systolic flow velocity; MFV, mean flow velocity; DFV, mean diastolic flow velocity; SBP, systolic blood pressure; MBP, mean blood pressure; DBP, diastolic blood pressure.

- Pryds O *et al* 1988: found that in neonates with GA of 26 to 36 weeks treated with indomethacin 0.2 mg/kg IV over 5 minutes, cerebral blood flow decreased in all patients with a mean fall of 24% ($p < 0.005$) and a range of 12% to 40%. There was no clinical sign of cerebral dysfunction.
- Ohlsson A *et al* 1993: demonstrated a mean reduction of 30% in mean peak velocity (MPV) and 33% in time-averaged mean velocity in the middle cerebral artery following indomethacin 0.2 mg given by IV bolus over less than 5 minutes.
- Austin NC *et al* 1992: reported a prospective cohort study of 11 preterm infants with PDA treated with 0.2 mg/kg indomethacin infused over 30 minutes. In the middle cerebral artery, time averaged mean velocity decreased by up to 40%, peak systolic velocity by 30.6% and end diastolic velocity by 75.5% ($p < 0.001$).
- Colditz P *et al* 1989: reported results from 12 neonates: seven with indomethacin infused over 5 minutes and five with the infusion over 20 minutes. Cerebral mean flow velocity decreased from baseline in the 5 minute infusion group by 20% and cerebral electrical impedance decreased by 26% ($p < 0.01$). In the 20 min infusion group mean cerebral flow velocity decreased by 4.2% (not statistically significant (NS)).
- Edwards AD *et al* 1990: reports a prospective, observational cohort study in 13 very preterm neonates; seven treated with indomethacin 0.1 to 0.2 mg/kg by rapid intravenous infusion over 30 seconds and six by IV infusion over 20 to 30 minutes. There was a statistically significant fall in cerebral blood flow in both treatment groups, with no significant difference between the treatment groups.
- Manon JNL *et al* 1999: reported that following indomethacin 0.1 mg/kg, intravenous over 5 minutes, there was no change in mean arterial blood pressure but left ventricular output decreased from a mean (standard error (SE)) of 354 (50) mL/min/kg to 272 (28) mL/min/kg at 12 h ($p < 0.05$). Cerebral mean velocity decreased from a mean (SE) 21 (2) cm/s to 15 (3) cm/s at 1 hour ($p < 0.05$).
- Benders MJ *et al* 1999: did not find any change in cerebral mean blood flow velocity following indomethacin 1 mg/kg.
- Benders MJ *et al* 1995: found in a study of six very preterm infants that during indomethacin administration cerebral blood flow increased by a mean of 13%, which was followed by a decrease in cerebral blood flow by a mean of 24%. This was followed by a decrease in cytochrome oxidase activity, suggesting decreased oxygenation.
- Liem KD *et al* 1994: reported a cohort study conducted in 14 preterm neonates with PDA treated with three rapid bolus doses of indomethacin. After each dose there were significant decreases in cerebral blood volume, cerebral blood flow velocity, concentration of oxyhaemoglobin and oxidised cytochrome aa₃.
- Laudignon N *et al* 1988: in a study of 13 neonates reported a 30% decrease in AUC for cerebral blood flow after the first dose of indomethacin 0.2 mg/kg IV injection, but no change after the third dose.
- Mardoum R *et al* 1991: reported a decrease in left internal carotid blood flow velocity following indomethacin 0.2 mg/kg IV over 15 to 20 seconds ($p < 0.006$). In contrast to indomethacin which decreases cerebral blood flow,

postoperatively following surgical ligation of the duct, cerebral blood flow increases.

- Lundell BPW *et al* 1986: reported a cohort observational study in 18 premature neonates, 10 treated with indomethacin and 8 with surgery. In the indomethacin group mean (SD) systolic blood flow velocity decreased from 19.2 (5.4) to 14.3 (4.7) cm/s ($p < 0.01$) and mean blood flow velocity decreased from 568 (214) to 361 (147) cm/min ($p < 0.05$). In the surgery group, diastolic blood flow velocity increased from 2.6 (3.0) to 6.8 (3.5) cm/s ($p < 0.05$) and mean blood flow velocity increased from 576 (186) to 868 (277) cm/min ($p < 0.05$). There does not appear to be a corresponding decrease in cerebral blood flow following ibuprofen.
- Mosca F *et al* 1997: indicated that although there was a decrease in blood flow observed with indomethacin an increase was observed with ibuprofen.
- Patel *et al* 1995: reported no change in cerebral blood volume or mitochondrial oxygenation after ibuprofen 5 or 10mg/kg. There was however a decrease in these variables with 0.1 mg/kg indomethacin ($p < 0.001$).
- Patel J *et al* 2000: reported a randomised controlled trial comparing the effects of indomethacin and ibuprofen on cerebral haemodynamics using near infrared spectroscopy. The treatment regimen for indomethacin was 0.2 to 0.25 mg/kg q12h for three doses. Similarly, the regimen for ibuprofen was 5 to 10 mg/kg IV every 24 h (q24h) for three doses. Treatments were administered IV over 15 minutes. Cerebral blood volume decreased by median (IQ range) of -0.2 (-0.3 to -0.1) mL/100g and cerebral blood flow decreased from mean (SD) of 13.6 (4.1) to 8.3 (3.1) mL/110g/min after indomethacin but not following ibuprofen ($p < 0.001$). However, there may be beneficial effects on cerebral oxygenation following treatment of PDA.
- Lemmers PMA *et al* 2008: reported that mean arterial pressure (MAP) and regional cerebral oxygen saturation were lower and fractional tissue oxygen extraction higher during PDA. Following indomethacin treatment these values normalized.

Evaluator's overall conclusions on pharmacodynamics

The pharmacokinetic pharmacodynamic data indicate that there is a relationship between plasma concentration and closure of a PDA. This relationship can be used to improve efficacy and decrease toxicity through the use of therapeutic drug monitoring.

Indomethacin by both bolus and slow infusion results in decreased intracerebral, renal and mesenteric blood supply. No long term adverse effects have been demonstrated on cerebral function. The decrease in organ blood supply has not been observed following ibuprofen or surgical ligation.

Efficacy

Comparing bolus and slow infusion

Literature search strategy and data extraction

Searches were performed on:

- CLIC (83 citations retrieved)
- Cochrane Library (78 citations retrieved)
- Excerpta Medica Database (EMBASE) (380 citations retrieved)
- Paediatric Academic Society Abstract Archives (220 citations retrieved)
- PubMed (239 citations retrieved)

The search criteria included terms such as: INDOMETHACIN, INDOMETACIN, PATENT DUCTUS ARTERIOSUS, INTRAVENOUS INFUSION, ADMINISTRATION, INFUSIONS, INTRAVENOUS and DOSAGE.

Two researchers reviewed the titles and abstracts of the citations for relevance to the objectives of the review. The criteria used were:

- Relevant to the research questions.
- Data representative of Australian patients and treatment environment.
- Published results that reported some or all of the outcomes of interest.
- Completeness of the reported outcomes enabling statistical summary.

Duplicate data were identified and an Adjusted Disaggregated Data Set was established. The dataset excluded mixed modes of administration, small case series, case reports, pharmacovigilance reports based on spontaneous reporting and reports with insufficient data of interest. Data were extracted by two researchers using data extraction forms.

Statistical analysis

Means and rates for the efficacy and toxicity outcomes were pooled separately for each method of infusion and compared using the meta-analytic random effects model as described by DerSimonian and Laird. Tests of heterogeneity were performed. Forrest plots were performed.

Results of the Meta-analysis

Data from 99 distinct clinical reports were included in the analysis. There were 35 randomised controlled trials (RCTs) including 1185 subjects: 474 treated by bolus and 711 by slow infusion. There were 32 prospective case series including 860 subjects: 272 treated by bolus and 588 by slow infusion. There were 32 retrospective case series including 2218 subjects in total; 595 had been treated by bolus and 1623 by slow infusion.

It is not clearly stated how many studies contributed data to the analysis. It is apparent that there were 46 studies where there had been bolus dosing and 53 studies where there had been slow infusion dosing. The submission states that there were five studies that directly compared bolus and slow infusion administration within the same study, but the tables indicate that there were six such studies. Hence it appears that a total of either 93 or 94 studies contributed data to the analysis. This included retrospective cohort studies, prospective cohort studies and randomised controlled trials. Unfortunately, the report did not clearly indicate which studies contributed the data and did not provide any tabulated summaries of the studies.

In addition, there were studies with “titrated to response schedules”. These dosing schedules used echocardiography to confirm that the PDA had not closed prior to each dose. Hence, a subject in such a dosing schedule would not have received all the scheduled doses if the PDA had closed prior to the completion of the dosing schedules. These dosing schedules would have minimised exposure to active treatment (indomethacin or ibuprofen).

For the pooled estimates there were no clinically or statistically significant differences for rates of PDA closure for bolus compared with slow infusion. After the first course of indomethacin the % rate of closure (95% CI) was 72.2 (67.4 to 77.0) for bolus and 70.7 (63.8 to 77.6) for slow infusion. The % rates of PDA closure after allocated treatment were 79.9 (76.1 to 83.7) and 78.8 (75.0 to 82.6) respectively, and the % rates of neonates requiring surgical ligation were 12.7% (8.5 to 16.9) and 12.7% (9.3 to 16.1), respectively. The best efficacy results when all the data were examined were from studies with titrated to response

schedules (Table 1). When only the head to head studies were examined there were similar efficacy results for bolus and slow infusion (Table 2).

Table 1. Summary estimates, expressed as proportion (95% CI): comparison of efficacy outcomes, RCT results in bold.

Treatment Regimen	Closure >1 st Course (primary outcome)		Closure >Allocated Treatment (secondary outcome)		Surgical Ligation >Allocated Treatment (secondary outcome)	
	Bolus	Slow	Bolus	Slow	Bolus	Slow
Dose range covered by Product Information						
0.2,0.1-0.25mg/kg/12h-24h	0.66(0.56,0.75)** 0.67(0.57,0.78)**	0.70(0.62,0.77)** 0.68(0.52,0.83)	0.76(0.68,0.85) 0.75(0.68,0.81) (0.61/0.65mg/kg)	0.78(0.74,0.82) 0.80(0.75,0.85) (0.67/0.70mg/kg)	0.17(0.09,0.26) 0.12(0.03,0.22) (0.62/0.68mg/kg)	0.13(0.10,0.17) 0.10(0.07,0.13) (0.66/0.70mg/kg)
Dose schedules covered by Product Information						
0.2x3mg/kg/12h (≤3 doses)	0.60(0.43,0.77) 0.58(0.42,0.75)*	0.68(0.58,0.78) 0.67(0.50,0.85)	0.75(0.68,0.82) 0.75(0.47,93) (0.62/0.75mg/kg)	0.72(0.67,0.77) 0.74(0.67,0.81) (0.61/0.63mg/kg)	0.20(0.07,0.34) (0.61mg/kg)	0.14(0.03,0.25) 0.06(0.008,0.21) (0.60/0.60mg)
0.2x3mg/kg/12h(>3≤6 doses)			0.69(0.42,0.96) 0.64(0.54,0.75) (0.76/0.79mg/kg)	0.79(0.73,0.84) 0.82(0.75,0.88)** (0.71/0.75mg/kg)	0.18(0.00,0.41) 0.04(0.00,0.08) (0.76/0.69mg/kg)	0.16(0.10,0.22) 0.11(0.06,0.15) (0.69/0.71mg/kg)
0.2x3mg/kg/24h (≤3 doses)	0.78(0.65,0.90) 0.73(0.47,0.98)		0.92(0.86,0.98) (0.62mg/kg)	0.77(0.72,0.72) (0.78mg/kg)	0.07(0.01,0.12) (0.60mg/kg)	
0.2x3mg/kg/24h(>3≤6 doses)			0.81(0.73,0.89) (0.52mg/kg)		0.12(0.00,0.28) (0.47mg/kg)	0.08(0.00,0.17) (0.81mg/kg)
0.2x3mg/kg/12-24h (≤3 doses)	0.79(0.70,0.87)	0.82(0.67,0.97)		0.90(0.82,0.99) (0.81mg/kg)		0.06(0.05,0.07)
0.2,0.1,0.1mg/kg/12h (≤3 doses)		0.73(0.67,0.80)				
0.2,0.1,0.1mg/kg/12h (>3≤6 doses)				0.88(0.80,0.95) (0.48mg/kg)		0.07(0.03,0.12) 0.06(0.01,0.21) (0.48mg/kg)
Titrated to response dose schedules	0.77(0.70,0.83) 0.88(0.79,0.96) (0.37/0.33mg/kg)	0.83(0.70,0.99) 0.81(0.72,0.90) (0.31/0.275mg)	0.81(0.77,0.85) (0.37mg/kg)	0.91(0.83,1.0)* (0.30mg/kg)	0.09(0.03,0.15) (0.42mg/kg)	0.006(0.11,0.22) (0.30mg/kg)

*p < 0.05 (relative to titrated/non titrated schedule), ** p < 0.01 (relative to titrated/non titrated schedule); ** p<0.01 (relative to equivalent schedule, Bolus); Shaded box: not applicable or insufficient data

> denotes after

Table 2. Comparative studies on efficacy outcomes: head to head studies.

Author	N	BOLUS			N	SLOW		
		Closure>1st Course (Failure rates)	Closure > Allocated Treatment (Failure rates)	Surgical Ligation> Allocated Treatment		Closure>1st Course (Failure rates)	Closure> Allocated Treatment (Failure rates)	Surgical Ligation> Allocated Treatment
Colditz 1989	7	NR	NR	NR	6	NR	NR	NR
Coombs 1990	9	4	3	0	10	4	4	1
Edwards 1990	7	2	2	NR	6	3	3	1
Ekici 2006	30	7	7	2	30	9	9	2
Simko 1994	10	5	2	2	9	3	2	0
Zecca 1994	16	4	4	NR	11	NR	3	NR
Summary	72	22/72	18/72	4/49	72	19/61	21/72	4/61
Est 95 CI%		10.6(19.9,41.2)	10.0(15.35)	7.67(0.5,15.8)		11.6(19.5,42.8)	10.5(18.7,39.7)	6.2(0.35,12.8)

> denotes after

Overall there were similar rates for mortality, oliguria and elevation of serum creatinine for bolus and slow infusion. However, in the RCT results there was a higher mortality in the bolus group (Table 3). Rates of intracranial haemorrhage (ICH) and periventricular leukomalacia (PVL) were lower in the bolus group (Table 4). Overall, rates of NEC and gastrointestinal (GI) were higher in the slow infusion group, but this was not apparent in the RCT group (Table 5). Rates for ventilatory support were higher in the bolus group (Table 6). The review did not find differences in the decrease in cerebral or mesenteric blood flow between bolus and slow infusion. For neither administration method was deterioration in cerebral function demonstrated.

Table 3. Comparison of mortality, proportion (95% CI), and renal toxicity, relative risk (95% CI), RCT results in bold.

Treatment Regimen	Mortality		Transient Urine Output		Transient SeCr	
	Bolus	Slow	Bolus	Slow	Bolus	Slow
Dose range covered by Product Information						
0.2,0.1-0.25mg/kg/12h-24h	0.10(0.06,0.15) 0.13(0.06,0.21)	0.08(0.05,0.10) 0.05(0.02,0.08) ***	1.79(0.57,3.01) 2.48(0.95,4.01)	2.25(1.94,2.56) 2.25(1.94,2.56)**	0.98(0.47,1.48) 1.19(0.92,1.45)	1.07(0.97,1.17) 1.19(1.03,1.34)
Dose schedules covered by Product Information						
0.2x3mg/kg/12h-<=3 doses	0.06(0.00,0.19) 0.00(0.00,0.20)	0.04(0.01,0.08) 0.04(0.0,0.09)				0.88(0.39,1.36) 1.13(0.34,1.92)
0.2x3mg/kg/12h->3<=6	0.09(0.00,0.18) 0.11(0.0,0.26)	0.08(0.04,0.11) 0.04(0.01,0.07)		2.25(1.94,2.56) 2.25(1.94,2.56)		1.11(1.06,1.16) 1.16(1.06,1.26)
0.2x3mg/kg/24h-<=3 doses	0.17(0.00,0.38) 0.31(0.09,0.61)					
0.2,0.1,0.1mg/kg/12h >3-<=6 doses		0.26(0.12,0.45)				
Titrated to response dose schedules	0.13(0.06,0.21)	0.10(0.00,0.21)				
** p < 0.01 (relative to Bolus equivalent schedule); *** p < 0.001 (relative to Bolus equivalent schedule)						

Table 4. Summary estimates, proportion (95% CI): comparison of cerebral toxicity, RCT results in bold.

Treatment Regimen	Any IVH		Any ICH		Any PVL	
	Bolus	Slow	Bolus	Slow	Bolus	Slow
Dose range covered by Product Information						
0.2,0.1-0.25mg/kg/12h-24h	0.07(0.00,0.21) 0.09(0.00,0.30)	0.10(0.06,0.13) 0.12(0.07,0.18)	0.01(0.00,0.04) 0.00(0.00,0.21)	0.09(0.04,0.14)** 0.09(0.01,0.16)	0.00(0.00,0.19) 0.00(0.00,0.23)	0.05(0.04,0.06) 0.05(0.03,0.08)
Dose schedules covered by Product Information						
0.2x3mg/kg/12h-<=3 doses						0.03(0.01,0.09)
0.2x3mg/kg/12h->3<=6		0.09(0.05,0.13) 0.12(0.05,0.18)				0.06(0.03,0.09) 0.06(0.03,0.09)
0.2x3mg/kg/24h-<=3 doses						
0.2x3mg/kg/12-24h >3-<=6 doses						
0.2x3mg/kg/12-24h-<=3 doses						
0.2,0.1,0.1mg/kg/12h-<=3 doses						
0.2,0.1,0.1mg/kg/24h->3<=6 doses						
Titrated to response dose schedules	0.007(0.00,0.06)	0.21(0.06,0.37)			0.00(0.00,0.10)	0.05(0.01,0.14)
** p < 0.01 (relative to Bolus equivalent schedule)						

Table 5. Summary estimates, proportion (95% CI): comparison of gastrointestinal toxicity, RCT results in bold.

Treatment Regimen	NEC		Perforation		GI	
	Bolus	Slow	Bolus	Slow	Bolus	Slow
Dose range covered by Product Information						
0.2,0.1-0.25mg/kg/12h-24h	0.05(0.02,0.07) 0.07(0.04,0.10)	0.10(0.07,0.13)* 0.07(0.03,0.11)	0.00(0.00,0.02) 0.03(0.00,0.07)	0.04(0.03,0.06)* 0.02(0.00,0.04)	0.08(0.00,0.18) 0.07(0.00,0.22)	0.13(0.06,0.21) 0.06(0.00,0.12)
Dose schedules covered by Product Information						
0.2x3mg/kg/12h-<=3 doses	0.00(0.00,0.20)	0.07(0.00,0.15) 0.07(0.00,0.15)	0.00(0.00,0.21)		0.0(0.0,0.20)	
0.2x3mg/kg/12h->3<=6		0.05(0.02,0.09) 0.23(0.08,0.38)	0.04(0.00,0.09) 0.03(0.00,0.11)	0.04(0.02,0.06) 0.03(0.02,0.04)	0.15(0.07,0.23) 0.14(0.07,0.26)	0.11(0.03,0.19) 0.03(0.00,0.05)**
0.2x3mg/kg/24h-<=3 doses					0.00(0.00,0.21)	
0.2x3mg/kg/12-24h-<=3 doses	0.06(0.00,0.12)	0.08(0.04,0.12) 0.04(0.01,0.10)				
0.2x3mg/kg/12-24h >3-<=6 doses	0.11(0.01,0.33) 0.10(0.01,0.33)	0.10(0.05,0.15) 0.07(0.02,0.12)				
0.2,0.1,0.1mg/kg/12-24h->3<=6 doses		0.17(0.02,0.31) 0.26(0.12,0.45)				
Titrated to response dose schedules	0.06(0.00,0.13) 0.10(0.02,0.17)	0.10(0.05,0.14) 0.12(0.05,0.23)	0.00(0.00,0.10)	0.08(0.03,0.19))	0.14(0.00,0.35)	0.17(0.10,0.24) 0.17(0.08,0.29)
p < 0.05 (relative to Bolus equivalent schedule); ** p < 0.01 (relative to Bolus equivalent schedule)						

Table 6 Comparison of retinal toxicity, proportion (95% CI), and pulmonary toxicity, mean days (95% CI), RCT results in bold.

Treatment Regimen	Any ROP		Ventilatory Support		CLD	
	Bolus	Slow	Bolus	Slow	Bolus	Slow
Dose range covered by Product Information						
0.2,0.1-0.25mg/kg/12h-24h	0.14(0.01,0.27) 0.26(0.09,0.51)	0.21(0.10,0.32) 0.21(0.10,0.32)	50.61(35.91,65.31)	17.79(13.92,21.67) 16.91(12.96,20.87)		
Dose schedules covered by Product Information						
0.2x3mg/kg/12h-≤3 doses				21.84(19.13,24.55) 21.50(18.57,24.43)		
0.2x3mg/kg/12h->3≤6			50.61(35.91,65.31)	14.74(11.82,17.66) 14.74(11.82,17.66)		
Titrated to response dose schedules						

Comments on Individual Studies

Relevant individual studies not previously discussed were:

- Zecca E *et al* 1994: reports a controlled trial in Italian, with an English abstract only. It is not clear whether the subjects were randomized. In total, 27 neonates were treated with indomethacin 0.25 mg/kg every 12 h (q12h) for three doses. In eleven neonates indomethacin was infused over 20 minutes and in 16 it was infused over 2 minutes. There was PDA closure in eight (73%) neonates in the 20 minute group and twelve (75%) in the 2 minute group. Clinical gastrointestinal side effects were reported in 56% of the 20 minute group and none in the 2 minute group. However, 44% of the 2 minute group had treatment interrupted because of oliguria.
- Abbasi S *et al* 2005: in a retrospective cohort study reported that an increased rate of non-response coincided with a shift from bolus administration to 30-60 minute infusion.

Efficacy in Comparison with Placebo

Gersony WM *et al* 1983: demonstrated that indomethacin was superior to placebo in closure of PDA, with overall fewer neonates requiring surgical ligation.

Yeh TF *et al* 1981a: reported a double blind, randomised controlled trial conducted in 55 neonates, comparing:

1. Indomethacin 0.3 mg/kg q24h for 3 doses, IV administration
2. Placebo

The PDA responded in 23 (82%) neonates in the indomethacin group and 5 (19%) neonates in the placebo ($p < 0.001$). Dynamic lung compliance also improved in the indomethacin group relative to placebo (Yeh TF *et al* 1981b). Urine output was significantly lower in the indomethacin group, mean (SD) 47.9 (24.8) mL/kg/day, compared with placebo, 77.6 (29.0) mL/kg/day, $p < 0.01$. Survival and neuro-developmental outcome at one year of age was reported in Yeh TF *et al* 1982. A total of 17 neonates died: nine in the indomethacin group and eight in the placebo group. Five (38%) neonates in the indomethacin group and seven (41%) in the control group had major or minor neurological defects. Three (23%) neonates in the indomethacin group and seven (41%) in the control had abnormal electroencephalogram (EEG).

Couser RJ *et al* 2000: was a randomised placebo controlled trial examining neuro-developmental outcome at 36 months in 90 infants treated with either: indomethacin 0.1 mg/kg in the first 24 h after birth, then q24h for 6 doses or placebo. A total of 42 (98%) in the indomethacin group and 37 (80%) in the placebo survived. Although the findings were not statistically significant, there was normal neuro-developmental outcome in 23 (79%) of 29

neonates in the indomethacin group and 26 (70%) of 37 in the placebo. Four (14%) of 29 infants in the indomethacin group were severely impaired compared with eight (22%) of 36 placebo treated neonates.

Ment LR *et al* 2000: was a randomised, placebo controlled trial of low dose indomethacin compared with placebo, with the outcome being neuro-developmental outcome at 54 months corrected age. The actual dose and regimen of indomethacin was not stated in the report. There were 384 survivors and out of these 337 (88%) underwent neuro-developmental evaluation: 170 in the indomethacin group and 167 in the placebo. However, only the English monolingual children, that is 223 (58%) of the study population, underwent cognitive testing. There was no difference in diagnosed neurological conditions. Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R) and Peabody Picture Vocabulary Test-Revised (PPVT-R) were higher in the indomethacin group ($p < 0.05$). According to WPPSI-R, 11 (9%) of the indomethacin group and 19 (17%) of the placebo had IQ < 70 .

Schmidt B *et al* 2001: was a randomised, placebo controlled trial of indomethacin 0.1 mg/kg q24h for 3 days, compared with placebo, for the outcome of death, cerebral palsy, cognitive delay, deafness and blindness at 18 months corrected age. A total of 1202 neonates were randomized: 601 in each group. Data were available for 574 (95.5%) in the indomethacin group and 569 (94.7%) in the placebo. Mean (SD) mental development index score was 83 (18) in the indomethacin group and 84 (18) in the placebo. There was no difference between the groups in death or impairment: 271 (47%) compared with 261 (46%) in the placebo. There was a decrease in severe intraventricular haemorrhage (IVH) in the indomethacin group: 52 (9%) compared with 73 (13%) in the placebo.

Setzer E *et al* 1987: reported a randomised controlled trial conducted in 199 neonates: 99 treated with prophylactic indomethacin (dose and regiment not stated) and 100 treated with placebo. Twenty-two (22%) of 99 neonates in the indomethacin group and 44 (44%) of 100 in the placebo had IVH Grades 1-IV $p < 0.0005$. There was no significant difference in Mental Developmental Index or Physical Developmental Index.

Fowlie PW and Davis PG 2003: reported a meta-analysis of studies performed on early prophylactic indomethacin in preterm neonates. The meta-analysis included 19 trials in 2872 infants, and included four trials which reported long term outcomes in 1862 infants. The meta-analysis included trials with a randomised design, enrolled preterm infants within 24 h of birth and reported any of the pre-specified outcome measures. The treatments were: indomethacin given as three to six doses, started before 24 h age. There was no difference between indomethacin and placebo in risk of death: relative risk (RR) (95% CI) 0.96 (0.81 to 1.12) or severe developmental delay 0.96 (0.79 to 1.17) (Table 7). There was a decrease in cranial ultrasound abnormalities (all IVH): 0.88 (0.80 to 0.96), severe (grades II and IV) IVH 0.66 (0.53 to 0.82), rate of PDA 0.44 (0.38 to 0.50) and surgical ligation for PDA 0.51 (0.37 to 0.71).

Peckham GJ *et al* 1984: reported similar mortality and neuro-development outcome one year after indomethacin, conservative management and surgical ligation.

Table 7. Outcomes for prophylactic indomethacin

Outcome	No of studies	Indomethacin	Control	Relative risk	Risk difference	NNT
Death at latest follow up	18	231/1372	245/1397	0.96 (0.81 to 1.12)	-0.01 (-0.04 to 0.02)	
All IVH	14	422/1258	482/1274	0.88 (0.80 to 0.96)	-0.04 (-0.08 to -0.01)	25
Severe IVH	14	115/1285	177/1303	0.66 (0.53 to 0.82)	-0.05 (-0.07 to -0.02)	20
Symptomatic PDA	14	204/1093	471/1100	0.44 (0.38 to 0.50)	-0.24 (-0.28 to -0.21)	4
PDA ligation	8	49/891	97/900	0.51 (0.37 to 0.71)	-0.05 (-0.08 to -0.03)	20
Pulmonary haemorrhage	4	104/795	123/796	0.84 (0.66 to 1.06)	-0.02 (-0.06 to 0.01)	
BPD (in oxygen at 28 days)	9	188/500	183/522	1.08 (0.92 to 1.26)	0.03 (-0.03 to 0.08)	
Necrotising enterocolitis	12	84/1187	77/1214	1.09 (0.82 to 1.46)	0.01 (-0.01 to 0.03)	
Gastrointestinal perforation	1	36/601	32/601	1.12 (0.71 to 1.79)	0.01 (-0.02 to 0.03)	
Diminished urine output	8	131/1045	70/1070	1.90 (1.45 to 2.47)	0.06 (0.04 to 0.08)	16‡
Raised creatinine	4	10/298	10/320	1.09 (0.47 to 2.51)	0.00 (-0.03 to 0.03)	
Excessive bleeding	5	16/880	23/896	0.74 (0.40 to 1.38)	-0.01 (-0.02 to 0.01)	
Severe developmental delay*†	3	143/641	151/645	0.96 (0.79 to 1.17)	-0.01 (-0.05 to 0.04)	
Cerebral palsy*	4	78/678	77/694	1.04 (0.77 to 1.40)	0.00 (-0.03 to 0.04)	
Blindness*	2	10/635	8/639	1.26 (0.50 to 3.18)	0.00 (-0.01 to 0.02)	
Deafness*	2	11/626	11/633	1.02 (0.45 to 2.33)	0.00 (-0.01 to 0.01)	
Severe neurosensory impairment*	3	164/682	173/706	0.98 (0.81 to 1.18)	0.00 (-0.05 to 0.04)	
Death or severe neurosensory impairment*	3	304/743	299/748	1.02 (0.90 to 1.15)	0.01 (-0.04 to 0.06)	

*In survivors examined.

†Either Bayley mental developmental index (MDI <68 or Wechsler preschool and primary scale of intelligence-revised (WPPSI-R) <70)

‡Number needed to harm.

NNT, Number needed to treat (calculated where significant result obtained); IVH, intraventricular haemorrhage; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia.

Data comparing alternative dosing regimens

Continuous infusion

Gork AS *et al* 2008: report a meta-analysis of bolus versus infusion administration of indomethacin. Two trials were eligible: Christmann 2002: 32 neonates; and Hammerman 1995: 18 neonates. The treatments were:

1. Bolus: either indomethacin 0.2 mg/kg, followed by 0.1 mg/kg at 12 and 36 h; or indomethacin 0.2 mg/kg followed by 0.1 mg/kg at 12 and 24 h
2. Infusion: indomethacin 0.4 mg/kg over 36 h

There was no difference in the number of for PDA closures on Day 2: RR (95% CI) 1.57 (0.54 to 4.60) or in reopening of the PDA: 2.77 (0.33 to 23.14). Both studies reported a decrease in MCA flow after the bolus doses but following the infusion.

Hammerman C *et al* 1990: was a randomised, double blind, controlled trial of prolonged indomethacin therapy conducted in 39 neonates. Both treatment groups received indomethacin 0.2 mg/kg IV bolus doses every 12 h for three doses. The maintenance group then received 0.2 mg/day for 5 days. In the maintenance group, two (10%) neonates required additional therapy, one of whom required surgical ligation. In the placebo group, nine (47%) neonates required additional therapy, seven of whom required surgical ligation (p<0.05).

Prolonged low dose indomethacin

Prolonged courses of lower dose indomethacin have the same efficacy with a reduced rate of oliguria but an increased risk of necrotizing enterocolitis (NEC).

Herrera C *et al* 2007: was a meta-analysis of randomised or quasi-randomised controlled trials comparing prolonged versus short course of indomethacin for the treatment of PDA. The meta-analysis included five trials in 431 neonates. With prolonged courses of indomethacin there was no difference in RR (95% CI) for failure of PDA closure: 0.82 (0.51 to 1.33), PDA re-opening: 0.63 (0.39 to 1.04), and PDA ligation after treatment: 0.86 (0.49 to 1.51). The RR of mortality was 1.36 (0.86 to 2.15), IVH 0.83 (0.54 to 1.28), severe IVH 0.64 (0.36 to 1.12), retinopathy of prematurity (ROP) 1.04 (0.57 to 1.88), bleeding diathesis: 0.69

(0.22 to 2.20) and chronic lung disease (CLD) 0.97 (0.58 to 1.64). There was a decreased risk of oliguria: 0.27 (0.13 to 0.6) and there was an increased risk of NEC: 1.87 (1.07 to 3.27).

Lee J *et al* 2001: reported a randomised, non-blinded clinical trial conducted in 140 neonates. The two dosing regimens were:

1. Indomethacin 0.2 mg/kg IV 12 hourly for 3 doses
2. Indomethacin 0.1 mg/kg IV 24 hourly for 6 doses

Following 0.2 mg/kg q12h: 48 (68.6%) infants' PDAs closed with one course, 6 (8.6%) with two courses and 13 infants (18.6%) required surgical ligation. With 0.1 mg/kg q24h: 49 (70%) PDAs closed with one course, six (8.6%) with two courses and eight (11.4%) infants required surgical ligation. There were three (4.3%) deaths in the 0.2 mg/kg group and six (8.6%) in the 0.1 mg/kg. There were more subjects with oliguria in the 0.2 mg/kg group compared with the 0.1 mg/kg group: 17 (24.3%) compared with 4 (5.7%), respectively, ($p=0.004$).

Lee J *et al* 2003: reported from a RCT of prolonged low dose versus conventional indomethacin in 140 neonates. A total of 69 neonates received conventional dose: indomethacin 0.2 mg/kg q12h for three doses. Seventy-one neonates received prolonged low dose: indomethacin 0.1 mg/kg q24h for six doses. The treatments were administered by IV infusion over 30 minutes. Closure of PDA occurred in 47 (68%) neonates of the conventional treatment group and 51 (72%) infants in the prolonged low dose group. Oliguria was more common in the conventional treatment group: 21 (31%) compared with six (9%) neonates, respectively, $p=0.006$. Gut perforation occurred in one (2%) neonate from the conventional treatment group and three (4%) from the prolonged low dose group. Death occurred in three (4%) neonates from the conventional treatment group and six (8%) from the prolonged low dose group.

Rennie JM and Cooke RWI 1990: reported a RCT comparing indomethacin 0.1 mg/kg q24h for 6 days with indomethacin 0.2 mg/kg q12h for 3 doses. Efficacy (ductal closure) was superior in the prolonged dose group but survival was worse in this group. Ductal closure occurred in 53 (90%) neonates in the prolonged dose group compared with 48 (77%) neonates in the conventional treatment group: treatment difference (95% CI) 13% (0% to 26%). Relapse occurred in 11 (21%) of the responders in the prolonged dose group compared with 19 (40%) in the conventional treatment group: treatment difference (95% CI) was 19% (3% to 37%). AEs were reported in ten neonates in the prolonged dose group and 13 neonates in the conventional treatment group: two in the conventional group had gastrointestinal perforation, two subjects had acute renal failure and six had bleeding complications. Death occurred in ten neonates in the prolonged dose group and three neonates in the conventional treatment group.

Tammela O *et al* 1999: reports a RCT conducted in 61 preterm neonates: 31 treated with a short course (indomethacin 0.2 mg/kg followed by 0.1 mg/kg at 12 and 24 h); and 30 treated with a prolonged course (indomethacin 0.1 mg/kg q24h for 7 doses) of indomethacin. Treatments were administered IV. There was primary PDA closure in 29 (94%) neonates in the short course and 20 (67%) neonates treated with the prolonged course ($p=0.011$). There was sustained closure in 23 (74%) neonates in the short course and 18 (60%) in the prolonged course treatment group. There were more infants with NEC in the prolonged course: 16 (53%) compared with 8 (36%), in the short course group ($p=0.037$). There were no significant differences in creatinine and electrolyte levels or urine output.

Dosing guided by echocardiography

Su B-H *et al* 1999: was a RCT comparing an initial dose of 0.2 mg/kg indomethacin followed by (at 12 and 24 h) 0.1 mg/kg if <48 h old and 0.2 mg/kg if >48 h old, with or without echocardiogram confirmation of PDA prior to administration of next dose. Whilst closure rates were similar between the groups, the complication rates were lower in the echocardiographic confirmation (ECHO) group. The PDA closed in 41 (87.2%) neonates in the ECHO group and 41 (89.1%) in the control group. Hypoglycaemia was reported in ten (21.3%) neonates in the ECHO group and 21 (45.7%) in the control. Impaired urine output was reported in twelve (25.5%) neonates in the ECHO group and in 25 (56.5%) neonates in the control. Gastrointestinal bleeding was reported in eight (17.0%) neonates in the ECHO group and 18 (39.1%) neonates from the control group. It was noted that these adverse event rates seem high in comparison with other studies.

Early intervention with indomethacin

Merritt TA *et al* 1981: indicated that early intervention with indomethacin, as opposed to waiting for symptomatic PDA, reduced mortality and also the incidence of broncho-pulmonary dysplasia (BPD).

Oral administration of indomethacin

Satar M *et al* 2004: performed a retrospective audit comparing oral with IV Indomethacin 0.2 mg/kg q12h for three doses. There was PDA closure in 17/21 (81%) neonates the oral group and 7/9 (77.8%) neonates in the IV group.

Efficacy Data in Comparison with Active Comparator

Ibuprofen compared with indomethacin

IV administration of indomethacin has similar efficacy to IV ibuprofen but with higher rates of oliguria. Ohlsson A *et al* 2010 reports a meta-analysis of ibuprofen treatment for PDA; there were 19 studies comparing ibuprofen with indomethacin that included a total of 490 neonates treated with ibuprofen and 466 treated with indomethacin. The rates of PDA closure were similar for ibuprofen and indomethacin: RR (95% CI) 0.94 (0.76 to 1.17). However, there was a lower risk of NEC with ibuprofen 0.68 (0.47 to 0.99). In addition, there was a lower risk of oliguria 0.28 (0.14 to 0.54) and the creatinine levels were lower in the ibuprofen group. There was no significant difference in mortality, neurological or pulmonary outcomes.

Su B-H *et al* 2007: reports a RCT comparing the two treatments:

1. Indomethacin 0.2 mg/kg initially then q24h for two further doses: at 0.1 mg/kg if <48 h old, or 0.2 mg/kg if >48 h old.
2. Ibuprofen 10 mg/kg, then 5 mg/kg q24h for two further doses.

Both treatments were administered as an IV infusion over 15 minutes. There was PDA closure in 52 (88.1%) of 59 neonates in the indomethacin group and 53 (88.3%) of 60 in the ibuprofen. Eight (13.6%) PDAs in the indomethacin group and nine (15%) PDAs in the ibuprofen group re-opened. Surgical ligation was performed in five (8.5%) neonates in the indomethacin and four (6.7%) neonates in the ibuprofen group. Oliguria occurred in nine (15.3%) neonates in the indomethacin group and in four (6.7%) from the ibuprofen group. There were similar rates of other complications in both groups.

Van Overmeire B *et al* 1997: reports a RCT in 40 preterm neonates comparing:

1. Indomethacin 0.2 mg/kg q12h for 3 doses; IV over 15 minutes
2. Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h; IV over 15 minutes

Closure of the PDA occurred in 15 (75%) neonates in the indomethacin group and in 16 (80%) from the ibuprofen group. Seven neonates required a second course of ibuprofen and five neonates required surgical ligation. Urine output decreased more in the indomethacin group than in the ibuprofen group. There were three deaths in the indomethacin group and one in the ibuprofen group.

Van Overmeire B *et al* 2000: reported a RCT conducted in 148 neonates with a GA 24 to 32 weeks, comparing the following two treatments:

1. Indomethacin 0.2 mg/kg q12h for three doses; IV over 15 minutes
2. Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h; IV over 15 minutes

Ductal closure occurred in 49 (66%) neonates in the indomethacin group and in 52 (70%) from the ibuprofen group. Nine (12%) neonates in the indomethacin group and ten (14%) in the ibuprofen group required surgical ligation. Oliguria occurred in 14 neonates from the indomethacin group and in five from the ibuprofen ($p=0.03$). NEC occurred in eight neonates in the indomethacin group and in four from the ibuprofen. One neonate in the ibuprofen group had an intestinal perforation.

Adamska E *et al* 2005: was a RCT conducted in 35 neonates comparing the two treatments:

1. Indomethacin 0.2 mg/kg, 3 doses (route of administration not reported)
2. Ibuprofen 10 mg/kg, then 5 mg/kg for two doses (route of administration not reported)

Ductal closure occurred in 15 (80%) neonates in the indomethacin group and eleven (69%) neonates from the ibuprofen group.

Aly H *et al* 2007: reported a RTC conducted in 21 neonates comparing:

1. Indomethacin 0.2 mg/kg q12h for 3 doses; IV administration
2. Ibuprofen 10 mg/kg, followed by 5 mg/kg q24h; oral administration

Ductal closure occurred in seven (78%) neonates from the indomethacin group and ten (83%) from the ibuprofen group. There was a greater decrease in haematocrit in the indomethacin group (mean (SD) 6.5% (6.6) compared to 1.2% (4.2) in the ibuprofen group).

Lago P *et al* 2002: reported a RCT conducted in 175 preterm neonates with respiratory distress syndrome (RDS) and haemodynamically significant PDA at 48-72 h age. A total of 81 neonates were treated with 0.2 mg/kg indomethacin q12h for three doses and 94 were treated with 10 mg/kg ibuprofen followed by 5 mg/kg at 24 and 48 h. The treatments were administered by IV infusion over 15 minutes. Some 56 (69%) PDAs closed in the indomethacin group and 69 (73%) PDS closed in the ibuprofen group. Serum creatinine was higher in the indomethacin group: mean (SD) 89 (29) mmol/L compared with 82 (20) mmol/L in the ibuprofen group ($p=0.03$). Oliguria was more frequent in the indomethacin group: twelve (15%) compared with one (1%) in the ibuprofen group ($p=0.017$). There were no differences noted in NEC, IVH or respiratory outcomes.

Su P-H *et al* 2003: reported a RCT conducted in 63 preterm neonates: 31 treated with 0.2 mg/kg indomethacin q12h for three doses and 32 treated with 10 mg/kg ibuprofen followed by 5 mg/kg at 24 and 48 h. The treatments were infused over 30 minutes. PDA closure occurred in 27 (84.4%) neonates in the ibuprofen group and 25 (80.6%) neonates in the indomethacin group. Serum creatinine was significantly lower in the ibuprofen group at 24, 48 and 72 h after treatment ($p<0.01$). Creatinine clearance and urine output were higher in the ibuprofen group ($p<0.01$ and $p<0.02$, respectively).

Navarro AG *et al* 2005: this RCT was only outlined in an abstract. No full published paper in English was provided. The study included 47 neonates: 24 treated with indomethacin and 23 treated with ibuprofen. The treatment regimens were not reported. There was PDA closure in 87.5% of the indomethacin group and 82.6% of the ibuprofen group. Two neonates in the indomethacin group had isolated bowel perforation and one neonate had NEC. There was transient renal dysfunction in seven (29%) infants in the indomethacin group and two (9%) infants from the ibuprofen group.

Chotigeat U *et al* 2003: a study comparing the efficacy of indomethacin and ibuprofen treatment for closure of the PDA. Although the dosing regimens were not reported, there was successful treatment in six (40%) of the indomethacin group and nine (60%) infants from the ibuprofen group.

Aspirin compared with ibuprofen

Indomethacin has superior efficacy to aspirin in closure of the PDA. Van Overmeire *et al* 1995 reported a RCT in 75 neonates comparing the two treatments:

1. Indomethacin 0.2 mg/kg q12h, three doses
2. Aspirin 15 mg/kg q6h, four doses

Thirty-five (92%) of the indomethacin treated PDAs closed but only sixteen (43%) of the aspirin treated PDAs closed ($p < 0.0001$).

Sulindac in comparison with indomethacin

Ng PC *et al* 1997 reports a controlled trial, using pseudo-randomised matched controls. The study was conducted in 16 neonates. Eight neonates received indomethacin 0.2 mg/kg followed by 0.2 mg/kg for neonates with weight >1250 g and 0.1 mg/kg if weight ≤ 1250 g at 12 and 24 h. The indomethacin was administered IV over 30 minutes. Eight neonates received sulindac 3 mg/kg q12h enterally via orogastric tube. There was successful PDA closure in all eight neonates in the indomethacin group and six in the sulindac group. There were two deaths in the sulindac group: one from gastrointestinal haemorrhage and one from sepsis. Urine output and plasma sodium decreased significantly in the indomethacin group and plasma creatinine increased relative to sulindac.

Evaluator's Overall Conclusions on Clinical Efficacy

The meta-analysis provided in the sponsor's Clinical Overview demonstrated no difference in efficacy between bolus and slow infusion administration. However, rates of ICH, PVL, NEC and GI perforation were lower in the bolus group. This might influence clinicians to prefer the bolus method of administration. The meta-analysis was not well presented. It is not clear which studies were included in the analysis and the tables were not self-explanatory.

Indomethacin has superior efficacy in comparison with placebo for closure of PDA.

There are few data comparing continuous infusion with bolus or slow infusion.

Prolonged courses of lower dose indomethacin have the same efficacy, with a reduced rate of oliguria but an increased risk of NEC.

When ibuprofen is compared with indomethacin the rates of PDA closure are similar but there are lower risks for NEC and renal impairment in the ibuprofen treated subjects. There is no significant difference in mortality, neurological or pulmonary outcomes.

There are sufficient data to support the changes to the indication. Specifically, early treatment with indomethacin can be beneficial without waiting for 48 h of medical management. In

addition, digoxin is no longer considered appropriate routine management for PDA. Efficacy has also been demonstrated in pre-term neonates regardless of birth weight.

Safety

Patient Exposure

Exposure to indomethacin in the preterm neonatal population is extensive and well in excess of that required for registration. In addition to the randomised controlled studies and other studies containing evaluable data, there were a number of studies that demonstrated exposure to indomethacin but were not of sufficient quality to contribute to the current application.

These reports were either: didactic reviews with no original data, cohort studies with non-randomised comparator group, cohort studies with no comparator group, case series or contained insufficient detail. Because the adverse events of primary interest (NEC, IVH, and renal failure) occur in the absence of intervention for PDA these studies did not contribute additional data with regard to the risks of AEs with indomethacin. However these reports did not identify any additional safety issues with indomethacin and were in general agreement with higher level evidence.

Adverse Events

Gastrointestinal effects

An increased risk of NEC with indomethacin has been demonstrated. In addition, as discussed previously, this risk of NEC appears to be higher than with ibuprofen.

Fujii AM *et al* 2002: reported that prophylaxis with 0.1 mg/kg indomethacin daily increased the risk of NEC with intestinal perforation, but not the risk of NEC overall or the risks of PVL or ROP.

Madan J *et al* 2008: the overall incidence of NEC in neonates treated with indomethacin for PDA was 15%.

Rennie JM and Cooke RWI 1990: reported two (3.2%) subjects with gastrointestinal perforation.

Coombs RC *et al* 1990: reported a study of superior mesenteric artery blood flow in 18 neonates treated with 0.2 mg indomethacin q12h for 3 doses. Eight of these were treated by rapid infusion over 20 seconds and ten were given a slow infusion over 30 to 35 minutes. Subjects with PDA had absent or retrograde end diastolic flow. After the rapid bolus, mean (SD) peak systolic velocity decreased from 74 (30) cm/sec to 38 (13) cm/sec ($p < 0.008$). Coeliac axis flow decreased from 63 (19) cm/sec to 43 (16) cm/sec ($p < 0.03$). There was no significant change following slow infusion. Antegrade diastolic flow returned in subjects where the PDA closed.

Fowlie PW and Davis PG 2003: there was no increase in the risk of NEC or gastrointestinal perforation with early prophylactic indomethacin in comparison with placebo (Table 7).

Pezzati M *et al* 1999: reported a RCT examining renal and mesenteric artery blood flow velocity conducted in 17 preterm neonates. Eight were treated with 0.2 mg/kg indomethacin and nine with ibuprofen 10 mg/kg. Both treatments were given IV over 15 minutes. Mesenteric and renal blood flow velocities were reduced significantly after indomethacin but not after ibuprofen treatment (Figure 3). Urine output decreased and serum creatinine increased in the indomethacin group but not in the ibuprofen group.

Figure 3. Doppler measurements of peak systolic flow velocity (PSV) mean velocity (MV), end diastolic velocity (DDV) and relative vascular resistance (RVR) in the superior mesenteric artery.

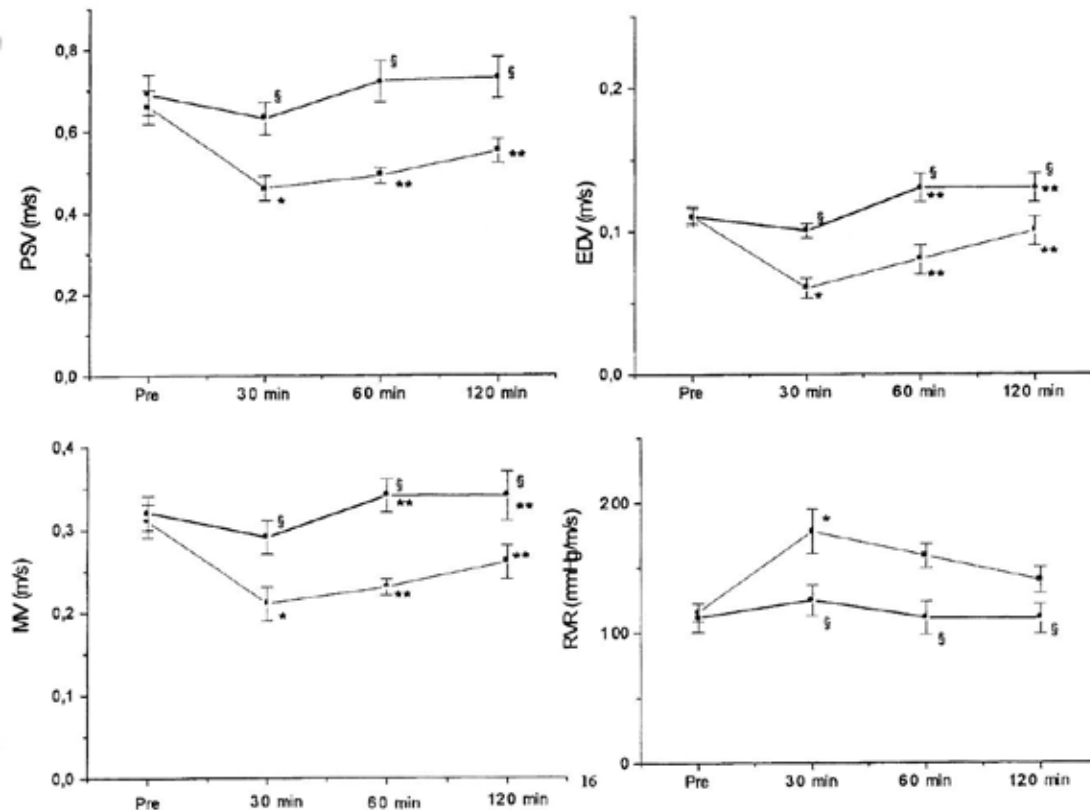


Fig 2. Doppler measurements (PSV, MV, and EDV) and RVR in renal artery before and at 30, 60, and 120 minutes after either indomethacin (■) or ibuprofen (●) administration (* $P < .05$ vs pretreatment; ** $P < .05$ vs 30 minutes; § $P < .0001$ vs indomethacin at the same time). All values are expressed as mean \pm SD.

Bleeding episodes

Corazza MS *et al* 1984: was a cohort observational study of bleeding time and haemorrhage in 25 preterm infants receiving indomethacin for closure of a PDA. The infants were treated with 0.2 mg/kg indomethacin followed by 0.1 mg/kg at 12 h and 24 h by IV bolus. Prior to indomethacin, the mean (SD) bleeding time was 3.6 (1.0) minutes. This increased to 8.7 (2.5) min at 2 h ($p < 0.0001$) and 8.9 (2.0) min at the end of the three doses. Bleeding time was still elevated at 48 h: 5.3 (2.2) min ($p < 0.01$). Platelet count decreased from 257 (68) $\times 10^3/\text{mL}$ to 228 (74) ($p < 0.01$). There was clinical evidence of bleeding in six neonates: occult haematuria in five infants and occult blood in stool/scant bleeding from endotracheal tube in one infant. At the start of the study, three infants had severe IVH and 19 had mild IVH. Five of the infants with mild IVH progressed to moderate or severe IVH.

Rennie JM and Cooke RWI 1990: reported six (9.7%) neonates with bleeding adverse events.

Fowlie PW and Davis PG 2003: no increase in the risk of IVH, severe IVH, pulmonary haemorrhage or severe bleeding with early prophylactic indomethacin compared with placebo was noted in this study (Table 7).

Impaired renal function

Although renal dysfunction is common after indomethacin, acute renal failure appears to be rare. Following IV indomethacin, there are significant decreases in renal blood flow (Christmann V *et al* 2002) and increases in serum creatinine levels following bolus dosing

compared to infusion at 48 h are noted (1.4 (6) mg/dL compared with 1.1 (0.2) mg/dL, $p=0.054$) (Hammerman C *et al* 1995).

In comparison with placebo, urine output decreases, serum creatinine increases, glomerular filtration rate (GFR) decreases and fractional excretion of sodium decreases following indomethacin treatment. Yeh TF *et al* 1981a reported that urine output was significantly lower in the indomethacin group (mean (SD) 47.9 (24.8) mL/kg/day) compared with placebo treatment (77.6 (29.0) mL/kg/day, $p<0.01$). Betkerur MV *et al* 1981 reported that at 24 h fractional excretion of sodium was reduced in the indomethacin group relative to the placebo group: 1.1 (0.4) compared with 2.8 (0.5). Fractional excretion of chloride was also reduced in the indomethacin group (1.5 (0.5)) compared with the placebo group (4.0 (0.9)). GFR was lower in the indomethacin group than in the placebo group at 12 h: mean (SE) 6.1 (1.1) mL/min/1.73m² and 8.4 (1.2) mL/min/1.73m², respectively, but this had recovered at 24 h in the indomethacin group (10.3 (2.4) mL/min/1.73m² and 7.7 (0.9) mL/min/1.73m²). Zanardo V *et al* 2005 reported that indomethacin treatment resulted in a decrease in fractional sodium excretion.

In a study comparing bolus dosing and slow infusions, Zecca E *et al* 1994 reported that 44% of the 2 minute group had treatment interrupted because of oliguria.

Rennie JM and Cooke RWI 1990 reported that two (3.2%) subjects had acute renal failure.

Trus T *et al* 1993 reported one death from renal failure following indomethacin.

The impairment in renal function appears to be related to dose size and to cumulative dose. Lee J *et al* 2001 reported more oliguria with indomethacin 0.2 mg/kg: 17 (24.3%) patients compared with four (5.7%) patients given 0.1 mg/kg ($p=0.004$). Shaffer CL *et al* 2002 reported renal toxicity in 5% of patients given a cumulative dose of 0.6 mg/kg compared with 10% given a cumulative dose of 1.75 mg/kg.

The impairment in renal function is greater with indomethacin than with ibuprofen. Su B-H *et al* 2007 reported oliguria in nine (15.3%) indomethacin treated patients and four (6.7%) ibuprofen treated patients. Van Overmeire B *et al* 2000 reported oliguria in 14 indomethacin treated patients and five ibuprofen treated patients ($p=0.03$). Serum creatinine levels were higher in the indomethacin group: mean (SD) 89 (29) mmol/L compared with 82 (20) mmol/L ($p=0.03$). Lago P *et al* 2002 reported that oliguria was more frequent in the indomethacin group: twelve (15%) patients compared with one (1%). Navarro AG *et al* 2005 reported transient renal dysfunction in seven (29%) infants in the indomethacin group and two (9%) infants in the ibuprofen group. Su P-H *et al* 2003 reported that serum creatinine levels were significantly lower in the ibuprofen group at 24, 48 and 72 h after treatment ($p<0.01$). Creatinine clearance was higher in the ibuprofen group ($p<0.01$). Urine output was higher in the ibuprofen group ($p<0.02$).

Fowlie PW and Davis PG 2003: reported an increased risk of diminished urine output with early prophylactic indomethacin treatment compared with placebo: RR (95% CI) 1.90 (1.45 to 2.47), risk difference (95% CI) 0.06 (0.04 to 0.08) (Table 7). There was no corresponding increase in the risk of raised creatinine levels.

Davis JM *et al* 1990: reported from a study of 102 neonates given indomethacin 0.2 mg/kg q12h to q24h, three doses by IV infusion. Fifty nine (58%) of the infants PDAs closed after a single dose of indomethacin. Overall, there was successful closure in 81 (79%). No neonates had renal failure. Twenty three (22%) had ICH prior to indomethacin and none had progression of the ICH after indomethacin treatment.

Neuro-developmental outcome

Peckham GJ *et al* 1984: reported similar neuro-development outcomes 1 year for indomethacin, conservative management and surgical ligation. Yeh TF *et al* 1981a, Couser RJ *et al* 2000, Ment LR *et al* 2000 and Setzer E *et al* 1987, all reported similar or improved neuro-developmental outcomes with indomethacin compared with placebo.

Fowlie PW and Davis PG 2003: there was an increase in the risk of blindness with early prophylactic indomethacin treatment in comparison with placebo. This was however neither statistically or clinically significant: RR (95% CI) 1.26 (0.50 to 3.18), risk difference 0.00 (-0.01 to 0.02). There was no increase in the risk of IVH, severe IVH, deafness or severe neuro-sensory impairment.

Serious Adverse Events and Deaths

Serious adverse events were not specifically addressed in the current Australian submission and the submitted literature did not distinguish AEs by severity.

Laboratory Findings

Betkerur MV *et al* 1981: reported that following indomethacin treatment, urinary sodium and chloride excretion were reduced compared with placebo over a 24 h period: 1.1 (0.4) compared with 2.8 (0.5) for sodium and 1.5 (0.5) compared with 4.0 (0.9) for chloride, respectively. GFR was lower in the indomethacin group at 12 h relative to placebo (mean (SE) 6.1 (1.1) mL/min/1.73m² compared with 8.4 (1.2) mL/min/1.73m²) but it had recovered by 24 h in the indomethacin group (10.3 (2.4) mL/min/1.73m² compared with 7.7 (0.9) mL/min/1.73m²).

Zanardo V *et al* 2005: found that following IV 0.2 mg/kg indomethacin q12h for three doses there was a decrease in fractional sodium excretion, urinary osmolality and urinary antidiuretic hormone (ADH) excretion. There was a decrease in fractional sodium excretion from 68.5 to 45.6 (p<0.05), in urinary osmolality from 276.2 to 226.4 (p<0.05) and in urinary ADH from 21.8 to 13.8. There were no corresponding changes following treatment with ibuprofen at 10 mg/kg followed by 5 mg/kg at 24 and 48 h.

Safety In Special Populations

Preterm neonates are a special population. The current Australian submission does not relate to other special populations.

Immunological Events

No data relating to immunological events were contained in the submission.

Safety Related To Drug-Drug Interactions And Other Interactions

Adamska E *et al* 2005: reported that concurrent corticosteroids and indomethacin treatment appeared to increase the risk of NEC (p=0.06).

Baenziger O *et al* 1999: reported that the addition of low dose dopamine (4 µg/kg/min) by IV infusion did not prevent the rise in serum creatinine after indomethacin 0.2 mg/kg q12h for three doses.

Furosemide together with indomethacin treatment may prevent oliguria but does not prevent the deterioration in renal function. Romagnoli C *et al* 1997: reported a RCT comparing 0.2 mg/kg indomethacin q12h for three doses, administered IV over 20 minutes, with and without furosemide 1 mg/kg after each dose. There was a significant decrease in urine output when indomethacin was administered without furosemide (from mean (SD) 4.0 (1.4) mL/kg/h to 2.5 (1.5) mL/kg/h, p<0.01), but not when administered with furosemide. However, mean

GFR decreased in both groups: by 20% in the group given furosemide and 16% in the group not given furosemide.

Struis N *et al* 2003: reported a case control study conducted in 64 preterm neonates; all neonates were treated with 0.2 mg/kg indomethacin q12h for 3 doses. Of these, 32 were also treated with furosemide 1 mg/kg as a co-medication. All treatments were administered IV. There was a significant increase in serum creatinine ($p < 0.001$) and decrease in serum sodium ($p < 0.01$) levels in the furosemide group. There was no difference in urine output between the treatment groups.

Discontinuation Due To Adverse Events

The reports included in the current Australian submission were not of sufficient quality to determine discontinuations due to AEs.

Post Marketing Experience

Itabashi K *et al* 2003: was a post-marketing surveillance study in Japan of 2538 low birth weight neonates treated with indomethacin from December 1994 to March 2001. Clinical closure of PDA occurred in 81.2% of the treated neonates. A multivariate logistic regression analysis indicated that clinical closure was associated with pregnancy induced hypertension and respiratory distress syndrome (RDS). However, this result is counterintuitive and not supported by other data contained in the current Australian submission. The Hosmer and Lemeshow goodness-of-fit test had a p-value of 0.6277 indicating an acceptable goodness-of-fit of the model to the data but this does not exclude bias in the dataset. The report did not include adverse event reporting.

There were no Periodic Safety Update Reports (PSURs) included in the current Australian submission.

Evaluator's Overall Conclusions on Clinical Safety

Indomethacin is associated with an increased risk of NEC and with impaired renal function. The impaired renal function usually resolves over 24 h following discontinuation. Electrolyte disturbances are common following indomethacin treatment in preterm neonates. Haemorrhagic AEs appear to be uncommon and there appears to be a decreased risk of ICH. Acute renal failure appears to be rare with indomethacin despite the high risk of transient renal dysfunction.

There are important interactions between indomethacin and corticosteroids and between indomethacin and furosemide.

List of Questions

PHARMACOKINETICS

Has the sponsor considered exploring the pharmacokinetics of indomethacin in preterm neonates using population pharmacokinetic methods?

PHARMACODYNAMICS

Has the sponsor considered making dosing recommendations on the basis of plasma indomethacin concentrations?

EFFICACY

Can the sponsor please clarify which studies contributed data to the meta-analysis and provide summary tables for these studies?

Can the sponsor please clarify whether five or six head-to-head studies were included in the meta-analysis?

SAFETY

Can the sponsor provide a Summary of Clinical Safety?

Can the sponsor provide incidence rates for the adverse events reported with IV indomethacin in neonates?

Clinical Summary and Conclusions

There is considerable variability in the pharmacokinetics of indomethacin in premature neonates. There is therefore scope for further evaluation of the pharmacokinetics of indomethacin in neonates, possibly using population pharmacokinetic methods in order to refine dosing guidelines. The sponsor might consider sponsoring such studies.

The pharmacokinetic pharmacodynamic data indicate that there is a relationship between plasma concentration and closure of a PDA. This relationship might be used to improve efficacy and decrease toxicity through the use of therapeutic drug monitoring.

Indomethacin by both bolus and slow infusion results in decreased intracerebral, renal and mesenteric blood supply. No long term adverse effects have been demonstrated on cerebral function. Decreases in organ blood supply have not been observed following ibuprofen treatment or surgical ligation.

Benefit Risk Assessment

Benefits

The meta-analysis provided in the sponsor's Clinical Overview demonstrated no difference in efficacy between bolus and slow infusion administration. However, rates of ICH, PVL, NEC and GI perforation were lower in the bolus group. This might influence clinicians to have a preference for the bolus method of administration.

Indomethacin has superior efficacy in comparison with placebo for closure of PDA.

There are few data comparing continuous infusion with bolus or slow infusion.

Prolonged courses of lower dose indomethacin have the same efficacy with a reduced rate of oliguria but an increased risk of NEC.

When ibuprofen is compared with indomethacin, the rates of PDA closure are similar but there are lower risks for NEC and renal impairment with the former. There is no significant difference in mortality, neurological or pulmonary outcomes with the two treatments.

Risks

Indomethacin is associated with an increased risk of NEC and impaired renal function. Electrolyte disturbances are common following indomethacin treatment in preterm neonates. Haemorrhagic AEs appear to be uncommon and there appears to be a decreased risk of ICH. Acute renal failure appears to be rare with indomethacin despite the high risk of transient renal impairment.

There are important interactions between indomethacin and corticosteroids and also between indomethacin and furosemide.

Safety Specification

The sponsor does not appear to be conducting pharmacovigilance activities for this indication.

Balance

Indomethacin has a favourable risk-benefit profile in comparison with placebo. However, ibuprofen appears to have similar efficacy with a more favourable safety profile. The proposed Australian Product Information document does not inform clinicians of the potential benefit of ibuprofen in comparison with indomethacin.

Conclusions

The changes that have been made to the *Indications* sections of the proposed PI document are supported by the data presented in the submission. However, it is not acceptable that the PI document does not inform clinicians of the potentially worse safety profile of indomethacin in comparison with ibuprofen.

Recommended Conditions for Registration

There are sufficient data to support the changes to the indication. Specifically, early treatment with indomethacin can be beneficial, without waiting for 48 h of medical management. In addition, digoxin is no longer considered appropriate routine management for PDA. Efficacy has also been demonstrated in preterm neonates regardless of birth weight.

However, the Product Information and Consumer Medicine Information documents require extensive amendments in order to be acceptable.

V. *Pharmacovigilance Findings*

There was no Risk Management Plan submitted with this application.

VI. *Overall Conclusion and Risk/Benefit Assessment*

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no new quality data submitted with this application.

Nonclinical

There were no new nonclinical data submitted with this application.

Clinical

- i) The sponsor's Clinical Overview consisted of a meta-analysis report and supporting tables dealing primarily with the comparison of bolus dosing and slow infusion dosing. It did not deal with any of the other changes proposed for the Australian PI and did not contain a Summary of Clinical Safety. The supporting literature was presented as three groups of studies in alphabetical order of first author. There was no explanation for the arrangement into the three alphabetical groupings. There was no summary table of studies and there would appear to have been no attempt in the sponsor's Clinical Overview or Summary to cross-reference the amendments requested in the Australian PI with the actual data supporting those changes.
- ii) The clinical evaluator considers that there are sufficient data to support the changes to the indication. Specifically, the clinical evaluator was of the opinion that early treatment with indomethacin can be beneficial, without waiting 48 h during which conservative medical management is employed. Digoxin is no longer considered appropriate routine management for PDA. Efficacy has also been demonstrated in preterm neonates regardless of birth weight.
- iii) Pharmacokinetics

There were five published studies relating to pharmacokinetics included in the submission and these demonstrated that there was considerable variability in the pharmacokinetics of indomethacin in premature neonates.

iv) **Pharmacodynamics:**

There were data from studies examining the relationship between plasma indomethacin concentrations and effect and also data examining the effects of indomethacin on cerebral, mesenteric and renal blood supply.

There were five studies assessing the relationship between plasma indomethacin concentrations and effect and broadly speaking, unsuccessful treatment courses were associated with lower plasma levels.

There were a large number of studies of organ blood flow. Following treatment with IV indomethacin, there were decreases noted in intracranial, mesenteric and renal blood flow. By contrast it has been found that following surgical ligation of the duct, cerebral blood flow increases (one study). Also confirmed in three studies was that there does not appear to be a corresponding decrease in cerebral blood flow following ibuprofen administered intravenously. One study reported that mean arterial pressure and regional cerebral oxygen saturation were lower and fractional tissue oxygen extraction higher with a patent ductus arteriosus but that following indomethacin treatment, these values normalised. No long term adverse effects on cerebral function have been demonstrated.

Efficacy in Patent Ductus Arteriosus:

v) **Efficacy data comparing bolus and slow infusions**

There is discussion of the search strategy and data extraction in the clinical evaluation report (CER). Rates, expressed as means, for the efficacy and toxicity outcomes were pooled separately for each method of infusion and compared using a meta-analytic random effects model.

There would appear to have been a total of 99 separate clinical study reports; 46 reporting on bolus dosing and 53 on slow infusion dosing. There were 35 RCTs including 1185 subjects; 474 treated by bolus and 711 by slow infusion. There were 32 prospective case series studies including 860 subjects: 272 treated by bolus and 588 by slow infusion. There were 32 retrospective case series studies including 2218 subjects: 595 treated by bolus and 1623 by slow infusion. Some of the studies had "titrated to response schedules", the latter schedules employing echocardiography to confirm that the PDA had not closed prior to each dose.

The chief complaint of the clinical evaluator is that it was not clearly stated exactly how many studies had contributed data to the analysis. Nor did the meta-analysis report clearly indicate which studies had contributed data. As well there was no tabulated summary of the relevant studies.

For the pooled estimates, there were no clinically or statistically significant differences for rates of PDA closure for bolus compared with slow infusion. After the first course of indomethacin the % rate of closure (95% CI) was 72.2% (67.4%, 77.0%) for bolus and 70.7% (63.8%, 77.6%) for slow infusion. The % rates of PDA closure after allocated treatment were 79.9% (76.1, 83.7%) and 78.8% (75.0, 82.6%), respectively and the % rates of neonates requiring surgical ligation were 12.7% (8.5%, 16.9%) and 12.7% (9.3%, 16.1%), respectively. The best efficacy results were from studies with titrated to response schedules. There were six (6) head to head studies and again there were similar efficacy rates for bolus and slow infusions.

Overall, there were similar rates for mortality, oliguria and elevation of serum creatinine for bolus and slow infusion but in the RCT results there was a higher mortality in the bolus group. Rates of intracranial haemorrhage and periventricular leukomalacia were lower in the bolus group. Overall, rates of necrotizing enterocolitis and gastrointestinal perforation were higher in the slow infusion group but this was not apparent for the randomized controlled trials (Table 5 above). Incidentally, in Table 5 there are three separate pairs of columns, headed 'NEC', 'Perforation' and 'GI'. Would the sponsor please confirm what the heading 'GI' refers to? [The sponsor confirmed that GI refers to *gastrointestinal*. See under *Response from sponsor* below.] Rates of ventilator support were higher in the bolus group (Table 6 above). The review did not find differences between bolus and slow infusions for decrease in cerebral or mesenteric blood flow. There was no deterioration in cerebral function demonstrated for either method of administration.

vi) **Efficacy in comparison with placebo**

There were eight papers reviewed. Indomethacin demonstrated superior efficacy to placebo in rates of closure of PDA. A number of the studies attempted to make comparisons with regards to longer-term survival and neuro-developmental outcomes. While, generally, there appeared to be no notable differences between the two treatments with regard to positive outcomes, the rates of serious negative outcomes did appear to be lower with indomethacin. For example in the study by Yeh *et al*, five (38%) neonates in the indomethacin group and seven (41%) in the control group had major or minor neurological defects. In the study by Couser *et al* 2000, four (14%) of the 29 infants in the indomethacin group were severely impaired compared with eight (22%) of the 36 placebo treated neonates. Incidentally, the clinical evaluator has reported the percentage in the indomethacin group for the Couser study as 4%. However, this would appear to be a typographical error. Would the sponsor please confirm that this is a typographical error? [The sponsor confirmed that this was a typographical error. See below under *Response from sponsor*.] In the study by Ment *et al* 2000, 11 (9%) of the indomethacin group and 19 (17%) of the placebo group had an IQ < 70 (WPPSI-R). In the study by Smidt *et al* 2001, while there were no differences between indomethacin and placebo treatment in mental development index scores or in rates of death or impairment outcomes. However, there was a decrease in severe intraventricular haemorrhage in the indomethacin group: 52 (95) compared with 73 (13%) in the placebo group. In the study by Setzer *et al* 1987, twenty-two (22%) of 99 neonates in the indomethacin group and 44 (44%) of 100 in the placebo had IVH grades II-IV (p-value for difference < 0.0005).

Efficacy data comparing alternative dosing regimens

- Continuous infusion: There were two papers, one of which was a meta-analysis of two studies. In the meta-analysis, there was no difference in rates of PDA closure but both studies of the meta-analysis reported a decrease in middle cerebral artery flow after bolus doses but not following infusions. The second paper reported a randomised, double-blind, placebo-controlled study; a greater proportion of patients in the placebo group than in the continuous infusion group required additional therapy (47% versus 10%, p-value for difference < 0.05).
- Prolonged low-dose indomethacin: Prolonged courses of lower dose indomethacin were shown to have the same efficacy with a reduced rate of oliguria but an increased risk of necrotizing enterocolitis. Also, in the study by Rennie *et al* 1991, ductal closure was superior in the prolonged dose group as

compared with indomethacin q12h for three doses but survival was worse – ten neonates died in the prolonged course group compared with three in other (conventional dosing) group.

- Dosing guided by echocardiography: There was one study in which closure rates were similar between the two groups (with or without echocardiographic confirmation of PDA closure prior to next dose). However, complication rates were lower in the echocardiographic confirmation group.
- Early intervention with indomethacin: One study showed that early intervention with indomethacin, as opposed to waiting for evidence of symptomatic PDA, reduced mortality and the incidence of broncho-pulmonary dysplasia.
- Oral administration of indomethacin: A retrospective audit showed similar rates of PDA closure between the oral and IV groups.

vii) Efficacy data in comparison with an active comparator

- Ibuprofen compared with indomethacin: There were ten (10) papers assessed, one of which was a meta-analysis of 19 studies (Ohlsson *et al* 1993). When ibuprofen was compared with indomethacin, the rates of PDA closure were similar but there were lower risks for necrotizing enterocolitis and for renal impairment following ibuprofen treatment. There was no significant difference in mortality or in neurological or pulmonary outcomes.
- Aspirin compared with indomethacin: There was one (1) paper. Indomethacin was shown to have superior efficacy to aspirin in the rate of closure of PDA (92% of indomethacin versus 43% aspirin treated PDAs closed, p-value for difference < 0.0001).
- Sulindac compared with indomethacin: There was one (1) study in 16 neonates with successful closure in 8/8 indomethacin neonates compared with 6/8 sulindac treated neonates. Two deaths were reported in the sulindac group and urine output and plasma sodium decreased significantly in indomethacin group.

viii) Evaluator's overall conclusions on clinical efficacy

The clinical evaluator was of the opinion that the meta-analysis provided in the sponsor's Clinical Overview demonstrated no difference in efficacy between bolus and slow infusion administration. The rates of intracranial haemorrhage, periventricular leukomalacia, necrotizing enterocolitis and GI perforation were lower in the bolus group. The clinical evaluator thought that this might influence clinicians to prefer the bolus method of administration. However, the differences between bolus and slow infusion for GI perforation are somewhat equivocal and, as noted previously by the clinical evaluator, the RCT results showed a higher mortality and rates for ventilatory support in the bolus group.

The meta-analysis was not well presented. It was not clear which studies were included in the meta-analysis, nor how many exactly.

When ibuprofen was compared with indomethacin, the rates of PDA closure were similar but there were lower risks for necrotizing enterocolitis and renal impairment.

Safety in Patent Ductus Arteriosus

- ix) As noted by the clinical evaluator, indomethacin use in preterm neonates is well documented and there were a large number of published studies included in the current Australian submission. There was one post-marketing surveillance study but no PSURs were included in the current submission. The clinical evaluator also

commented that, in addition to the randomised, controlled studies and other studies containing evaluable data, there were a number of studies which indicated exposure to indomethacin but these were not of sufficient quality to contribute to the current application. The evaluator listed 46 such studies.

- x) From the evaluable data, indomethacin is associated with an increased risk of necrotizing enterocolitis and with impaired renal function. The impaired renal function usually resolves over the 24 h following discontinuation of indomethacin dosing. Electrolyte disturbances are common following indomethacin infusion in preterm neonates. Despite the high risk of transient renal dysfunction, acute renal failure appears to be rare with indomethacin. The impairment in renal function is greater with indomethacin than with ibuprofen. Haemorrhagic adverse events appear to be uncommon and there appears to be a decreased risk of intracranial haemorrhage.
- xi) There appears to have been little attempt by the sponsor to provide estimates of the rates of adverse events in the neonatal population being treated with indomethacin. In fact, as pointed out by the clinical evaluator, the only information provided in the proposed PI regarding frequencies of adverse events is that in adults taking oral indomethacin for very different indications. The clinical evaluator has provided the following estimates of certain adverse events in the neonatal population:
- Oliguria 44%.
 - Necrotizing enterocolitis 15%.
 - Bleeding 10%.
 - Gastrointestinal perforation 3.2%.
 - Acute renal failure 3.2%.
 - Blindness < 1%.
- xii) Serious adverse events were not specifically addressed in the submission. The literature collated for this submission did not distinguish adverse events by severity.
- xiii) The reports in the submission were not of sufficient quality to determine discontinuations due to adverse events.
- xiv) Concurrent corticosteroid and indomethacin treatment use appeared to increase the risk of necrotizing enterocolitis. Furosemide and indomethacin co-treatment may prevent oliguria but does not prevent the deterioration in renal function. As indicated in the clinical evaluation report there is uncertainty about the precise relationship between furosemide and indomethacin with regard to renal function.
- xv) There was one post-marketing surveillance study of 2538 low birth weight neonates treated with indomethacin in Japan from December 1994 to March 2001. Clinical closure of PDA occurred in 81.2% of those treated. A multivariate logistic regression analysis indicated that clinical closure was associated with pregnancy induced hypertension and RDS. As noted by the clinical evaluator, this is somewhat perplexingly expressed. However, the Delegate assumed that what is meant is that treatment of PDA with indomethacin was more successful in association with these two pathologies than with other pathologies. The sponsor is requested to clarify this result. [The sponsor answered this question in their Pre-ACPM response; see *Response from sponsor* below.]
- xvi) No PSUR Data or other post-marketing data were included in the submission.
- xvii) **Summary of safety**
From the evaluable data, indomethacin is associated with an increased risk of necrotizing enterocolitis and with impaired renal function. The impaired renal function usually resolves over 24 h following discontinuation of indomethacin dosing. Electrolyte disturbances are common following indomethacin infusion in preterm neonates. Despite the high risk of transient renal dysfunction, acute renal failure

appears to be rare with indomethacin. The impairment in renal function is greater with indomethacin than with ibuprofen treatment. Haemorrhagic adverse events appear to be uncommon and there appears to be a decreased risk of intracranial haemorrhage. There are important interactions between indomethacin and corticosteroids (increased risk of NEC) and also between indomethacin and furosemide (worsening of renal function despite improvement in oliguria).

xviii) **Summary of clinical evaluator's recommendation**

Indomethacin has a favourable risk-benefit profile in comparison with placebo. The changes that have been made to the *Indications* are supported by the data presented in the submission. However, the clinical evaluator was of the opinion that it was not acceptable that the PI does not inform clinicians of the potentially worse safety profile of indomethacin in comparison with ibuprofen. The clinical evaluator also made a number of recommendations for amendments to the PI, the principal one of which was for the provision of estimates of adverse event frequencies in the neonatal population being treated with indomethacin for PDA.

Risk-Benefit Analysis

Delegate Considerations

In the meta-analysis there were no clinically or statistically significant differences between the rates of PDA closure for bolus compared with slow infusion administration. The best efficacy results were from studies which used schedules of indomethacin dosing which were titrated to response. This in itself is a reassuring result.

- xix) Overall, there were similar rates of mortality, oliguria and elevation of serum creatinine for both bolus and slow infusion administration but in the results for the RCTs, there was a higher mortality in the bolus group. Rates of intracranial haemorrhage, periventricular leukomalacia and necrotizing enterocolitis were lower in the bolus group. Differences in the rates of GI perforation between the two groups were equivocal. Rates for ventilator support were higher in the bolus group. There were no differences in the decreases in cerebral or mesenteric blood flow following the bolus injection and the slow infusions method. Nor was there any deterioration in cerebral function noted for either administration method.
- xx) The clinical evaluator expressed concerns that neither the precise number nor the identity of the studies comprising the meta-analysis had been stated in the submission. The Delegate shares these concerns. For example, with respect to efficacy outcomes there appear to be 32 studies of which the results have been summarised and 11 of these were RCTs. However, we are told that there were 35 randomised controlled trials, 32 prospective case series trials and 32 retrospective case series trials. Therefore there is a shortfall of 24 randomised controlled trials whose efficacy results have not been summarised as well as a shortfall in the other types of studies. The sponsor is requested to clarify these deficiencies, particularly that involving the results for the 24 RCTs unaccounted for and is asked to give a full, accurate and detailed accounting of those studies which were actually part of the meta-analysis. There also appears to be eight studies which have results for one arm only, that is either for bolus or slow infusion administration, and even more perplexing is that two of these eight are RCTs. How is it that a RCT has only the results for one of its two arms reported? Again, the sponsor is requested to clarify these apparent inconsistencies [For the sponsor's response see under *Response from sponsor below*].
- xxi) The clinical evaluator has provided a list of questions for the sponsor and the sponsor is requested to provide answers to all of these questions in its pre-ACPM response.

There is some overlap between these questions and those asked by the Delegate. For the sponsor's answers see *Response from sponsor* below.

- xxii) There probably are sufficient data to support consideration of the use of slow infusions compared with bolus injections. However, the final decision in this matter will depend on how well the sponsor can respond to the requests for clarification under the previous two points. The ACPM was also asked to express its opinion on the quality of the reporting of the meta-analysis data.
- xxiii) The Delegate agrees with the clinical evaluator that there are sufficient data to support the proposed changes to the indication. Early treatment with indomethacin can be beneficial, without waiting for 48 h of medical management. Digoxin is no longer considered part of the appropriate routine management for PDA. Efficacy has also been demonstrated in preterm neonates regardless of birth weight.

Recommendation:

- xxiv) The Delegate proposed to approve the submission by Invida Australia Pty Ltd to register major changes to the Product Information for Indocid PDA, including changes to the Dosage and Administration and to the Indications, based on the quality, safety and efficacy of the product having been satisfactorily established for the indication below and for the reasons stated above in the Risk/Benefit Discussion:

“Indocid PDA is indicated for the closure of patent ductus arteriosus in premature babies. Clear-cut 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. Indocid PDA should only be used in a hospital under supervision of a specialist neonatologist.”

- xxv) The sponsor should address the following issues in their Pre-ACPM response:
- a) An update to the registration status (with dates) for Indocid PDA in the USA, Europe/UK, Canada, New Zealand and Switzerland including any withdrawals, rejections or deferrals.
 - b) Please provide an up-date of the likelihood of resumption of supply of the US-manufactured product which is the Australian-registered product.
 - c) Does the sponsor have any knowledge of a similar submission to the present one having been presented, or intended for presentation, to any overseas regulatory agencies?
 - d) Please clarify the meaning of the columns headed by ‘GI’ in Table 5 and then explain the significance of the results in those columns. Also then please clarify the meaning of ‘Perforation’ in the same table. Does it refer to GI perforation?
 - e) Provide answers to the list of questions asked by the clinical evaluator.
 - f) Provide responses to the concerns of the Delegate and of the clinical evaluator with regard to the number and identity of the studies which contributed to the meta-analysis summarised in the sponsor’s Clinical Overview and to the reporting of the results of that meta-analysis. The sponsor is once again reminded that any final decision regarding approval will be dependent upon satisfactory resolution of all issues which are of concern to both the clinical evaluator and the Delegate.
 - g) Does the sponsor have any explanation as to why the supporting literature submitted with the current Australian submission was presented as three groups of studies by alphabetical order of first author?

- h) Would the sponsor please confirm that there was a typographical error in the CER in the reporting of the percentage of infants severely impaired in the indomethacin group of the study by Couser (see above).
- i) The sponsor was requested to explain the result from the Japanese post-marketing surveillance study that clinical closure was associated with pregnancy induced hypertension and RDS.

The application was submitted for ACPM advice.

Response from Sponsor

The following are response to the Delegate's issues:

a). An updated registration status of Indocid PDA was provided (see Regulatory Status above).

b). Lundbeck Inc has worked diligently to develop and secure a new long-term source for Indocid.

Unfortunately during the technical transfer process the company encountered some recent and unexpected delays. Since the prior manufacturing source is no longer in a position to produce additional product, the company has incurred an extended global back order.

The company is doing everything it can to resolve the situation permanently. Although it is not currently in a position to predict when the technical issues will be fully resolved and when it will be in a position to support a variation for a site change, the company believes that this is unlikely before the second half of 2011.

c.) Similar submissions have been presented to the UK, USA, Canadian and NZ regulatory agencies. In the UK, INDOCID PDA is indicated for closure of PDA in premature infants. In Canada & NZ, the product is indicated for closure of PDA in premature infants when usual medical management is ineffective. In the US, the product is indicated to close PDA in premature infants weighing between 500 and 1750 mg when after 48 hours usual medical management is ineffective. Each agency has approved the statement: *While the optimal rate of injection has not been established, published literature suggests an infusion rate over 20-30 minutes.* .

d.) The sponsor referred to the explanatory details on this table within the *Clinical Trials* section of the proposed Australian PI.

The following answers refer to the list of 5 questions posed by the clinical evaluator

Q1 PHARMACOKINETICS: Has the Sponsor considered exploring the pharmacokinetics of indomethacin in preterm neonates using population pharmacokinetic methods?

The sponsor has no current plans to incorporate population pharmacokinetic methods in its ongoing research.

Q2 PHARMACODYNAMICS: Has the sponsor considered making dosing recommendations on the basis of plasma indocid concentrations?

This analysis was examined during the course of the review. However a lack of clear correlation between plasma levels and outcomes made clear dosage recommendations difficult to validate from the available data.

Q3 EFFICACY Part 1: Can the Sponsor clarify which studies contributed data to the meta-analysis and provide summary tables for these studies.

A summary of the studies and their criteria included in the meta-analysis was provided in the sponsor's response. This information complements the complete listings of the studies which was provided to the TGA as an annexure to the Sponsor's Clinical Summary.

Q3 Part 2 EFFICACY Part 2: Can the sponsor clarify whether five or six head-to-head studies were included in the meta-analysis.

Five small head-to-head studies comparing bolus to slow were identified in the review; Colditz 1989, Coombs 1990, Edwards 1990, Simko 1994, Zecca 1994.

Q4 SAFETY Part 1: Can the Sponsor provide a Summary of Clinical Safety.

The adverse effects occurring with Indocid PDA in premature infants are well known: a transient fall in cerebral blood flow, transient impairment of renal function and gastrointestinal problems, decreased platelet function and increased bleeding other than intracerebral haemorrhage. The pooled estimates on the toxicity outcomes of the infants studied by treatment regimen (unadjusted for outliers) are summarised in the Sponsor's Clinical Summary. The following measures occurred less frequently in the Bolus group: NEC [5.0% (2.7 to 7.3) versus 10.4% (7.1 to 13.7), $p=0.012$], Any ICH [2.0% (0.4 to 5.8) versus 9.0% (4.3 to 13.7); $p=0.002$] and ventilatory support [5.0% (1.4 to 12.3) versus 35.9% (24.6 to 47.2), $p<0.001$].

The pooled estimates on all studies and the RCTs for the toxicity outcomes on the dose range covered by the review showed:

- - mortality in the RCTs for the Bolus group, not observed in the All studies
- - urine output in the RCTs for the Bolus group, not observed in the All studies
- - events for any ICH for the All studies Slow group, not replicated in the RCTs
- - NEC and Perforation for the All studies Slow group, not replicated in the RCTs

A paucity and selective reporting of toxicity events in the Bolus group complicated the interpretation of these findings. Notwithstanding this, in assessing the significance of these findings it is worth considering the significantly lower mean cumulative dose of indomethacin administered in the bolus group (0.49mg versus 0.635 mg), the time lag bias arising from significant technological improvements to the present slow infusion era and the delayed pharmacological treatment of the Bolus infants until after Usual Management Therapy has failed (on average 8 days from birth). Close review of the mortality results show significantly heightened outcomes for three studies representing 73.5% of the bolus group results. The average age at which indomethacin was first administered in these studies was 8.5, 10 and 7 days respectively following Usual Management Treatment (UMT). This compares with an average of 4.71 days for the Slow group (>95% of which

received indomethacin at 3.36 days). Delay or suboptimal dosing puts the child at increased risk.

Closure of the PDA when initiated in the second week may necessitate prolonged mechanical ventilation that is not without inherent risk, since a relationship exists between bronchopulmonary dysplasia and duration of mechanical ventilation using elevated inspired oxygen concentrations. One of the studies (Gersony 1983) included a number of infants with cardiac abnormalities and was associated with a significant level of SAEs including sepsis (16%), NEC (5%), unspecified SAEs (15%) resulting from stratification bias (poorer results associated with certain centres) and broad inclusion criteria. Based on the Grubbs' outlier test, also called the ESD method (extreme studentised deviate) the Gersony result for mortality is a significant outlier from the rest of the group and the review ($p<0.05$). Applying this methodology to remove these and other outliers from the summary results on mortality and other SAE measures shows comparability between the bolus and slow groups on most measures with significant differences observed on mortality and GI bleeding (reduced for slow infusion). A clinical pharmacology expert opinion informs us there is no recognised mechanism by which infusion rate of indomethacin would contribute directly to an infant's death. Special consideration was given to the comparative effects of the two infusion modalities on blood flow velocities. It is well known that indomethacin causes a decrease in cerebral, renal and mesenteric blood flow velocity, probably caused by vasoconstriction, which can subsequently reduce organ perfusion. The frequently observed side effects of

indomethacin treatment, such as impairment of renal function and gastrointestinal problems have often been related to the changes in organ blood flow. Although the evidence remains equivocal, concerns of increased risk of neurodevelopmental impairment due to hypoxia/ischaemia with the rapid infusion method was a key rationale for the shift in clinical practice to the slower infusion rates [Greisen and colleagues showed that reduction of PaCO₂¹ (and hence cerebral blood flow and oxygen delivery) lowered the incidence of periventricular haemorrhage but increased the risk of neurodevelopmental impairment apparently due to hypoxia/ischaemia]. Administering indomethacin over 15-30 minutes has been suggested as a safer and more effective option to prevent reduction of the changes in organ blood flow thereby reducing the side effects of indomethacin treatment.

Results gathered on 17 studies which investigated reductions in cerebral blood flow and cerebral, renal and mesenteric blood flow velocities arising in the context of standard therapeutic doses of indomethacin used in PDA (summarised in sponsor's Clinical Summary), indicated that a therapeutic dose of indomethacin administered either by rapid infusion or during a 30-minute infusion produced a significant decrease in cerebral blood flow and the cerebral blood flow velocity. The decrease in the CBF² and velocities was maximal at 2-10 minutes after rapid infusion and by 20-40 minutes when indomethacin was given over 15-30 minutes. The comparative median values for the maximal changes in mean CBF and CBF velocity parameters were (bolus v slow): CBF: -40% versus -36.5%; ICA: -30.5% versus -30%; MCA: -39 versus -31% and ACA: -23% versus -29.5%. Afterwards a slow gradual recovery of the blood flow and velocities occurred towards baseline levels.

Q4 Part 2 SAFETY Part 2: Can the sponsor provide incidence rates for the adverse events reported with intravenous indomethacin in neonates?

A separate document giving cumulative incidence rates was submitted with this Pre-ACPM response to TGA. Estimates of risk for the population of the various S/AEs are provided in the Sponsor's Clinical Summary.

Q5 Part 1 CONSUMER MEDICINE INFORMATION: Does the Sponsor have data indicating improved renal function with co-administration of furosemide?

The sponsor does not have data on this association. The impact of the co-administration of furosemide on renal function was considered for this review however inadequate reporting made such an analysis difficult.

Q5 Part 2 CONSUMER MEDICINE INFORMATION: Does the Sponsor have additional data indicating the frequency of adverse events following indomethacin in the neonatal population?

The incidence rates from post-marketing activities are not available.

f *Number and identity of the studies contributing to the meta-analysis summarised in the Clinical Overview.*

This question has been addressed in Q3 EFFICACY part 1 above.

g *Why the supporting literature was presented as three groups of studies by alphabetical order of first author.*

This presentation of the references was essentially to align to the reference list described in the sponsor's Clinical Summary document. Specifically, the reference list described under the sections "Studies included in review" and "Additional references" were in alphabetical order of first author. Alignment provides ease of locating the relevant references and their citations. The apparent grouping of studies was purely editorial in nature.

h *Was there a typographical error in the CER reporting the percentage of infants severely impaired in the indomethacin group of the study by Couser. Refers point xiii of Overview.*

¹ Partial pressure of carbon dioxide in the blood.

² cerebral blood flow

Yes, there would appear to be a typographical error in the CER: 4 of 29 (14%) subjects treated with indomethacin had significant impairment as compared to 8 of 36 (22%) of the placebo-treated subjects.

i *Explanation why pregnancy-induced hypertension (PIH) & RDS in the Japanese PM report by Itabishi (2003) were associated with effectiveness of indomethacin administration in clinical closure of PDA.*

Both these antenatal factors are common co-morbidities in preterm infants, the population at most risk of PDA. Additionally it is generally accepted that vasodilator prostaglandins are involved in the pathogenesis of PDA in preterm infants with RDS. The reason for the association of PIH with ductal closure may be a reflection of the probability that women with PIH tend to be delivered before the onset on labour as compared with those who deliver spontaneously.

Product Information

This response addresses those queries that fall within the ambit of this review (comparison of indomethacin bolus versus slow infusion on standard dose schedules). A number of questions raised by the Clinical Evaluator and Delegate are outside the scope of this analysis and would require separate comprehensive reviews to address (in line with Good Evidential Practice). In particular, matters pertaining to the update of the *Pharmacokinetics* and *Pharmacology* sections [comparison of indomethacin with ibuprofen & surgical ligation] would require separate reviews. Descriptive summaries of the titrated studies are outside the scope of this review (summaries of these are currently available on efficacy and safety risk estimates and are detailed in the revised PI).

Additionally, we are of the view that incorporation into the indomethacin PI of statements comparing it with ibuprofen in, for example, renal impairment is likely to result in an unbalanced or uninformed view by the prescriber of the overall risk/benefits of treatment with ibuprofen in PDA. These statements are seen from a separate partial analysis conducted by the evaluator of data which was submitted by MSD for a different objective.

The sponsor confirmed that current certificates of Good Manufacturing Practice (GMP) remain enforceable.

The proposed amendments have been incorporated into the updated PI and CMI.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission from Invida Australia Pty Ltd to register indomethacin (as sodium trihydrate) (Indocid PDA) injection, powder 1 mg for an extension of indications and a new dosage regime for the indication:

For the closure of patent ductus arteriosus in premature babies.

Clear-cut 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. Indocid PDA should only be used in hospital under supervision of a specialist neonatologist.

In making this recommendation, the ACPM considered the overall risk benefit to be positive and the quality, safety and efficacy to have been demonstrated.

Changes to the Product Information (PI) and Consumer Medicines Information (CMI) recommended prior to approval include: Information regarding the clinical trials conducted using ibuprofen as a comparator.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Indocid P.D.A. containing 1 mg indomethacin for the new dosage regimen and **new indication**. The **new indication** is:

For the closure of patent ductus arteriosus in premature babies. Clear-cut 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. Indocid P.D.A. should only be used in a hospital under supervision of a specialist neonatologist.

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Additional study reference included by the Clinical Evaluator:

Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants (Review). The Cochrane Collaboration. The Cochrane Library 2010, Issue 4

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PRODUCT INFORMATION

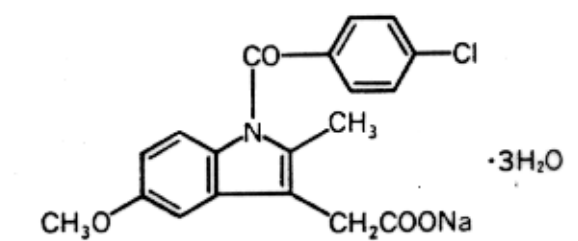
INTRAVENOUS INJECTION

INDOCID® P.D.A.

(Indomethacin Sodium Trihydrate, MSD)

Sterile INDOCID® P.D.A. (indomethacin sodium trihydrate, MSD) for intravenous administration is lyophilised indomethacin sodium trihydrate. Each vial contains indomethacin sodium trihydrate equivalent to 1 mg indomethacin as a white to yellow lyophilised powder or plug. Variations in the size of the lyophilised plug and the intensity of colour have no relationship to the quality or amount of indomethacin present in the vial.

Indomethacin sodium trihydrate is designated chemically as 1-(4 chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-acetic acid, sodium salt, trihydrate. Its molecular weight is 433.82. Its empirical formula is $C_{19}H_{15}ClNaO_4 \cdot 3H_2O$ and its structural formula is:

**CLINICAL PHARMACOLOGY**

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. 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, PGE₁ dilates the ductus arteriosus. In fetal and newborn lambs, E type prostaglandins have also been shown to maintain the patency of the ductus, and as in human newborns, indomethacin causes its constriction.

In double-blind placebo-controlled studies of INDOCID P.D.A. in 460 small pre-term infants, weighing 1750g or less, the infants treated with placebo had a ductus closure rate after 48 hours of 25 to 30 percent, whereas those treated with INDOCID PDA had a 75 to 80 percent closure rate. In one of these studies, a multicentre study, involving 405 pre-term infants, later reopening of the ductus arteriosus occurred in 26 percent of infants treated with INDOCID P.D.A., however, 70 percent of these closed subsequently without the need for surgery or additional indomethacin.

INDOCID P.D.A. is less effective than surgical ligation. Available information shows it is less safe than surgical ligation.

INDOCID P.D.A. should not be given without echocardiographic confirmation that symptoms are due to a patent ductus arteriosus and that no other significant cardiac defect exists.

There is no evidence to support the use of INDOCID P.D.A. in an attempt to prevent the development of patent ductus arteriosus (so-called prophylactic use), nor for the use of INDOCID P.D.A. before an adequate period of conservative treatment has been tried.

PHARMACOKINETICS AND METABOLISM

The disposition of indomethacin following intravenous administration (0.2 mg/kg) in pre-term neonates 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 infants who could be evaluated, the plasma half-life in those infants less than 7 days old averaged 20 hours (range: 3-60 hours, n=18). In infants older than 7 days, the mean plasma half-life of indomethacin was 12 hours (range: 4-38 hours, n=10). Grouping the infants by weight, the mean plasma half-life in those weighing less than 1000g was 21 hours (range: 9-60 hours, n=10); in those infants 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 plasma half-life of indomethacin is estimated to be about 4.5 hours. In the absence of enterohepatic circulation, it is 90 minutes.

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 an increased incidence of bilirubin encephalopathy (kernicterus).

INDICATIONS

INDOCID P.D.A. is indicated to close a 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, etc.) is ineffective. Clear-cut 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. The drug should only be used in a hospital under supervision of a specialist neonatologist.

CONTRAINDICATIONS

INDOCID P.D.A. is contraindicated in:

- infants with proven or suspected infection that is untreated;
- infants who are bleeding, especially those with active intracranial haemorrhage or gastrointestinal bleeding;
- infants with thrombocytopenia;
- infants with coagulation defects;
- infants with or who are suspected of having necrotising enterocolitis;
- infants with significant impairment of renal function;
- 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).

WARNINGS

Gastrointestinal Effects

In the collaborative study, major gastrointestinal bleeding was no more common in those infants receiving indomethacin than in those infants on placebo. However, gastrointestinal bleeding (i.e. chemical detection of blood in the stool) was more commonly noted in those infants treated with indomethacin. Severe gastrointestinal effects have been reported in adults with various arthritic disorders treated chronically with oral indomethacin.

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. However, in the large multi-centre study of INDOCID P.D.A. (See CLINICAL PHARMACOLOGY), the incidence of intraventricular haemorrhage in babies treated with INDOCID P.D.A. was not significantly higher than in the control infants.

Renal Effects

INDOCID P.D.A. may cause significant 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. These effects in most infants are transient, disappearing with cessation of therapy with INDOCID P.D.A. However, because adequate renal function can depend upon renal prostaglandin synthesis, INDOCID P.D.A., may precipitate renal insufficiency, including acute renal failure, especially in infants 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 drug, hepatic dysfunction). When significant suppression of urine volume occurs after a dose of INDOCID P.D.A., no additional dose should be given until the urine output returns to normal levels.

INDOCID P.D.A. in pre-term infants may suppress water excretion to a greater extent than sodium excretion. When this occurs, a significant reduction in serum sodium values (i.e. hyponatraemia) may result. Infants should have serum electrolyte determinations done during therapy with INDOCID P.D.A. Renal function and serum electrolytes should be

monitored. (See PRECAUTIONS, DRUG INTERACTIONS and DOSAGE AND ADMINISTRATION).

PRECAUTIONS

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 an 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

Gastrointestinal bleeding*, vomiting, abdominal distention, melaena, transient ileus, gastric perforation, localised perforation(s) of the small and/or large intestine, necrotising enterocolitis.

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 or 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 or serious gastrointestinal toxicity.

The concurrent use of aspirin and NSAIDs also increases the risk or 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.

GENERAL

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

Severe hepatic reactions including jaundice and hepatitis have been reported on rare occasions in adults treated chronically 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 P.D.A. should be discontinued.

INDOCID P.D.A. may inhibit platelet aggregation. In one small study, platelet aggregation was grossly abnormal after indomethacin therapy (given orally to premature infants to close the ductus arteriosus). Platelet aggregation returned to normal by the tenth day. Premature infants should be observed for signs of bleeding.

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

DRUG INTERACTIONS

Digitalis:

Since renal function may be reduced by INDOCID P.D.A., consideration should be given to reduction in dosage of those medications that rely on adequate renal function for their elimination. Because the half-life of digitalis (given frequently to pre-term infants with patent ductus arteriosus and associated cardiac failure) may be prolonged when given concomitantly with indomethacin, the infant should be observed closely; frequent ECGs and serum digitalis levels may be required to prevent or detect digitalis toxicity early.

Aminoglycosides:

Furthermore, in one study of premature infants treated with INDOCID P.D.A. and also receiving either gentamicin or amikacin, both peak and trough levels of these aminoglycosides were significantly elevated.

Frusemide:

Therapy with indomethacin may blunt the natriuretic effect of frusemide. This response has been attributed to inhibition of prostaglandin synthesis by nonsteroidal anti-inflammatory drugs. In a study of 19 premature infants with patent ductus arteriosus treated with either INDOCID P.D.A. alone or a combination of INDOCID P.D.A. and frusemide, results showed that infants receiving both INDOCID P.D.A. and frusemide had significantly higher urinary output, higher levels of sodium and chloride excretion, and higher glomerular filtration rates than did those infants receiving INDOCID P.D.A. alone. In this study, the data suggested

that therapy with frusemide helped to maintain renal function in the premature infant when INDOCID P.D.A. was added to the treatment of patent ductus arteriosus.

INDOCID P.D.A. causes marked reduction of glomerular filtration rate and creatinine clearance for 24-96 hours. All drugs relying on renal excretion should be avoided during this period or should be monitored with plasma levels and dose modification accordingly.

Antihypertensive medications:

In some patients with compromised renal function, the co-administration of an NSAID and an ACE inhibitor may result in further deterioration of renal function, including possible acute renal failure, which is usually reversible.

NEONATAL EFFECTS

There is a serious lack of long-term follow-up studies of babies who have received INDOCID P.D.A. in controlled trials. The long term safety of INDOCID P.D.A. is unknown. In view of the widespread prostaglandin inhibiting effects of INDOCID P.D.A. and immaturity of the very low birthweight population, its long-term safety must be considered as in doubt, especially in comparison with surgical ligation.

In rats and mice, oral indomethacin 4.0 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 liveborn fetuses was observed. At 2.0 mg/kg/day, no increase in neuronal necrosis was observed as compared to the control groups. Administration of 0.5 or 4.0 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 2.0 mg/kg/day and 4.0 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.

ADVERSE REACTIONS

In a double-blind placebo-controlled trial of 405 premature infants weighing less than or equal to 1750g with evidence of large ductal shunting, in those infants treated with indomethacin (n=206), there was a statistically significantly greater incidence of bleeding problems, including 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 haemorrhage.

The infants treated with indomethacin sodium trihydrate also had a significantly higher incidence of transient oliguria and elevation of serum creatinine (greater than or equal to 0.18mmol/L) than did the infants treated with placebo.

The incidence of retrolental fibroplasia (grades III and IV) and pneumothorax in infants treated with INDOCID P.D.A. were no greater than in placebo controls and were statistically significantly lower than in surgically-treated infants.

The following additional adverse reactions in infants 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. The rates are based on the experience of 849 indomethacin-treated infants reported in the medical literature, regardless of the route of administration. One year follow-up is available on 175 infants and shows no long-term sequelae which could be attributed to indomethacin. In controlled clinical studies, only electrolyte imbalance and renal dysfunction (of the reactions listed below) occurred statistically significantly more frequently after INDOCID P.D.A. than after placebo.

Renal

Renal dysfunction in 41 percent of infants, 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; elevated serum creatinine or BUN; uraemia.

Gastrointestinal

Gastrointestinal bleeding*, vomiting, abdominal distention, melaena, transient ileus, gastric perforation, localised perforation(s) of the small and/or large intestine, necrotising enterocolitis.

Metabolic

Hyponatraemia*, elevated serum potassium*, reduction in blood sugar including hypoglycaemia, increased weight gain (fluid retention).

Coagulation

Decreased platelet aggregation (See PRECAUTIONS).

Cardiovascular

Pulmonary hypertension; intracranial bleeding**.

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.

General

Exacerbation of infection.

The following adverse reactions have also been reported in infants treated with indomethacin, however, a causal relationship to therapy with INDOCID P.D.A. has not been established:

Cardiovascular - bradycardia.

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

Metabolic - Acidosis/alkalosis.

Haematologic - Disseminated intravascular coagulation.

Ophthalmic - Retrolental fibroplasia**.

A variety of additional adverse experiences has been reported in adults treated with oral indomethacin for moderate to severe rheumatoid arthritis, osteoarthritis, ankylosing

spondylitis, acute painful shoulder and acute gouty arthritis (See section ADDITIONAL ADVERSE REACTIONS - oral indomethacin - adults). Their relevance to the pre-term neonate receiving indomethacin for patent ductus arteriosus is unknown, however, the possibility exists that these experiences may be associated with the use of INDOCID P.D.A. in pre-term neonates.

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- * Incidence 3-9 percent. Those reactions which are unmarked occurred in 1-3 percent of patients.
 - ** Incidence of both indomethacin and placebo-treated, infants 3-9 percent. Those reactions which are unmarked occurred in less than 3 percent.

ADDITIONAL ADVERSE REACTIONS - oral indomethacin - adults.

The following adverse reactions have been reported in adults treated with oral indomethacin for moderate to severe rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute painful shoulder and acute gouty arthritis. Complaints not of relevance in the treatment of the premature infant, such as anorexia, psychic disturbances, and blurred vision, are not listed.

Gastrointestinal

(Incidence 1% to 3%)

Diarrhoea; Constipation

(Incidence less than 1%)

Bloating (includes distention), epigastric distress, abdominal pain, flatulence, peptic ulcer, gastroenteritis, rectal bleeding, proctitis; single or multiple ulcerations, including perforation and haemorrhage of the oesophagus, stomach, duodenum or small and large intestines; intestinal ulceration associated with stenosis and obstruction; gastrointestinal bleeding without obvious ulcer formation and perforation of pre-existing sigmoid lesions; development of ulcerative stomatitis; gastritis, toxic hepatitis and jaundice (some fatal cases have been reported).

Central Nervous System

(Incidence less than 1%)

Central nervous system adverse effects are headache, dizziness, light-headedness, depression, vertigo and fatigue (including malaise and listlessness). Reactions reported infrequently include mental confusion, anxiety, syncope, drowsiness, convulsions, coma, peripheral neuropathy, muscle weakness, involuntary muscle movements, insomnia, psychic disturbances such as depersonalisation, psychotic episodes and rarely paraesthesias, dysarthria, aggravation of epilepsy and parkinsonism. These are often transient and disappear frequently with continued treatment or with a reduction in dosage. However, the severity of these may, on occasion, require stopping therapy.

Special Senses

(Incidence less than 1%)

Hearing disturbances, deafness, tinnitus.

Cardiovascular

(Incidence less than 1%)

Hypertension, hypotension, tachycardia, arrhythmia, congestive heart failure, thrombophlebitis, palpitations, chest pain.

Metabolic

(Incidence less than 1%)

Oedema, weight gain, flushing, hyperglycaemia, glycosuria, hyperkalaemia.

Integumentary

(Incidence less than 1%)

Rash, pruritus, urticaria, angitis, petechiae or ecchymosis, exfoliative dermatitis, erythema nodosum, loss of hair, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis.

Haematologic

(Incidence less than 1%)

Leucopenia, bone marrow depression, anaemia secondary to obvious or occult gastrointestinal bleeding, aplastic anaemia, haemolytic anaemia agranulocytosis, thrombocytopenic purpura, thrombocytopenia and disseminated intravascular coagulation. There have been several reports of leukaemia. The supporting information is weak.

Hypersensitivity

(Incidence less than 1%)

Acute anaphylaxis, acute respiratory distress, rapid fall in blood pressure resembling a shock-like state, dyspnoea, asthma, purpura, angitis, pulmonary oedema, angioneurotic oedema.

Genitourinary

(Incidence less than 1%)

Haematuria, vaginal bleeding, renal insufficiency including renal failure, proteinuria, nephrotic syndrome, interstitial nephritis, urinary frequency.

Miscellaneous

(Incidence less than 1%)

Epistaxis, breast changes (including enlargement and tenderness, or gynaecomastia), ulcerative stomatitis, sweating.

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 recommendations for closure of the ductus arteriosus depends on the age of the infant at the time of therapy. A course of therapy is defined as three intravenous doses of INDOCID P.D.A. 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 P.D.A., no additional doses should be given until laboratory studies indicate that renal function has returned to normal. (See WARNINGS, Renal Effects).

Dosage according to age is as follows:

<u>AGE at 1st Dose</u>	<u>DOSAGE (mg/kg)</u>		
	<u>1st</u>	<u>2nd</u>	<u>3rd</u>
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 patent 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 P.D.A. 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.

Some studies have found that indomethacin has a greater effect in reducing mortality and bronchopulmonary dysplasia when given at 2-3 days rather than 7-10 days of age. Also, there is a significant decrease in time to regain birthweight, duration of oxygen therapy, the number of infants who will develop a large shunt and the number of surgical ligations required if indomethacin is given when a murmur is asymptomatic rather than waiting until a large shunt has developed.

If the infant remains unresponsive to therapy with INDOCID P.D.A. after 2 courses, surgery may be necessary for closure of the ductus arteriosus. As surgical ligation is more effective and probably safer it should certainly be used when indomethacin fails. If severe adverse effects occur, STOP THE DRUG.

Directions for Use:

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

THE SOLUTION SHOULD BE PREPARED ONLY WITH 1 TO 2 mL OF PRESERVATIVE-FREE STERILE SODIUM CHLORIDE INJECTION, 0.9 PERCENT, OR PRESERVATIVE-FREE STERILE WATER FOR INJECTION. Benzyl alcohol as a preservative has been associated with toxicity in newborns. Therefore, all diluents should be preservative free. 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. A fresh solution should be prepared just prior to each administration. Once reconstituted, the indomethacin solution may be injected intravenously over 5-10 seconds.

Further dilution with intravenous infusion solutions is not recommended. INDOCID P.D.A. is not buffered, and reconstitution with solutions at pH values below 6 may result in precipitation of the insoluble indomethacin free acid moiety.

Storage: The shelf life is 3 years when stored below 25°C. Protect from light. Store container in the carton until contents have been used.

OVERDOSAGE

Overdosage is unlikely to occur due to the small package size (1 mL.), the single dose vial and the limited dosing frequency for the defined indication. Contact the Poisons Information Centre regarding overdose management.

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, paraesthesias, numbness and convulsions. There are not specific measures to treat acute overdosage with INDOCID PDA. The patient should be followed for several days because of intestinal ulceration and haemorrhage have been reported as adverse reactions of indomethacin.

AVAILABILITY

Sterile INDOCID P.D.A. is a lyophilised white to yellow powder or plug supplied as single dose vials containing indomethacin sodium trihydrate, equivalent to 1 mg indomethacin.

MANUFACTURER/SUPPLIER

Pharmalink Pty. Ltd.
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Date Approved by Therapeutic Goods Administration 21 August 1990. Safety Related Changes notified 20 December 2004. Safety Related Changes notified 14 June 2005. Safety Related Changes notified 3 April 2007

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