Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for ibuprofen

Proprietary Product Name: Pedea

Sponsor: Emerge Health Pty Ltd

First round report: June 2016

Second round report: November 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The 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 <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviations	Meaning
ABR	Auditory Brainstem Responses
AE	Adverse Event
AFF	Atrial filling fraction
Ao	Aorta
Ao VTI	Aortic velocity time integral
AUC	Area under the plasma drug concentration-time curve over one dosing interval
AUC0-t	Area under the plasma drug concentration versus time curve from time zero to the time (t) corresponding to the last quantifiable concentration
AUC0-∞	Area under the concentration-time curve from time zero to infinity
BP	Blood pressure
BPD	Broncopulmonary dysplasia
BW	Birth weight
CBF	Cerebral blood flow
CHMP	Committee for Medicinal Products for Human Use (EU)
Cmax	Maximum plasma drug concentration
CNS	Central nervous system
CO	Cardiac output
COMP	Committee for Orphan Medicinal Products
COX	Cyclooxygenase
CP	Cerebral palsy
CRIB	Clinical risk index for babies
CPAP	Continuous positive airway pressure
CSR	Clinical study report
CYP	Cytochrome P450

Abbreviations	Meaning
DA	Ductus arteriosus
DIC	Disseminated coagulation disorder
DBP	Diastolic blood pressure
EMPP	Early motor pattern profile
Fi02	Fraction of inspired oxygen
Frel	Relative bioavailability
GA	Gestational age
GCP	Good Clinical Practice
HFO	High frequency oscillatory
HMD	Hyaline membrane disease
HsPDA	Haemodynamically significant patent ductus arteriosis
HPLC	High-performance liquid chromatographic
IM	Intramuscular
IV	Intravenous
IVH	Intraventricular haemorrhage
LA	Left atrium
LA/Ao	Left atrium / Aortic root ratio
LLOQ	Lower limit of quantification
LVD	Left ventricular diameter in diastole
LVS	Left ventricular diameter in systole
NIRS	Near Infrared spectroscopy
NSAIDs	Nonsteroidal anti-inflammatory drugs
MED	Minimal effective dose
NEC	Necrotising enterocolitis
PaO2	Partial arterial pressure of oxygen
PaCO2	Partial arterial pressure of carbon dioxide

Abbreviations	Meaning
PCA	Post-conceptional age
PDA	Patent ductus arteriosus
PD	Pharmacodynamics
PG	Prostaglandin
PGE1/PGE2	Prostaglandin E1, E2 etc
PHT	Pulmonary hypertension
PK	Pharmacokinetics
PFO	Persistent foramen ovale
PI	Product Information
PPHN	Persistent pulmonary hypertension of the newborn
PPV	Positive pressure ventilation
PSUR	Periodic safety update report
PVL/PVLM	Periventricular leukomalacia
PVR	Peripheral vascular resistance
PV VTI	Pulmonary valve flow velocity time integral
RDS	Respiratory distress syndrome
RI	Resistance index
RSVP	Right systolic ventricular pressure
SAE	Serious adverse event
SD	Standard deviation
SIDS	Sudden infant death syndrome
SmPC	Summary of Product Characteristics (EU)
T½	Terminal plasma half life
Tmax	Time to reach Cmax
TB	Total bilirubin
UB	Unbound bilirubin

Abbreviations	Meaning
VLBW	Very low birth weight
Vmax PFO	Maximum flow velocity through the persistent foramen ovale
Vmean PFO	Mean flow velocity through the persistent foramen ovale
Vmax TI	Maximum flow velocity of the tricuspid valve regurgitation
V	Flow velocity
VTI	Flow velocity time integral
WGA	Weeks of gestational age

1. Introduction

This is a full submission to register a new indication, new formulation and new patient population for ibuprofen.

1.1. Drug class and therapeutic indication

Ibuprofen is a non-steroidal anti-inflammatory drug.

The proposed indication is:

> *Pedea is indicated for the treatment of haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age.*

Multiple ibuprofen formulations for oral administration (tablet, capsule, liquid suspensions; as OTC products) are approved in Australia (for a large number of sponsors) for the treatment of acute mild to moderate pain and inflammation and in combination with codeine for strong pain or inflammation.

Ibuprofen for IV injection is also approved (for sponsor bioCSL Pty Ltd) as a 100 mg/mL concentrated injection for the following indications:

> *Caldolor is indicated in adults for the management of acute mild to moderate post-operative pain and moderate to severe post-operative pain with adjunctive reduced morphine dosage, where an intravenous route of administration is considered clinically necessary.*
>
> *Caldolor is indicated for the reduction of fever in adults where an intravenous route of administration is considered clinically necessary.*

1.2. Dosage forms and strengths

The proposed dose form and strength is:

- Ibuprofen 5 mg/mL solution for injection, 2 mL glass ampoule

1.3. Dosage and administration

The proposed PI contains the following information for dosage and administration:

- Treatment with PEDEA should only be carried out in a neonatal intensive care unit under the supervision of an experienced neonatologist.
- A course of therapy is defined as three intravenous injections of PEDEA given at 24-hour intervals. The first injection should be given after the first 6 hours of life.
- The ibuprofen dose is adjusted to the body weight as follows:
  - 1st injection: 10mg/kg,
  - 2nd and 3rd injections: 5mg/kg.

If anuria or manifest oliguria occurs after the first or second dose, the next dose should be withheld until urine output returns to normal levels. If the ductus arteriosus does not close 48 hours after the last injection or if it re-opens, a second course of 3 doses, as above, may be given.

If the condition is unchanged after the second course of therapy, surgery of the patent ductus arteriosus may then be necessary.

1.3.1. Administration

The product is for intravenous use only.

Chlorhexidine should not be used to disinfect the neck of the ampoule, as it is not compatible with the PEDEA solution. Therefore, for asepsis of the ampoule before use, ethanol 60% or isopropyl alcohol 70% is recommended. When disinfecting the neck of the ampoule with an antiseptic, to avoid any interaction, the ampoule must be completely dry before opening.

PEDEA should be administered as a short infusion over 15 minutes, preferably undiluted. If necessary, the injection volume may be adjusted with either sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection. Any unused portion of the solution should be discarded.

The total volume of solution injected should take into account the total daily fluid volume administered.

Before and after administration of PEDEA, to avoid contact with any acidic solution, rinse the infusion line over 15 minutes with 1.5 to 2 mL of either sodium chloride 9 mg/ml (0.9%) or glucose 50 mg/mL (5%), solution for injection.

2. Clinical rationale

Ibuprofen is an original molecule that was developed as a result of the safety problems associated with the use of other NSAIDs, initially in the treatment of rheumatoid arthritis. Products currently available on the market include oral, rectal, topical and intramuscular presentations. Ibuprofen as a free acid is poorly soluble at low pH and salts and derivatives, such as ibuprofen lysine, have been developed to increase its solubility and consequently, its speed of absorption.

The EU sponsor Orphan Europe has developed Pedea as an ibuprofen lysine formulation to provide a formulation of ibuprofen lysine as a safer alternative to indomethacin.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The dossier documented a development program of pharmacology, dose finding, efficacy and safety clinical trials relating to the new indication, new formulation and new patient population for ibuprofen.

The submission contained the following clinical information

- 1 x bioequivalence study (IBU/00/BIOEQ/FR)
- 1 x pharmacokinetic study (9-33/93)
- 2 x pharmacodynamic studies (IBU/BILICLIN and IBU/GER/2003)
- 2 x population pharmacokinetic studies (CP025329 and P60243)
- 1 x dose ranging study (IBU/99/DoseRange)
- 1 x pivotal efficacy study (IBU/PROPHYL/2000 curative group)
- 3 x other studies (IBU/PROPHYL/2000 – total group, LONG TERM FU/2004 and IBU/20mg/2009)
- 1 x safety study (IBU/Survey)

3.2. Paediatric data

The dossier contains paediatric data as the indication is only relevant to neonates.

3.3. Good clinical practice

Study 9-33/93 was conducted before the introduction of ICH-GCP. The CSR states that the protocol was approved by an independent ethics committee before the beginning of the study and the study conducted according to European GCP guidelines.

Studies are stated as complied with GCP, the Helsinki principles and applicable local requirements and parents/guardians of all infants had given their written informed consent at screening.

It is noted that in almost all of the study documents, including CSRs, tables and/or patient screening log forms are included that identify the patients included in the studies (includes patient initials, age, maternal initials and other demographic data). This is a breach of GCP (item 4.8.10(o)) and unless prior permission has been granted (not stated in CSRs) it may be in breach of privacy laws. These tables should have been removed or the initials redacted when included in the CSR and associated tables.

3.4. Evaluator's commentary on the clinical dossier

This submission was evaluated from the electronic version which was not easy to navigate. The clinical study reports (CSRs) were not consistently named, in many cases not named at all, causing confusion in relating the studies referenced in the summaries to the CSRs. Also the Clinical Overview appears to identify the studies by the later publication reference rather than the study name/code making it difficult to be sure of the correlation. In this report the study ID/report ID or name has been used rather than "study 1, 2 and 3" as in the electronic dossier.

Most of the studies are old, conducted in period 1993 to 2004. Not all study reports therefore complied with current guidelines for CSR format or content. Many of the studies were missing abbreviation lists making it difficult to clarify the meaning of some of the abbreviations.

Not all the studies were indexed in the electronic version and not all the study reports allowed easy or indeed in some, any copying of the text or tables.

The Clinical Overview was clearly written for the EU submission (which was a mixed literature based plus clinical studies submission) and so relies heavily on the literature based elements. The pharmacokinetic (PK) and pharmacodynamic (PD) data is almost entirely derived from the literature as only minimal studies were conducted by the sponsor. The Summary of Safety is not an integrated report and is very poorly written as it simply repeats selected parts of the safety sections of the CSRs for each individual study with no conclusions and no critical assessment of the data.

The Clinical Expert identified in Module 1 is not the same as the signatures on the Clinical Overview and Clinical Expert Report. The CSRs and Summaries of Clinical Efficacy and Safety are not well written with frequent spelling, grammatical and sentence composition errors suggesting the writer(s) were not proficient in written English.

The Clinical Overview is dated January 2009 which predates the completion of study IBU/20 mg/2009 which is therefore not included. The Summary of Clinical Efficacy and Summary of Clinical Safety are dated October 2015 and are very brief but do not contain all the clinical studies included in the submission. In many areas they do not include information about the studies provided in the Clinical Overview.

No studies were identified as pivotal in any of the summaries. The studies were presented in the summaries as they are presented in the CTD format of controlled, uncontrolled or other.

Therefore, based on the requested indication (the "treatment" of PDA) and the controlled study design, Study IBU/PROPHYL/2000 – curative was identified as pivotal in this report and study IBU/PROPHYL/2000 – prophylactic was identified as a supportive study as it was needed to be evaluated to understand the context of the curative group (the prophylactic treatment is outside the scope of the requested indication). However, studies in this submission raise concerns based on their age, design and objectives.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic information

See Table 1.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	Primary aim
PK in healthy adults	General PK - Single dose	9-33/93	PK
	- Multi-dose		
	Bioequivalence † - Single dose	IBU/00/BIOEQ/FR	BE
	- Multi-dose		
PK in special populations	Target population § - Single dose	IBU/BILICLIN 04	PD
		IBU/GER/2003	PD
Population PK analyses	Healthy subjects		
	Target population	CP025329	PopPK
		P060243	PopPK

† Bioequivalence of different formulations; § Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The Clinical Overview (including the Clinical Expert Report) contains a selected literature review of the pharmacology of ibuprofen. Only 2 clinical PK studies were conducted, the first was a bioequivalence study comparing the proposed IV formulation with a currently approved in Europe IM formulation. The second study was a PK study conducted in adult healthy volunteers using a single 400 mg IV injection of a formulation that comprised 400 mg in 50 mL infusion. The formulation is not provided and the relevance to the formulation proposed for marketing is unclear. No explanation for this study is provided.

> *Comment: The summary of study 9-33/93 provided in the Summary of Clinical Pharmacology is very brief (1 sentence) and does not make sense. It appears to be incomplete with information missing. The sentence is taken directly from the Clinical Expert Report without any explanation. The Clinical Overview provides no further information.*

4.2.1. Physicochemical characteristics of the active substance

Ibuprofen is (2RS)-2-[4-(2-Methylpropyl)phenyl]propanoic acid. Ibuprofen is a chiral nonsteroidal anti-inflammatory drug (NSAID) of the 2-arylpropionic acid class, and it is a

racemic mixture of S(+) and R(-) enantiomers. In vivo and in vitro studies indicate that the S(+) isomer is responsible for the clinical activity. The S-enantiomer possesses most of the anti-inflammatory activity and ibuprofen demonstrates marked stereoselectivity in its PK with substantial unidirectional inversion of the R- to the S-enantiomer. The active ingredient of Pedea is the racemic form.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

The proposed route of administration is IV.

4.2.2.2. Bioavailability

Bioequivalence of IV vs IM formulations

Study IBU/00/BIOEQ/FR - P000241 was an open, randomised, single dose, 2-way cross-over study in 18 healthy male volunteers. The study was divided into study periods 1 and 2, each with a duration of 1 day. Each subject received the treatments in a randomised order. Each subject received on Day 1 of both study periods a short 15 minutes injection of 5 mg/kg of ibuprofen base, in either the Orphan Europe ibuprofen formulation (Treatment A) or the Reference ibuprofen lysine IM formulation (Imbun - Treatment B) to evaluate the bioequivalence of the 2 ibuprofen formulations. Serial blood samples were collected immediately pre-dose and up to 12 hours after each dose. There was a 1 week wash-out period between the 2 treatments.

Results are presented for both the R- and S- enantiomers of ibuprofen.

The results demonstrated that for R-ibuprofen, the mean C_{max} were not significantly different after injection of the Test and of the Reference formulation. The 90 % CI (0.98-1.10) was included in the pre-specified range for bioequivalence (0.70-1.43). The inter-individual variability calculated for C_{max} and expressed by the CV, was comparable between treatments (13 % and 10 % for the Test and the Reference formulation, respectively).

Mean AUCs were not significantly different between the 2 formulations. The 90 % CI (0.98-1.11 for AUC_{0-t} and $AUC_{0-\infty}$) were included in the pre-specific range for bioequivalence (0.80-1.25). The inter-individual variability calculated for AUCs was comparable between treatments (17 % for the Test and 12 % for the Reference formulation). Based on $AUC_{0-\infty}$, the mean (±S.D.) relative bioavailability for R-ibuprofen was 1.06 ± 0.17.

The results demonstrated that for S-ibuprofen, the mean C_{max} were not significantly different after injection of the Test and of the Reference formulations. The 90 % CI (0.98-1.08) was included in the pre-specified range for bioequivalence (0.70-1.43). The inter-individual variability calculated for C_{max} was comparable between treatments (about 12 %).

Mean AUCs were significantly increased by about 5% after injection of the Test formulation while the 90 % CI (1.01-1.08 for AUC_{0-t} and $AUC_{0-\infty}$) were included in the pre-specified range for bioequivalence (0.80-1.25). The inter-individual variability calculated for AUCs was comparable between treatments (about 17 %). Based on $AUC_{0-\infty}$, the mean (±S.D.) relative bioavailability for S-ibuprofen was 1.05 ± 0.08.

The conclusion was that the test formulation (Treatment A) was bioequivalent to the reference formulation (Treatment B).

> *Comment: Study IBU/00/BIOEQ/FR - P000241 was conducted in 2000 and the study report is dated July 2002. The bioequivalence acceptance range is stated to be "the intraindividual ratios of Cmax and AUC have to fall into the bioequivalence range of 0.80-1.25 for AUC and into the wider acceptance range of 0.70-1.43 for Cmax (16)". The reference provided is to V.W. Steinijans and D. Hauschke, International harmonisation of regulatory bioequivalence requirements, Clin. Research and Reg. Affairs 10 (4): 203-220, 1993. This reference was not included in the submission. The EU guideline on*

*bioequivalence (Guideline on the investigation of bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) came into effect in Europe in January 2002 (in its original version) and states that "90% confidence interval for the ratio of the test and reference products [for AUC(0-72h), and Cmax] should be contained within the acceptance interval of 80.00-125.00%. The results of the study were that both AUC(0- 72h), and Cmax are within the acceptance range of 80 to 125% for both AUC and for both enantiomers*

Influence of food

Not applicable.

Dose proportionality

Formal dose proportionality was not presented. In the dose ranging study (IBU/99/DoseRange, a range of doses of initial and maintenance doses were investigated and plasma concentrations of ibuprofen were measured. The dose regimes were 5 mg / 2.5 mg / 2.5 mg; 10 mg / 5 mg / 5mg; 15 mg / 7.5 mg / 7.5 mg and 20 mg / 10 mg / 10 mg. The different doses were studied in 2 patient cohorts (20 preterm neonates with 27 to 29 weeks GA, termed the +27 group and 20 preterm neonates with 24 to 26 weeks GA, termed the -27 group. The results of the plasma concentrations following the initial loading doses demonstrate a dose proportional response.

Figure 1: Study IBU/99/DoseRange: Ibuprofen plasma concentrations at T0 in relation to the actual dose received +27 WGA.

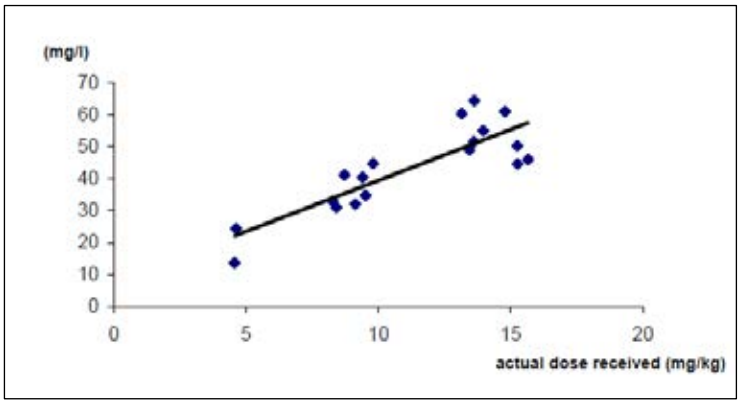
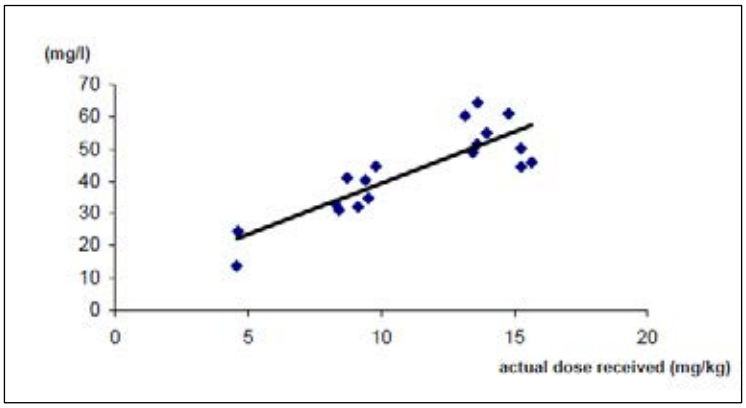


Figure 2: Study IBU/99/DoseRange: Ibuprofen plasma concentrations at T0 in relation to the actual dose received -27 WGA.



Dose proportionality was further confirmed in Study IBU/20mg/2009 where the PK results of the high dose regimen (20/10/10) was compared to the results of study IBU/BILICLIN/2004 which used the recommended dose.

4.2.2.3. Metabolism

Ibuprofen is extensively metabolised in the liver, mainly via oxidation and glucuronidation, and several metabolites have been identified in adults. Furthermore, chiral inversion is a unique

metabolic pathway which involves a unidirectional conversion of a fraction of the dose of R-ibuprofen to S-ibuprofen. Finally, inhibition of COX-1 and COX-2 derived prostanoids has been shown to be mediated by the S-enantiomer whereas the metabolites are inactive.

Biotransformation of ibuprofen in the liver largely involves cytochrome P450 2C complex and UDP glucuronyl transferase. These enzymatic activities are known to be very low in the foetus and during the first weeks of life, which potentially affects the metabolic capacities of the preterm newborn. The sponsor states that since the pattern of metabolites is not expected to differ between the preterm and the adult, complete determination of all metabolites in the urine does not seem justified in view of the technical difficulties encountered to carry out such a study in the preterm population.

4.2.3. Pharmacokinetic parameters

See Table 2.

Table 2: PK parameters in adult healthy subjects.

R-IBUPROFEN (n=18)	**C_{max} (µg/mL)**	**T_{max} (min)**	**AUC_{0-t} (µg/mL.h)**	**$AUC_{0-\infty}$ (µg/mL.h)**	**T½ (h)**
Ibuprofen ORPHAN EUROPE IV formulation					
Mean	28.380		45.72	46.68	3.04
SD	3.678	15-20#	7.77	7.92	0.94
Median	28.005	15	45.23	46.32	2.85
S-IBUPROFEN (n=18)	**C_{max} (µg/mL)**	**T_{max} (min)**	**AUC_{0-t} (µg/mL.h)**	**$AUC_{0-\infty}$ (µg/mL.h)**	**T½ (h)**
Ibuprofen ORPHAN EUROPE IV formulation					
Mean	26.469		61.30	63.06	2.35
SD	3.191	15-25#	10.82	11.61	0.31
Median	26.664	15	61.86	63.14	2.33

4.2.4. Pharmacokinetics in the target population

Two studies in preterm infants were conducted that included blood sampling in 17 preterm infants (median 25 weeks of GA) just after and at 72 h post loading dose (IBU/GER/2003), and in 34 preterm infants (median 27.1 weeks of GA) at 1h, 6h, 24h, 25h, 48h, and 72h post loading dose (IBU/BILICLIN/2004), respectively. In these 2 studies both enantiomers of ibuprofen were analysed.

Plasma concentrations were similar in both studies with peak levels around 35-40 mg/L after the initial loading dose of 10 mg/kg as well as after the last maintenance dose, whatever GA and postnatal age. Residual concentrations were around 10-15 mg/L 24 hours after the last dose of 5 mg/kg in 3 studies.

Table 3: Study IBU/BILICLIN 04: PK parameters in preterm infants.

N=33	**V1 mL/Kg**	**V2 mL/Kg**	**CLs mL/h/Kg**	**CLr mL/h/Kg**	**T½s h**	**T½r h**	**C_{max}s µg/mL**	**C_{max}r µg/mL**	**AUCs* h.µg/mL**	**AUCr* h.µg/mL**
Mean	154	194	3.8	86.0	35.2	1.6	40.7	27.0	868.9	32.5
SD	35	58	2.8	26.8	14.7	0.3	9.2	10.0	341.9	12.2
Min	99	83	1.8	38.0	7.7	1.2	26.6	15.9	154.2	18.6
Median	155	194	2.9	88.7	34.3	1.5	40.3	24.5	890.5	28.2
Max	270	300	16.7	134.4	74.	2.5	62.2	56.6	1456.9	65.8

N=33	V1 mL/Kg	V2 mL/Kg	CLs mL/h/Kg	CLr mL/h/Kg	T½s h	T½r h	C_{max}s µg/mL	C_{max}r µg/mL	AUCs* h.µg/mL	AUCr* h.µg/mL
					0					
CV%	23	30	75	31	42	18	23	37	39	38
GeoM	151	185	3.3	81.6	31.9	1.6	39.7	25.6	788.7	30.6

* AUC corresponding to a dose of 5 mg/kg of ibuprofen.

Exposure to S-ibuprofen, expressed as the AUC, was about 26-fold greater than that to R-ibuprofen (considering mean values).

Mean estimated clearance and volume of distribution were about 3.8 mL/h/kg and 154 mL/kg with a calculated half-life (T½s) of 35 h for S-ibuprofen.

Mean estimated clearance at birth and volume of distribution were about 86 mL/h/kg and 194 mL/kg with a calculated half-life (T½r) of 1.6 h for R-ibuprofen.

4.2.5. Pharmacokinetics in special populations

4.2.5.1. Pharmacokinetics in subjects with impaired hepatic function

Not done.

4.2.5.2. Pharmacokinetics in subjects with impaired renal function

Not done.

4.2.5.3. Pharmacokinetics according to age

Not applicable.

4.2.6. Population pharmacokinetics

4.2.6.1. PopPK analysis ID

Data from 3 clinical studies (61 infants from IBU/PROPHYL/2000, 14 infants from IBU/GER/2003 and 33 infants from IBU/BILICLIN/2004) totalling 108 preterm infants were included in the PopPK analysis (PO60243). A previous PopPK analysis (CP025329) which included data only from 1 study (IBU/PROPHYL/2000) had developed a PopPK model and the new study used the same model with some improvements. The final population model included a unidirectional bioconversion of R-ibuprofen to S-ibuprofen and an effect of post-natal age in the elimination rate of R-ibuprofen. Overall individual predictions adequately fitted the observed concentrations and the final model was acceptable to describe R and S-ibuprofen PK from the 3 clinical studies.

Mean half-lives (T½) for S and R-ibuprofen estimated from the final model were about 24 h and 8 h respectively. This was consistent with previously reported values. Mean clearance for S and R-ibuprofen was 3.5 and 25.5 mL/h/kg respectively. From the final model, T½ of R-ibuprofen dramatically decreased within the first days of life while the T½ of S-ibuprofen was unchanged. Modifications of metabolic capabilities during the first days of life might explain the increase of R-ibuprofen elimination. Indeed, postnatally the hepatic cytochrome P450 mono-oxygenase system is known to mature rapidly and R-ibuprofen and S-ibuprofen have 2 different metabolic pathways including cytochrome P450 2C9 (CYP2C9) and CYP2C8 respectively.

The volume of distribution of R-ibuprofen was found to be greater (306 mL/kg) than the volume of distribution of S-ibuprofen (173 mL/kg). Differences between the distribution of R and S-ibuprofen might be related to the binding to serum albumin. Indeed the affinity to serum albumin is known to be different between R and S ibuprofen and the binding level to albumin might vary during the first day of life.

The mean predictions of racemic ibuprofen concentrations obtained from the final model at the end of the 15 mg/kg and 20 mg/kg infusions (about 67 and 89 µg/mL respectively) were in good agreement with median concentrations observed during previous dose range study (IBU/99/DoseRange) at these dose levels (about 60 and 105 µg/mL respectively). Therefore, mean predictions seem to be accurate, even for doses greater than those used during the 3 clinical studies taken into account for the analysis.

The conclusions of the PopPK analysis were:

- A model including unilateral bioconversion of R-ibuprofen into S-ibuprofen and an effect of post-natal age on the elimination rate of R-ibuprofen was developed. R and S-ibuprofen plasma concentrations were adequately fitted by this model
- Estimated clearance and volume of distribution were 3.5 mL/h/kg and 173 mL/kg with a calculated half-life (T½) of 34.3h for S-ibuprofen during the first week of life
- Estimated clearance at birth and volume of distribution were 25.5 mL/h/kg and 306 mL/kg with a calculated half-life (T½) at birth of 8.3 h for R-ibuprofen
- R-Ibuprofen elimination increased during the first week of life
- S-Ibuprofen PK was weakly modified during the first week of life
- Different treatment regimens were simulated from the final model. Overall, confidence in mean simulated plasma profiles should be greater than confidence in individual simulated plasma profiles, particularly for R-ibuprofen

4.2.7. Pharmacokinetic interactions

No interactions studies were conducted. The sponsor acknowledged that a great number of interactions have been reported for ibuprofen and other NSAIDs based on extensive experience with oral administration.

Preterm infants receive a large number of drug combinations and this was reflected in the clinical studies in the submission. The subjects in the trials received drugs commonly used in the management of preterm infants, such as antibiotics, inotropics, sedatives, steroids, respiratory stimulants, diuretics and bronchodilators. No specific interaction was reported in any of the studies.

4.3. Evaluator's overall conclusions on pharmacokinetics

The data provided on the PK of ibuprofen comprised 2 clinical studies and 2 PopPK reports and PK data collected during 3 efficacy studies. One study was not useful as it involved a very different strength and formulation. The other study was to evaluate the sponsor's IV formulation with an IM formulation (given IV) which was used in most of the published literature included in the EU submission. This is not relevant to the Australian submission as the published literature was not included as evaluable data.

The main data comes from the population PK analysis. The summaries do not provide much help as they were written over very wide time frames and do not include all the studies. The *Clinical Overview* includes mostly an analysis of the literature which was not submitted to support efficacy and safety in Australia. No summary of the pharmacokinetics is provided in any of the more recent summaries (only in the 2003 *Clinical Expert Report*). It is sometimes difficult to identify in the *Clinical Overview* when it is referring to unpublished clinical studies and when to published literature studies as it appears to identify the clinical studies by the subsequent publications but this cannot always be verified.

From the studies submitted it is clear that the PK of ibuprofen is very different in preterm infants compared with adults and older children with elimination rate and clearance markedly lower and elimination half-lives substantially longer.

The dose-range study showed that median plasma concentrations (range) significantly increased ($p<0.001$) with increasing doses of ibuprofen, with values of 27.8 (24-32.8), 40.6 (34.4-44.5), 55.3 (49.6-64) and 68 mg/L in the 5, 10, 15 and 20 mg/kg dose regimen groups, respectively.

Plasma concentrations were similar in the 3 clinical studies that measured PK parameters with peak levels around 35-40 mg/L after the initial loading dose of 10 mg/kg as well as after the last maintenance dose, regardless of the GA and postnatal age. Residual concentrations were around 10-15 mg/L 24 h after the last dose of 5 mg/kg.

The peak plasma levels are stated to be comparable to those reported in infants and children after oral ingestion of ibuprofen. However the data indicate that ibuprofen is eliminated very slowly in preterm newborn with a half-life more than 10 fold compared to older infants. It is suggested that this may be due to deficient liver activity in the first neonatal week but many other factors, including the presence of a haemodynamically significant PDA resulting in hypoperfusion of liver and kidney, may influence ibuprofen metabolism and elimination.

The plasma concentrations of the S-enantiomer are much higher than those of the R-enantiomer, which reflects a rapid chiral conversion of the R to the S-form in a proportion stated to be similar to adults (about 60%). The clearance of both enantiomers increases with GA, at least in the range of 24 to 28 weeks.

There was quite a wide interpatient variability noted, but this is consistent with the numerous factors that affect preterm infants and lead to interference with drug metabolism and elimination.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic information

Comment: The Summary of Clinical Pharmacology does not include any discussion of the pharmacodynamics of ibuprofen. It specifically does not discuss the 2 clinical PD studies which were included in the submission. The 2 clinical PD studies were completed after the Clinical Expert Report was written and so are not included in that report. They are included in the Clinical Overview however it does not include study IBU/20mg/2009 which was not completed until after the Clinical Overview was written.

Table 4 shows the studies relating to each PK topic and the location of each study summary.

Table 4: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	Primary aim
Primary Pharmacology	Effect on PD parameter – pulmonary vascular resistance	IBU/GER/2003	PD
Secondary Pharmacology	Effect on PD parameter – effect on bilirubin	IBU/BILICLIN/04 IBU/20mg/2009	

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

5.2. Summary of pharmacodynamics

5.2.1. Mechanism of action

Ibuprofen is a NSAID that possesses anti-inflammatory, analgesic and antipyretic activity. Ibuprofen inhibits the 2 isoforms of the COX enzyme, leading to reduced PG synthesis within cells. Since PG are involved in the persistence of the DA after birth, their inhibition is therefore expected to decrease the vasodilatory effects of PGE2 and PGI2, which are involved in the pathogenesis of ductal patency. This effect is believed to be the main mechanism of action of ibuprofen in this indication.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Pulmonary vascular resistance

Study IBU/GER/2003 was conducted to specifically investigate the effect of IV ibuprofen on pulmonary perfusion and left ventricular function. Pulmonary vascular resistance (PVR) was assessed by measuring the mean flow velocity of the main pulmonary artery, the estimated systolic pulmonary artery pressure (equivalent to the right systolic ventricular pressure "RSVP", in the absence of right ventricular outflow tract obstruction), and the mean and maximum flow velocity (V) through the persistent foramen ovale (Vmean and Vmax PFO). The maximum flow velocity of the tricuspid valve regurgitation (Vmax TI) was also assessed to estimate the right systolic ventricular pressure. The shape of the PV-VTI flow curve remained unchanged during repeated echocardiographic assessments and did not arouse suspicion of pulmonary hypertension at any time. None of the parameters that were assessed changed significantly during the treatment course. The median variation of parameters measured from baseline to 24 h after the 3rd dose of Vmean PA, Vmean PFO and Vmax PFO were 0.4 (p=0.80), -2.5 (p=0.27) and -1.8 (p=1.0) cm/s respectively, indicating no tendency to increase during ibuprofen treatment. This study underlines that a systematic echography follow-up of pulmonary haemodynamics would be of no use in case of HsPDA treated with ibuprofen, particularly in regard to the small number of infants presenting with a secondary pulmonary hypertension.

Table 5: Study IBU/GER/2003: Echocardiographic Assessment.

	Baseline	**24 hours after the 3rd dose**	**p**
Patients with L/R PDA	15	8	-
Patients with L/R PFO	15	15	
Vmax PFO (mmHg)	39.2 ±12.12 (26.5- 63.6)	39.4 ± 14.46 (20.1- 69.8)	1.000
Vmean PFO (mmHg)	24.7 ± 8.06 (14.4 -46.1)	23.5 ± 5.62 (15.6- 36.1)	0.266
Vmean PA (mmHg)	47.2 ± 15.8 (31.2 -86.9)	50.7 ± 22.48 (30.9 -120.0)	0.804
SaO_2 pre-ductal (%)	90.9 ± 5.74 (77.0 -98.0)	88.8 ± 5.45 (80.0- 96.0)	0.173
SaO_2 post-ductal (%)	89.9 ± 5.66 (75 -99)	89.9 ± 5.49 (73 - 96)	0.816
Systolic blood pressure (mmHg)	49.3 ± 11.58 (33.0 -70.0)	48.3 ±9.12 (29.0- 63.0)	0.729
Vmax-TI (mm/s)	258.7 ± 30.44 (N= 8) (210 – 310)	230.0 (N= 1)	-
Estimated RSVP (mmHg)	32.13 ± 6.27 (N= 8) (23 - 43)	26.16 (N= 1)	-

5.2.2.2. Secondary pharmacodynamic effects

Effect on Bilirubin

Two studies were conducted which investigated the effect of IV ibuprofen on the unbound unconjugated bilirubin in preterm infants (IBU/BILICLIN/04 and IBU/20mg/2009). The studies were conducted because in-vitro studies indicated the potential for an effect of ibuprofen on the unbound fraction of bilirubin.

In vitro studies showed that ibuprofen at concentration equivalent to 155 µg/mL is highly bound to plasma albumin, although this seems to be significantly lower (95 %) in cord blood compared with adult plasma (99 %). In 1 in vitro study the unbound fraction of bilirubin was increased by a factor of 4 and therefore ibuprofen may increase the risk of bilirubin encephalopathy in sick, premature infants.

Jaundice is present in 60% of newborn infants. In sick preterm newborn <32 GA, nearly all the infants present some degree of jaundice. Kernicterus has become synonymous with the acute and chronic neurological manifestations of bilirubin encephalopathy. Initial phases are characterised by lethargy, hypotonia, poor sucking, followed by a phase of hypertonia and seizures, which subsides to be replaced by hypotonia. The classical sequelae comprise a tetrad of athetoid cerebral palsy, deafness or hearing loss, impairment of upward gaze and enamel dysplasia of the primary teeth. Significant neonatal hyperbilirubinemia with signs of encephalopathy is considered a neurologic emergency and treated immediately because outcome is related in part to the duration of exposure to excessive unbound bilirubin.

The risk of kernicterus as a function of total plasma bilirubin is not known precisely. Total plasma bilirubin (TB) is an unsatisfactory marker of the risk of kernicterus. Unbound ("free") plasma bilirubin (UB) has been shown to be a more specific predictor of neurotoxicity than total bilirubin. Unbound bilirubin depends on albumin concentration, total bilirubin and ibuprofen concentrations, and respective affinity of albumin for bilirubin and ibuprofen.

The combined peroxidase diazo method was used in the studies to evaluate the potential changes in the concentration of unconjugated UB during a treatment course. However, no population reference values were available to help determine the levels associated with bilirubin toxicity. Therefore, these measurements were not used for the clinical management of the newborn. The protocol used in the Neonatology Unit was followed, which relied on TB measurements, and UB assays using the peroxidase method in cases of high TB levels.

In study IBU/BILICLIN/04 TB and UB bilirubin were measured before and during treatment and the results did not show any increase in UB or TB from the baseline values or any increase after any injection of ibuprofen. No bilirubin displacement could be elicited under the study conditions. Pedea did not alter the albumin-bilirubin binding capacity.

Bilirubin toxicity was evaluated by the occurrence of intercurrent AEs, auditory brain stem responses (ABR) and neurological examinations. In the context of the study it was not possible to conclude to any toxicological effects of bilirubin.

In study IBU/20mg/2009 which used double the proposed does of ibuprofen, TB and unconjugated UB were evaluated over time. The results were similar to the lower dose study, ie that a high dose regimen of Pedea (20 -10- 10 mg/kg at 24 h intervals) did not significantly alter the albumin-bilirubin binding capacity and no bilirubin displacement could be elicited.

Effect on cerebral, renal and mesenteric blood flow

No studies that were submitted investigated the effect of ibuprofen on cerebral, renal or mesenteric blood flow. However, this is addressed in both the *Clinical Overview* and the *Clinical Expert Report* based on the literature review. The conclusion was that these studies suggested a neutral effect of ibuprofen on cerebral circulation and cerebral blood flow autoregulation. Compared with indomethacin, ibuprofen does not appear to reduce cerebral perfusion or oxygen availability.

5.3. Evaluator's overall conclusions on pharmacodynamics

Only 3 PD studies were submitted as part of the Australian dossier. These studies were primarily related to assessing possible potential toxicity effects due the PD of ibuprofen in preterm infants. The studies did not demonstrate any negative effects on either the development of pulmonary hypertension or of significant worsening of the level of unbound bilirubin.

As ibuprofen has been known for some time and its mode of action is well documented there do not appear to be any concerns with the PD actions of the drug.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

Clinical trials on ibuprofen were all conducted with the same dose regimen as in the first published study (Varvarigou 1996). This included a loading dose followed by 2 maintenance doses at 24-hour intervals based on analogy with the recommended dose regimen of indomethacin and on the doses and dosing intervals recommended for young infants and neonates for fever control based on PD data.

6.1.1. Phase II dose finding studies

The sponsor conducted 1 dose ranging study (IBU/99/DoseRange). Infants were enrolled in 2 groups according to GA: those aged from 27 to 29 weeks and from 24 to 26 weeks. Four dose regimens bracketing the empirical dose were chosen: 5/2.5/2.5 mg/kg, 10/5/5 mg/kg, 15/7.5/7.5 mg/kg and 20/10/10 mg/kg.

In the older infants group, the probability of closure was slightly higher for the 15-7.5-7.5 mg/kg dose regimen but with more frequent renal AEs, and therefore the optimal benefit/risk ratio was achieved with the dose regimen of 10-5-5 mg/kg.

It was expected that the efficacy would be lower in the most immature preterm newborns, and therefore, a different target closure rate was chosen to define efficacy in relation to GA: 50% in the < 27 weeks group vs 80% in the ≥ 27 weeks group. The analysis concluded that the minimum effective dose regimen for the lower GA group was 20-10-10 mg/kg. The actual closure rate was 33% (2/6) for both the 10-5-5 and 15-7.5-7.5 mg/kg dose regimens. Because of the study design, the highest dose regimen was only administered to 1 evaluable patient, due to the Bayesian approach with continuous reassessment method and predetermined stopping rules after 20 evaluable patients had been included.

The result in the lower GA group is consistent with the known inverse relationship between efficacy of pharmacological intervention and GA. Younger infants being less responsive to medical treatment undergo surgical ligation more frequently. This is also known for indomethacin and was found within each category of GA in the dose ranging study.

6.1.2. Phase III pivotal studies investigating more than one dose regimen

Not applicable.

A non-pivotal study (IBU/20mg/2009), conducted post approval in Europe, addressed the issue of a higher dose regimen of IV ibuprofen. The dose used in this study was 20/10/10 rather than the proposed recommended dose of 10/5/5. The results, though not powered for this evaluation, showed a benefit of the high dose regimen in terms of closure of HsPDA in the VLBW infants, confirming the preliminary findings of the dose range study (IBU/99/DoseRange). In total, the absolute failure rate as assessed by the surgery of the PDA was rather low (4/23) and the total ductus closure confidence interval was a little above 50%

which seems to indicate a better efficacy, than at half dose regimen in this population where the rate of closure is classically around 30%.

6.2. Evaluator's conclusions on dose finding for the pivotal studies

The optimal dose and regimen of ibuprofen has not been determined, particularly in the very low GA infants. The regimen of a loading dose and then 2 maintenance doses was chosen based on the results of a single study (*Varvarigou et el 1996*) in 30 infants which compared the 3 dose regimen (10 mg/kg loading dose plus 2 maintenance doses of 5 mg/kg (identified as 10/5/5) with a single dose of 10 mg/kg and a placebo. The intent of the treatment was to prevent PDA and the infants were treated within 3 h of birth. The results were clearly in favour of the 3 dose regimen versus 1 dose.

The dose range study (IBU/99/DoseRange) compared 3 dose regimens and found that for the infants with GA range from 27 to 29 weeks the optimal dose regimen was 10/5/5 based on safety rather than efficacy. For the younger group (24 to 26 weeks) the results are more confusing as they appeared to require a higher dose, This was associated with more toxicity but insufficient patients were treated to obtain satisfactory results. The higher dose regimen of 20/10/10 was investigated in a further study (IBU/20mg/2009) in low GA infants and was conducted post approval in EU and was primarily aimed at investigating safety rather than efficacy. The study was not powered to determine efficacy but the results did suggest a response rate of ~50% which is comparable to the 10/5/5 regimen in higher GA infants.

The proposed dose regimen is an appropriate compromise of efficacy and safety based on the very small numbers of patients included in the trials but may not be optimal for the low GA group.

The studies all allowed for a second dose regimen of 10/5/5 to be given and the proposed PI allows for this, or surgery, at the discretion of the treating physician.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

The studies providing evaluable efficacy data are:

7.1.1. Pivotal Study

- Study IBU/PROPHYL/2000 – curative group: Multicentre Controlled Randomised Study to Compare the Effect of Prophylactic versus Curative Administration of Intravenous-Ibuprofen on the Incidence of Surgical Ligations of Patent Ductus Arteriosus in Preterm Newborn Less than 28 Weeks' Gestational Age.

7.1.2. Other studies

- Study IBU/PROPHYL/2000 – prophylactic group: Multicentre Controlled Randomised Study to Compare the Effect of Prophylactic Versus Curative Administration of Intravenous Ibuprofen on the Incidence of Surgical Ligations of Patent Ductus Arteriosus in Preterm Newborn Less than 28 Weeks' Gestational Age.
- Study Long Term FU: Long Term Follow-Up of Premature Infants: Indomethacin vs Ibuprofen - Retrospective Analysis of 182 Cases.
- Study IBU/20 mg/2009: Multicentre Open-Label Pilot Study to Evaluate the Safety, Pharmacology and Efficacy of a New Dose Regimen (ie, 20-10-10 mg/kg) of Pedea® (Intravenous Ibuprofen) in Preterm Newborn Infants of Less than 28 Weeks of Gestation.

7.2. Pivotal or main efficacy study

7.2.1. Study IBU/PROPHYL/2000 – Curative group

7.2.1.1. Multicentre Controlled Randomised Study to Compare the Effect of Prophylactic versus Curative Administration of Intravenous-Ibuprofen on the Incidence of Surgical Ligations of Patent Ductus Arteriosus in Preterm Newborn Less than 28 Weeks' Gestational Age.

Comment: This study is reported in 2 CSRs. The first is for the "curative group" which is a subset of the whole trial. The introduction to the study states "the study was conducted to compare 2 approaches in the pharmacological management of PDA using either prophylactic or curative intravenous ibuprofen" however the cohorts are then reported separately with the CSR for the "curative" group provided in "Controlled trials" and the second CSR for the "prophylactic group" included in Module 5.3.4 "Other studies". The summary below is for the curative group. The CSR for the prophylactic group contains more details of the trial and this summary should be read in combination with the summary of the whole trial which is provided. Data from the total trial such as the participant flow is included in this summary as it is useful to understand the study structure and flow. It should be noted that the whole study was terminated before full enrolment due to a safety concern. Details of the safety issues are discussed.

7.2.1.2. Study design, objectives, locations and dates

The curative treatment regimen of the study was an open label study conducted at 9 sites in France from March 2001 to March 2002.

The whole trial was a double-blind, randomised, placebo-controlled study, designed to include 220 (110 patients per group) conducted at 11 sites in France. The initial double blind phase involved one group of patients administered a placebo while the other group were administered a (loading) dose of IV ibuprofen at 10 mg/kg followed by 2 x 5 mg/kg maintenance doses at 24 h intervals.

After the prophylactic treatment course with active or placebo, if the DA was still patent, a curative treatment regimen with ibuprofen (same dose regimen as the prophylactic course) was administered (without breaking the blinding). If this treatment failed to achieve closure of the DA the choice of the back-up therapy was left to the investigator, i.e., indomethacin and/or surgical ligation.

The CSR describing the curative group is based on the 25 patients who received placebo in the double blind phase. These patients had the PDA confirmed after the double blind treatment and were then deemed to require curative treatment. However at the time of their PDA confirmation it was not known whether they had received placebo or ibuprofen.

Objective: To describe the efficacy and safety of the curative administration of intravenous ibuprofen (this was a secondary outcome of the main trial).

7.2.1.3. Inclusion and exclusion criteria

Male or female preterm infants with GA strictly < 28 weeks who received 3 injections of saline on their first 3 days of life and were then repeatedly evaluated by cardiac echo-Doppler for the presence of a PDA. In order to qualify for a curative treatment with ibuprofen they had to meet echographic criteria defining a "significant" PDA, i.e. a PDA had to be visible and, in addition, at least 2 of the 4 following criteria had to be fulfilled:

- LA/aortic root ratio > 1.48
- retrograde or absent diastolic flow in the cerebral anterior artery or in the descending thoracic aorta
- pulsatile flow in the DA

- diastolic flow velocity in the pulmonary artery > 20 cm/s

7.2.1.4. Study treatments

All neonates received 3 doses of curative ibuprofen with an interval of 1 day between each dose administered IV as a bolus or slow infusion. The first dose was 10 mg/kg and the subsequent doses were 5 mg/kg administered.

7.2.1.5. Efficacy variables and outcomes

The efficacy outcome was the need for back-up treatment with indomethacin and/or surgical ligation.

7.2.1.6. Randomisation and blinding methods

Not applicable as this was an open study.

7.2.1.7. Analysis populations

Not defined, but all treated infants (25) appeared to be included in the analysis of efficacy and safety.

7.2.1.8. Sample size

Not defined.

7.2.1.9. Statistical methods

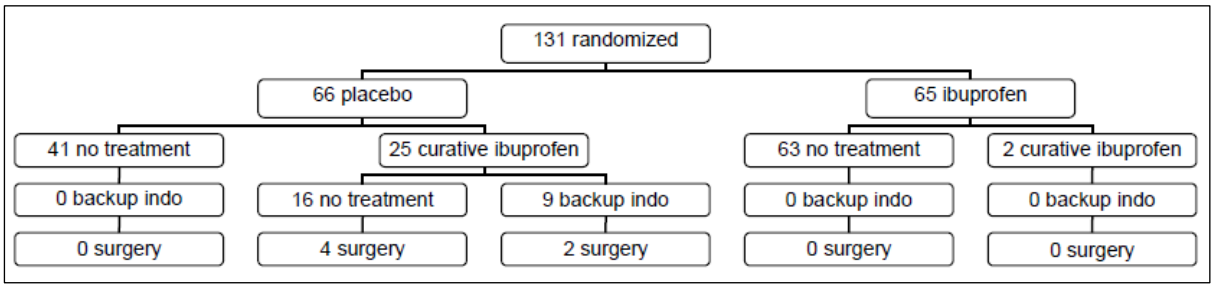
Not discussed but only descriptive statistics are provided.

7.2.1.10. Participant flow

Twenty five patients were enrolled and all completed treatment. Three of the 9 sites enrolled only 1 patient each and 6 were enrolled from 1 site.

The following figure shows how the curative group fits in the whole trial.

Figure 3: Study IBU/PROPHYL/2000: Patient outcomes (whole trial).



7.2.1.11. Major protocol violations/deviations

Not discussed.

7.2.1.12. Baseline data (curative group)

There were 52% male and 48% female; median birth weight was 850 g with 36% with a birth weight < 750 g. The median gestational age was 26 weeks. Preterm neonates with gestational age of 24-25 weeks and 26-28 weeks represented respectively 44% and 56% of neonates.

Table 6: Study IBU/PROPHYL/2000 – curative group: Patient demographics

Sex	
Male	13 (52.0%)
Female	12 (48.0%)
Born	
Inborn	19 (76.0%)
Outborn	6 24.0%
Birth weight (g)	
Mean (SD)	858.9 (155.5)
Median	850.0
(Min; Max)	630.0; 1180.0
<750	9 (36.0%)
750 - 1000	10 (40.0%)
1000 - 1250	6 (24.0%)
Gestational age (weeks)	6
Mean (SD)	25.7 (1.0)
Median)	26.0 ()
Min; Max	24.0; 27.0
24- 25	3 (12.0%)
25- 26	8 (32.0%)
26- 27	7 (28.0%)
27- 28	7 (28.0%)

Table 7: Study IBU/PROPHYL/2000 – curative group: Patient medical history

APGAR at 1 minute (N=25)	
Mean (SD)	5.9 (2.7)
Median	5.0
Min ; Max	1.0; 10.0
APGAR at 5 minutes (N=24)	
Mean (SD)	7.9 (2.4)
Median	9.0
Min; Max	1.0; 10.0
Intubation in delivery room	23 (92.0%)
First surfactant intake within 24h after birth	20 (80.0%)
Calculation of CRIB index before prophylaxis	
N = 24	
Mean (SD)	6.7 (2.6)
Median	7.0
Min; Max	2.0; 11.0

All newborn were mechanically ventilated after birth but, on their third day of life, 4 were already under nasal CPAP.

Table 8: Study IBU/PROPHYL/2000 – curative group: Maternal therapy

Any Maternal Treatment	20 (80.0%)
Systemic corticosteroids	20 (80.0%)
Tocolytics	15 (60.0%)
Salbumatol	14 (56.0%)
Atosiban	5 (20.0%)
Indometacin	1 (4.0%)
Antibacterial for systemic use	11 (44.0%)
Antihypertensive	7 (28.0%)
Acetylsalicylate	2 (8.0%)

7.2.1.13. Results for the primary efficacy outcome

The success rate after 1 single course of ibuprofen was 48% (12/25). In this sample the response rate did not seem to be correlated to GA.

Table 9: Study IBU/PROPHYL/2000 – curative group: Success rate according to gestational age.

Overall	25	12	(48.0%)
Gestational Age			
24- 25	N=3	1	(33.3%)
25- 26	N=8	5	(62.5%)
26- 27	N=7	1	(14.3%)
27- 28	N=7	5	(71.4%)

Following curative ibuprofen, 9 infants (36%) received a course of indomethacin due to the persistence of the PDA. However, only seven had a significant PDA as defined in the protocol. Six patients (24%) underwent a surgical ligation. Among them 2 had failed to respond to indomethacin.

7.2.1.14. Results for other efficacy outcomes

Not applicable.

7.2.1.15. Conclusions

In a population of very preterm infants with very low birth weight (median of 850 g) the response rate to one single course of ibuprofen was not very high and 24% of the infants had eventually to be operated.

However, it was emphasised that these results may partly be due to the protocol which did not allow a second course of ibuprofen in the curative setting, since it was not known whether the newborn had received prophylactic treatment with ibuprofen, it had been decided to avoid exposing any infant to a third course of ibuprofen if 2 courses had already failed.

7.2.1.16. Evaluator commentary

This is an old study and the CSR is not fully compliant with the requirements of a CSR in that it omitted many of the required sections eg objectives, ethics, statistical methods, details of conduct (deviations), efficacy criteria etc. Some details are provided in the synopsis and some additional information is provided in the CSR for the Prophylactic group (whole trial).

The results are taken from a subset of a study which was investigating prophylactic treatment with ibuprofen. The study was not powered to investigate the curative treatment with ibuprofen and the study has insufficient patients to provide conclusive results. The overall response rate was ~50%.

This study is not really a pivotal study but is included in this section as it was the only randomised controlled study which included the investigation of the efficacy of curative treatment as a primary objective.

7.3. Other efficacy studies

7.3.1. Study IBU/PROPHYL/2000 – prophylactic group

7.3.1.1. Multicentre Controlled Randomised Study to Compare the Effect of Prophylactic Versus Curative Administration of Intravenous Ibuprofen on the Incidence of Surgical Ligations of Patent Ductus Arteriosus In Preterm Newborn Less than 28 Weeks Gestational Age.

This study was planned to last for 1 year (initiation of the protocol: December 2000 - end of the study: December 2001) but it was prematurely stopped after recruitment of only 135 of planned 220, (60% of the patients), in December 2001 for a safety issue (3 separate occurrences of refractory hypoxaemia after prophylactic treatment with ibuprofen).

Objectives

To compare the incidence of surgical ligation of the patent ductus arteriosus (PDA) after prophylactic versus curative administration of intravenous ibuprofen.

Secondary outcomes included: incidence of PDA on Day 3, incidence of curative treatment of PDA with ibuprofen, incidence of back-up treatment of PDA with indomethacin; actuarial curve of PDA permanent closure; incidence of cystic periventricular leukomalacia (PVLM), intraventricular haemorrhage grade III-IV (IVH), and bronchopulmonary dysplasia (BPD); actuarial curve of survival during the study period; effects on renal function (creatinine and urine output) during the prophylactic treatment (IV ibuprofen versus placebo) and to evaluate the PK of ibuprofen enantiomers in extremely premature infants using a population PK approach.

Methodology

Design: A double blind, randomised, placebo controlled study conducted at 11 sites in France from March 2001 to March 2002.

Entry criteria: Male or female premature newborn infants strictly less than 6 h and GA strictly <28 weeks. Infants were excluded if they had major congenital malformations, hydrops fetalis, proved severe maternofoetal infection, IVH grade III or IV or significant right to left shunt through the ductus defined as a sus-to-subductal difference in oxygen saturation superior or equal to 5%.

Treatments: The solution of ibuprofen IV (Orphan Europe) or placebo was administered as follows:

- 1 x loading dose of 10 mg/kg at inclusion, within the 6 first h of life, followed by
- 2 x maintenance doses of 5 mg/kg administered at 24 h intervals.

The dose had to be adjusted to the birth weight and the drug was administered undiluted as a bolus, followed by a 1.5 mL flush with saline.

Efficacy outcomes: Echocardiographic evaluations were performed on Days 3, 7, 14 and 21 of life. A significant PDA which was defined as follows:

- a PDA visible on the echographic examination
- in addition to at least 2 of the 4 following criteria:
  - LA/aortic root ratio > 1.48

- Retrograde or absent diastolic flow in the cerebral anterior artery or in the descending thoracic aorta
- Pulsatile flow in the DA
- Diastolic flow velocity in the pulmonary artery > 20 cm/s.

Statistical analysis: The comparison of the incidence of surgery ligation at 36 weeks of PCA would be performed using a 2-tailed Fisher's exact test (alpha < 0.05). A sample size of 83 subjects randomised to each treatment regimen with balanced number of patients per group, would have had at least 80 % power to detect a difference of 20% between the 2 treatment regimens (difference from 41% to 21%) with a 2-sided test with significance level alpha = 0.05 and beta = 0.20.

Study participants

· Enrolled: 131 enrolled (66 curative and 65 prophylactic).

· Completed: 131 completed.

· Analysed: 131 analysed.

· Baseline: The 2 treatment groups did not significantly differ for baseline parameters. Most preterm newborns (84%) included in the study were inborn. There was overall slightly more male than female newborns but the sex ratio was reversed in the treatment groups with more females in the curative group and more males in the prophylactic group. This might account for a slightly better prognosis in the curative group. The birth weight was less than 1,000 g in 80% of newborn and less than 750 g in almost one third of the population. The median birth weight was 860 g and the median gestational age was 26 weeks.

Efficacy results

The primary endpoint was the incidence of surgical ligation of a clinically significant PDA, confirmed by ultrasound examination.

Six patients, all in the curative group (9.1%), underwent a surgical ligation of PDA (p=0.028). When considering the 94 patients alive at 36 weeks of post conceptual age (PCA) the rate of surgical ligation then became 5/47 (10.6%) versus 0/47 for the curative and prophylactic approaches, respectively (p=0.056).

The overall incidence (at any time of the follow-up) of a detectable PDA using the cardiac echo-Doppler was significantly lower in the prophylactic group (29%) than in the curative group (59%) (p=0.001). In both groups, most cases of PDA were first detected during the first week of life.

Table 10: Study IBU/PROPHYL/2000: Incidence of PDA.

	Curative group	**Prophylactic group**	**All**	**Comparative Test**
At least one visible PDA	N = 61	N = 62	N = 123	p=0.001
During study	36 (59.0%)	18 (29.0%)	54 (43.9%)	
First detected				
During Day 1 to 7	34 (55.7%)	14 (22.6%)	48 (39.0%)	
During Day 8 to 21	2 (3.3%)	3 (4.8%)	5 (4.1%)	
After Day 21	0	1 (1.6%)	1 (0.8%)	
Gestational age				

	Curative group	Prophylactic group	All	Comparative Test
24-25	N = 5	N = 3	N = 8	p=1.00
	4 (80.0%)	2 (66.7%)	6 (75.0%)	
25-26	N = 11	N = 4	N = 15	p=0.004
	10 (90.9%)	0	10 (66.7%)	
26-27	N = 22	N = 24	N = 46	P=0.55
	11 (50.0%)	9 (37.5%)	20 (43.5%)	
27-28	N = 23	N = 31	N = 54	P=0.08
	11 (47.8%)	7 (22.6%)	18 (33.3%)	

This analysis was carried out in the 123 newborn that had at least 1 echographic assessment. It should also be mentioned that these figures include any PDA visible and not only "significant PDA" as defined in the protocol.

The number of patients who needed curative ibuprofen treatment was significantly higher in newborn having received placebo (25/66; 38%) than in those having received prophylactic ibuprofen (2/65; 3%) (p = 0.001). In all cases but one (in the placebo group) the curative treatment was administered after a "significant PDA" had been detected as defined in the protocol. In all cases the reason was that the DA was still patent except for one case in the placebo group where the DA had reopened.

All infants from the curative group (previously placebo) received the full regimen of 3 doses of curative ibuprofen whereas the 2 infants from the prophylactic group (previously the full 3 doses of ibuprofen as prophylaxis) received only the first (loading) dose in the curative phase (post confirmation of the PDA:

- The treatment was discontinued in 1 patient who had an infectious alveolitis due to Pseudomonas and developed severe pulmonary hypertension on the day following the first infusion
- 1 patient died on the same day from severe hypoxaemia following a grade III IVH

Table 11: Study IBU/PROPHYL/2000: Incidence of curative treatment.

	Curative group N = 66	Prophylactic group N = 65	All N = 131	Comparative Test
Curative treatment	25 (37.9%)	2 (3.1%)	27 (20.6%)	p=0.001
Age at 1st infusion (days)				
Mean (SD)	5.8 (5.37)	6.5 (2.12)	5.8 (5.18)	
Median	4.0	6.5	4.0	
Min ; Max	3; 30	5; 8	3; 30	p=0.17
Gestational age				
24-25	N = 5	N = 5	N = 10	p=0.17
	3 (60.0%)	0 (0.0%)	3 (30.0%)	
25-26	N = 13	N = 4	N = 17	p=0.082
	8 (61.5%)	0 (0.0%)	8 (47.1%)	
26-27	N = 24	N = 24	N = 48	p=0.048

	Curative group N = 66	Prophylactic group N = 65	All N = 131	Comparative Test
	7 (29.2%)	1 (4.2%)	8 (16.7%)	
27-28	N = 24	N = 32	N = 56	p=0.016
	7 (29.2%)	1 (3.1%)	8 (14.3%)	

Incidence of backup treatment

After having received a course of curative ibuprofen, 9 out of 25 patients from the curative group (9/66; 13.6%) received a back-up course of indomethacin. In all cases this was because the DA was still patent and 7 presented with a "significant PDA" as defined in the protocol.

Efficacy conclusions

Despite the premature discontinuation of the trial and the relatively small number of neonates recruited these results indicate that prophylactic treatment with ibuprofen significantly decreases the incidence of PDA in preterm newborn less than 28 weeks of GA. Furthermore, these results also showed that this approach may decrease the need for surgical ligation since the difference (0% vs 9%) was at least significant in the whole population ($p<0.03$) if not in the population of infants surviving at 36 weeks of GA ($p<0.06$).

Prophylaxis, however, is not the indication requested.

7.3.2. Study Long Term FU

7.3.2.1. Long Term Follow-Up of Premature Infants; Indomethacin vs Ibuprofen - Retrospective Analysis of 182 Cases.

Comment: This was not a formal clinical study and so the report is not in the format of a CSR. In order to retrieve the data a protocol titled: "IBU/LT/2004 – Multicentre Post-Marketing Long-Term Surveillance of preterm newborns treated with Pedea (intravenous ibuprofen)" (provided in Appendix 2) was submitted to the Charité Virchow-Hospital "in order to let data be collected". The study reported does not comply with the protocol and it is stated that for data collection "no firm protocol is followed for this systematic data collection." Only results directly relevant to PDA closure are reported here.

Objectives

Not stated.

Methodology

Design: The study is a retrospective analysis of a comprehensive clinical and socio-demographic database originating from the Charité Virchow-Hospital, Berlin, Germany. The report is dated December 2007.

Entry criteria: Data were collected from the files of 182 premature neonates born between January 1998 and December 2003 who presented with a hemodynamically significant PDA.

Treatments: For the pharmacological closure of the PDA they received 1 or more courses of either indomethacin or ibuprofen.

Efficacy outcomes: PDA diagnosis, treatment and outcome: age at admission, number and duration of indomethacin/ibuprofen courses, echocardiographic assessments of PDA prior to intervention as well as under treatment, PDA reopening due to infection, time of PDA surgery if applicable, age at discharge as well as the presence of PDA (hemodynamically relevant or not) at the time of discharge and the global outcome (discharge, transfer, death).

Safety outcomes: AEs related to treatment, acute and long term neurological/sensory events (IVH, cystic PVL, ventriculomegaly, hydrocephalus, microcephaly, occurrence of seizures and

cerebral palsy); respiratory parameters (supplemental oxygen dependency at 28 days of life, duration of positive pressure ventilation (PPV), continuous positive airway pressure (CPAP), BPD at 36 weeks GA, pulmonary haemorrhage and persistent pulmonary hypertension of the newborn (PPHN), number of hospital admissions for respiratory disease after discharge and the duration of each hospitalisation; occurrence of renal failure (creatinaemia ≥ 140 µmol/L), oliguria and hyponatraemia; necrotising enterocolitis, gastrointestinal perforation, thrombocytopenia and disseminated intravascular coagulation (DIC).

Statistical analysis: No formal statistical plan was written. The statistics was generally descriptive. The Fisher's exact test was used for qualitative non ordinal parameters, and the Mantel-Haenszel test if ordinal. Wilcoxon test was used for quantitative variables.

Study participants

- Enrolled: 182 enrolled - 89 received indomethacin between February 1998 and May 2001 and 93 received ibuprofen between May 2001 and December 2003.
- Completed: 182 completed
- Analysed: 182 analysed
- Baseline: The proportion of boys was almost significantly higher for children who received ibuprofen (65.6% vs 50.6%, p=0.051) which is relevant as in premature infants, male gender is classically associated with a poorer prognosis. The proportions of elective caesarean section, caesarean section during labour or vaginal delivery were almost identical. GA was very low and similar in both groups (26.4 ± 1.8 weeks for indomethacin and 26.5 ± 2.0 weeks for ibuprofen), as was the birth weight (903 ± 243 grams for indomethacin and 911 ± 239 grams for ibuprofen).

Efficacy results

For almost all patients, PDA closure was achieved with 1 or 2 treatment courses. The number of courses necessary to achieve PDA closure was significantly lower with indomethacin (p=0.0002).

One single course was sufficient for 77.3% of indomethacin treated patients versus 58.2% of ibuprofen treated patients.

However, the duration of courses was much shorter for ibuprofen treated patients (at most 3 days for all of them, whereas only 10% of indomethacin treated patients were treated over 3 days or less and the mean duration of each course (and consequently global treatment exposure) was significantly lower with ibuprofen (p<0.0001, p<0.0001 and p=0.301, respectively).

Table 12: Survey LT-FU: Type of PDA intervention

prob. Fisher (without missing data) = 0.7430		Indomethacin		Ibuprofen		All	
		N	%	N	%	N	%
Non-missing	Treatment alone	65	73.0	65	69.9	130	71.4
	Treatment + Surgical ligation	24	27.0	28	30.1	52	28.6
	All	89	100.0	93	100.0	182	100.0

Table 13: Survey LT-FU: Time from birth to first medical treatment of PDA

prob. Wilcoxon = 0.0673		Indomethacin	Ibuprofen	All
Time from birth to 1 cycle	Mean	5.17	5.29	5.23
	Std	3.32	5.37	4.48

prob. Wilcoxon = 0.0673		Indomethacin	Ibuprofen	All
	Min	2.00	1.00	1.00
	Max	19.00	32.00	32.00
	Median	4.00	3.00	4.00
	N	88	93	181
	NMiss	1	0	1

Table 14: Survey LT-FU: Number of total treatment courses

prob. CMH = 0.0002		Indomethacin		Ibuprofen		All	
		N	%	N	%	N	%
Non-missing	1	76	85.4	57	61.3	133	73.1
	2	12	13.5	32	34.4	44	24.2
	3	1	1.1	4	4.3	5	2.7
	All	89	100.0	93	100.0	182	100.0

Table 15: Survey LT-FU: Duration of treatment courses in days

			Course rank		
			1	2	3
No of days	Indomethacin	Mean	6.09	6.54	8.00
		Std	1.93	2.03	
		Min	1.00	1.00	8.00
		Max	8.00	8.00	8.00
		N	88	13	1
		NMiss	1	0	0
	Ibuprofen	Mean	2.98	2.83	2.5
		Std	0.15	0.56	1.00
		Min	2.00	1.00	1.00
		Max	3.00	3.00	3.00
		N	93	36	4
		NMiss	0	0	0
		Prob. Wilcoxon	<0.0001	<0.0001	0.301

A higher proportion of remaining PDA was observed after the first treatment course for patients who received ibuprofen (41.8% versus 22.7% for those who received indomethacin, p=0.007). However, the course duration of ibuprofen was a third that of indomethacin, (longer than 3 days for >90% of patients on indomethacin).

Among those infants without echocardiographic PDA evaluation after the first COX-inhibitor treatment cycle:

- 1 patient in the indomethacin group died after the eighth dose of indomethacin due to unmanageable disseminated intravascular coagulation (DIC) on Day 10
- In the 2 infants in the ibuprofen group a second treatment course was started right after the end of the first course without prior echocardiographic evaluation, since both patients still fulfilled the criteria of a hemodynamically significant PDA with a decreased end diastolic flow in the anterior cerebral artery on the cerebral ultrasound and dependency on supplemental oxygen above 30%.

Table 16: Survey LT-FU: Echocardiography after 1st COX-inhibitor cycle

prob. Fisher (without missing data) = 0.0002		Indomethacin		Ibuprofen		All	
		N	%	N	%	N	%
Missing		1	100.0	2	100.0	3	100.0
	All	1	100.0	2	100.0	3	100.0
Non-missing	No – PDA closed	68	77.3	53	58.2	121	67.5
	Yes – PDA open	20	22.7	38	41.8	58	32.4
	All	88	100.0	91	100.0	179	100.0

The percentage of reopening after the first treatment course was similar with both drugs (32.6% for ibuprofen versus 36.4% for indomethacin) despite a much longer course of indomethacin, showing that a longer course of indomethacin did not increase efficacy while it was leading to a poorer safety profile.

Table 17: Survey LT-FU: Reopening after 1st COX-inhibitor cycle

prob. Fisher (without missing data) = 0.6396		Indomethacin		Ibuprofen		All	
		N	%	N	%	N	%
Missing		1	100.0	1	100.0	2	100.0
	All	1	100.0	1	100.0	2	100.0
Non-missing	No	56	63.6	62	67.4	118	65.6
	Yes	32	36.4	30	32.6	62	34.4
	All	88	100.0	92	100.0	180	100.0

Overall, PDA reopening was due to infection for 19.3% of patients after indomethacin treatment versus 12.9% after ibuprofen (p=0.311).

After the second course, a higher proportion of remaining PDA was observed for patients who received ibuprofen (65.7% versus 30.8% for those who received indomethacin, p=0.049). The percentage of reopening after the second treatment course was 33.3% for ibuprofen versus 15.4% for indomethacin (p=0.293), but the "courses" were not comparable, as they lasted 3 days with ibuprofen and 7-8 days with indomethacin. Nevertheless, a second ibuprofen course seemed to be less effective in infants in whom the PDA failed to close during the first treatment course, since a PDA reopening occurred in almost all of those patients.

Only 1 patient in the indomethacin group and 3 patients in the ibuprofen group still presented with remaining PDA at the end of the third course. Reopening after the third course was observed for 1 and 3 patients, respectively, after indomethacin and ibuprofen treatment.

Surgical ligation was necessary for 24 patients out of 89 (27.0%) after indomethacin treatment versus 28 patients out of 93 (30.1%) after ibuprofen treatment (p= 0.743). The time to surgery was similar with both treatments (17.4 ± 9.2 days after indomethacin versus 17.8 ± 7.85 days after ibuprofen, p=0.851), indicating that access to surgery (number of PDA ligations and timing of these ligations) was increased under prolonged regimen of indomethacin.

Table 18: Survey LT-FU: Number and timing of PDA ligation.

Prob. Wilcoxon = 0.6347		Indomethacin	Ibuprofen	All
PDA surgery (Days of life)	Mean	17.4	17.8	17.6
	Std	9.2	7.8	8.4

Prob. Wilcoxon = 0.6347		Indomethacin	Ibuprofen	All
	Min	6.00	5.00	5.00
	Max	43.00	35.00	43.00
	Median	16.00	18.00	18.00
	N	24	28	52
	NMiss	65	65	130

The proportion of patients still presenting with PDA at the time of discharge was almost the same after both treatments (18.0% after indomethacin versus 18.3% after ibuprofen, p=1.000). Of those infants presenting with a PDA in the echocardiography prior to discharge, the PDA was hemodynamically relevant only for 1 and 3 patients, respectively, after indomethacin and ibuprofen (p=0.621). Both missing infants died before an echocardiographic re-evaluation of the haemodynamic significance of their PDA was performed.

Conclusions

- It must be noted that the 2 groups of patients reported were not prospectively constituted, but only retrospectively analysed, and that no firm conclusion based on any advantage of 1 drug over the other can be supported; the conclusions should remain indicative.
- Similar percentages of PDA closure were achieved with both drugs.
- A shorter drug exposure was seen with ibuprofen in comparison to indomethacin.

7.3.3. Study IBU/20 mg/2009

7.3.3.1. Multicentre Open-Label Pilot Study to Evaluate the Safety, Pharmacology and Efficacy of a New Dose Regimen (ie, 20-10-10 mg/kg) of Pedea (Intravenous Ibuprofen) in Preterm Newborn Infants of Less than 28 Weeks of Gestation.

Comment: The primary objective of this study is safety. The safety aspects are reported. The efficacy results which were a secondary objective are reported in this section. The PD/PK results are presented.

Objectives

- Primary: To determine whether the administration of Pedea (intravenous ibuprofen) starting between 12 and 72 h of life at a dose of 20-10-10 mg/kg was safe and well tolerated in a population of preterm newborn infants of less than 28 weeks of GA with a HsPDA. In particular, whether it was or not inducing any significant increase in the unbound fraction of bilirubin assessed by the peroxidase diazo method.
- Secondary: To determine at serial time points plasma concentrations of ibuprofen enantiomers and of total and unbound unconjugated bilirubin as well as to evaluate the global PDA closure rate after the treatment course.

Methodology

- Design: An open label study conducted at 3 sites in France from February 2010 to March 2011.
- Entry criteria: Preterm newborn male or female infants presenting with a HsPDA, on mechanical or non-invasive ventilation and with respiratory acidosis, who were of GA < 28 weeks and aged from 12 – 72 h of life.
- Exclusion criteria were: Ductus-dependent cardiopathy, right-to-left shunt over a persisting ductus arteriosus, hydrops fetalis, severe intra-ventricular haemorrhage (Papile's grade 3 or 4), neurological functional disorders: seizures, coma, life threatening infection, thrombocytopenia < 30000/mm^3, necrotising enterocolitis, severe uncontrolled

hyperbilirubinemia (TB > 171 µmol/L or 10 mg/dL), hepatocellular disease, or hepatic insufficiency.

- Treatments: All subjects received Pedea (ibuprofen) at a loading dose of 20 mg/kg followed by 2 maintenance doses of 10 mg/kg at 24 h intervals. Birth weight was used for the calculation of respective doses. A backup dose (same regimen) was possible at the discretion of the investigators.
- Efficacy outcomes: PDA closure (by Doppler echocardiography) 24 h after the therapeutic course of ibuprofen by echocardiography. The flow through the ductus, the retrograde flow in the pulmonary trunk, and the ductus arteriosus diameter were also evaluated.
- Statistical analysis: Descriptive only.

Study participants

- Enrolled: 23 enrolled.
- Completed: 20 completed (3 patients had SAE leading to death, none were withdrawn).
- Analysed: 20 analysed for efficacy and 23 for safety analysis.
- Baseline: There were 13 males and 10 females aged between 24.0 and 27.9 weeks of GA (median 25.7 weeks) and with a birth weight ranging from 575 to 1155 g (median 835 g); most mothers (96%) had received antenatal glucocorticosteroids; 4 infants (17%) were considered as being small for their GA; all infants were on phototherapy at baseline.

Table 19: Study IBU/20 mg/2009: Baseline characteristics and demographic data

Characteristics	Study infants* N = 23	Range	Median
Gestational age (weeks)	26.2 ± 1.3	24.0 – 27.9	25.7
	24-26 [N=12]		
	26-28 [N=11]		
Birth weight (g)	815.4 ± 149.0	575.0 - 1155.0	835.0
Male/Female	13 / 10		
Antenatal glucocorticosteroids	22 (95.7)		
Premature rupture of membranes	6 (26.1)		
Maternal hypertension	3 (13.0)		
Caesarean delivery	9 (39.1)		
Apgar score at 5 min	5.9 ± 2.5	1 – 10	6.0
CRIB score	5.3 ± 3.5	1 - 12	6.0
Ventilation at inclusion**	15 (65.2) / 4 (17.4) / 4 (17.4)		
Surfactant therapy at inclusion	23 (100)		
Inspired oxygen at inclusion (FiO_2%)	23.0 ± 3.2	21.0 – 30.0	21.0
Phototherapy at inclusion	23 (100)		
Postnatal age at T0 (days)	2.2 ± 0.5	1.0 – 3.0	2.0
Total bilirubin (mg/dL) at T0	5.6 ± 2.1	3.0 – 10.0	4.7
Unbound bilirubin (µg/dL) at T0	4.3 ± 5.3 (N= 21)	0.2 - 23.1	2.3
Albumin (g/L)	23.3 ± 3.0	18.0 – 32.0	23.0
Total bilirubin/albumin molar ratio	0.3 ± 0.1	0.1 – 0.5	0.3
Apparent albumin binding constant (Ka)	12.8 ± 11.5	0.8 – 42.1	8.4

* Data are presented as mean SD or N (%) unless otherwise specified

** Conventional mechanical ventilation/high frequency oscillation/nasal continuous positive airway pressure.

Efficacy results

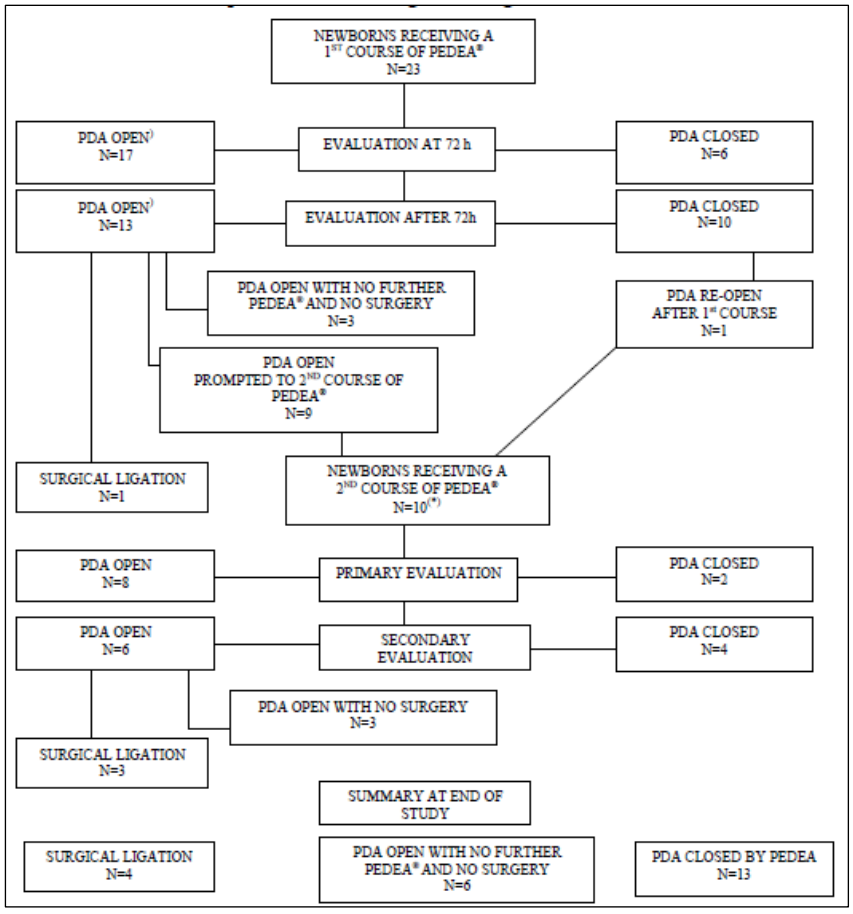
After the 1st course of high dose regimen of Pedea administered between 12 and 72 h of life, the ductus arteriosus evaluated at 72 h was closed in a total of 6 children out of 23 cases (26%, 95% CI = 0.08;0.44). Without further intervention a DA closure occurred later in 4 cases resulting in a success closure rate after the 1st course of 10/23 (43.5%) with a 95% CI = 0.23;0.64. In 1 patient the DA was closed at 72 h and re-opened secondarily.

The PDA status is shown in the following flow diagram.

The median time (extremes) to DA closure was 4 days (3-51) with a mean (SD) of 12.8 (15.5) days.

Ten children (43.5%) received a 2nd course of Pedea. In only 2 infants amongst these 10 infants who received a 2nd course of Pedea, was the PDA closed after this backup course, representing an additional 18% closure after Pedea with a 95% CI = 2%; 34%. Without further intervention after the backup course 2 additional patients presented a delayed closure of the DA.

Figure 4: Study IBU/20 mg/2009: PDA status after therapeutic courses of high dose regimen of Pedea.



(*) Incomplete course or not at the high dosage regimen in 4/10 cases

Conclusions

The high dose regimen of Pedea resulted in a success rate of 13/23 (56.5%) with a 95% CI of 36%; 77% in this very young GA population sample. In addition, at the end of the study, the PDA remained open in 6 patients, 3 with 1 course only and 3 with 2 courses but the PDA was not hemodynamically significant and was well tolerated clinically. Among these 6 latter patients 3 died.

7.3.4. Evaluator commentary: other efficacy studies

The other efficacy studies comprise a study investigating prophylactic use of ibuprofen which was terminated early due to a potential safety issue, a retrospective survey of patients treated at 1 centre in Germany and higher dose regimen study primarily investigating safety.

The efficacy data is therefore extracted from studies not primarily powered to investigate efficacy.

The retrospective survey provides the only data submitted which compares ibuprofen with indomethacin, which is different in time for each drug and reflects only 1 centre. However, with these reservations, it showed similar efficacy between ibuprofen and indomethacin and comparable results to the other studies.

7.4. Analyses performed across trials: pooled & meta analyses

The sponsor did not perform any pooled or meta-analyses. However, they did include the series of Cochrane Reviews which have been conducted as references. A brief summary of the reviews is provided below.

7.4.1. Cochrane review – Ohlsson 2003, 2005, 2008, 2010, 2011

A series of Cochrane Review were conducted from 2003 to 2011 which reviewed the use of ibuprofen in treatment of PDA.

The Reviews are:

- Ohlsson A, Walla R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants (Cochrane Review). In: *The Cochrane Library, Issue 2, 2003. Oxford: Update software*
- Ohlsson A, Walla R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants. *The Cochrane Database of Systematic Reviews 2005, Issue 4, Art No.: CD003481.pub2. DOI: 10.1002/14651858.CD003481.pub2.*
- Ohlsson A, Walla R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants. *The Cochrane Database of Systematic Reviews 2008, Issue 1, Art No.: CD003481. DOI: 10.1002/14651858.CD003481.pub3.*
- Ohlsson A, Walla R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants. *The Cochrane Database of Systematic Reviews 2010, Issue 4, Art No.: CD003481. DOI: 10.1002/14651858.CD003481.pub4.*
- Ohlsson A, Walla R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants. *The Cochrane Database of Systematic Reviews 2011, Issue 7, Art No.: CD004213. DOI: 10.1002/14651858.CD004213.pub3.*

Objectives

The objectives of the first 4 reviews were the same, namely

- To determine the effectiveness and safety of ibuprofen compared with placebo or no intervention for closing a PDA in preterm and/or low birth weight infants
- To determine the effectiveness and safety of ibuprofen compared with other cyclooxygenase inhibitors (including indomethacin, mefenamic acid for closing a PDA in preterm and/or low birth weight infants.

The 2011 Review had the following objective:

- To determine the effectiveness and safety of prophylactic ibuprofen compared with placebo/no intervention in the prevention of PDA in preterm infants.

Search Strategies

Randomised or quasi-randomised controlled trials (RCTs) comparing ibuprofen to placebo or indomethacin or mefenamic acid for therapy of PDA were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2009), MEDLINE (1996 - December 2010), CINAHL (1982 - December 2010), EMBASE (1980 - December 2010), reference lists of published RCTs and abstracts from the Pediatric Academic Societies and the European Society for Pediatric Research meetings published in Pediatric Research (1991 - April 2005) or on their website (2006 to 2010). No language restrictions were applied.

Studies identified

- 2003: 8 studies including 509 patients – all studies comparing Ibuprofen to indomethacin. There were no studies that compared ibuprofen to placebo or to mefenamic acid.
- 2005: 11 studies including 620 patients comparing ibuprofen to indomethacin. No studies using mefenamic acid were identified. One study compared ibuprofen to placebo but abstract only and results were not reported unblinded to group of allocation.
- 2008: 16 studies enrolling 876 patients – 15 studies including 740 infants comparing ibuprofen to indomethacin (2 studies previously only in abstract now available as full articles), 1 study comparing ibuprofen to placebo (same as in 2005).
- 2010: 20 studies enrolling 1092 patients comparing ibuprofen to indomethacin. One study comparing ibuprofen to placebo previously published as abstract now available as full article. No studies using mefenamic acid were identified.
- 2011: 7 studies enrolling 931 patients comparing prophylactic ibuprofen with placebo/no intervention.

Figure 5: Cochrane review: Forrest plot of comparison – Ibuprofen vs indomethacin – failure to close PDA.

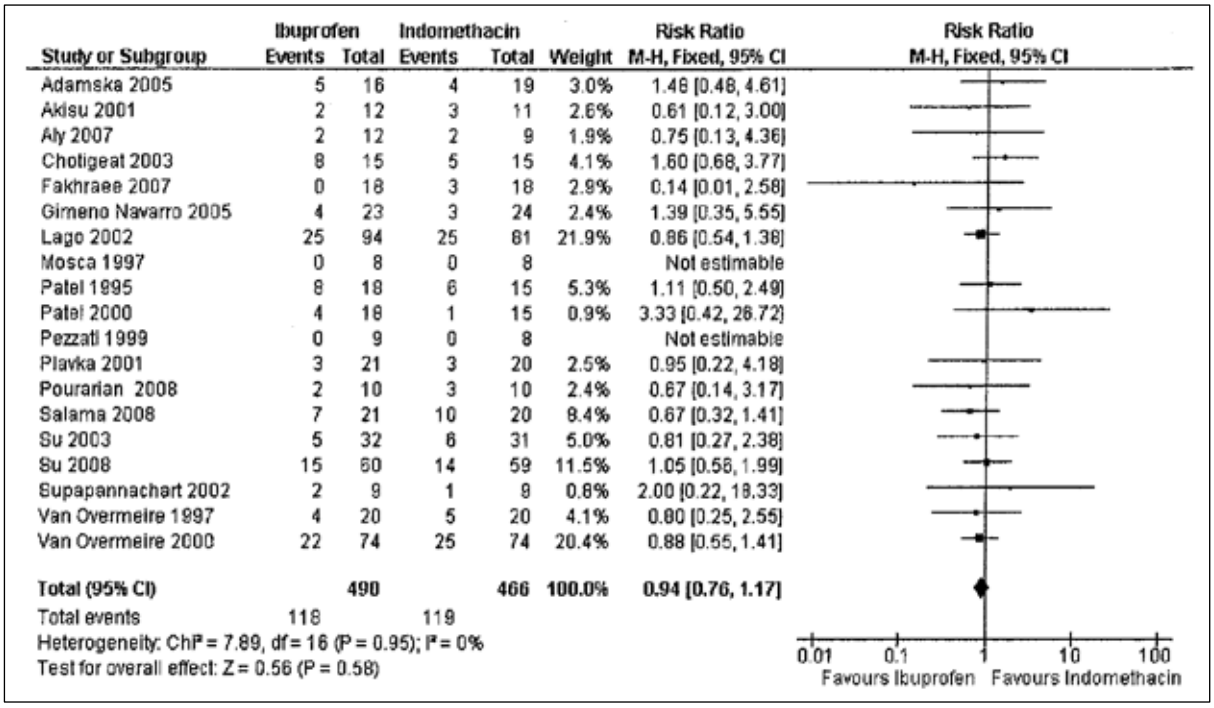
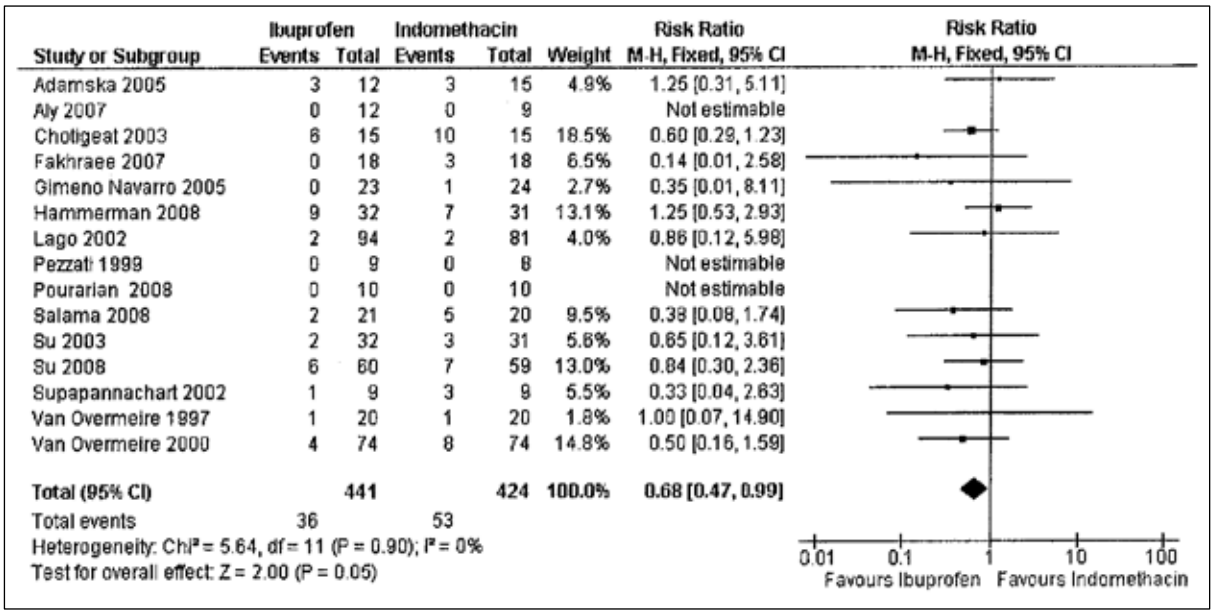


Figure 6: Cochrane review: Forrest plot of comparison – Ibuprofen vs indomethacin – necrotising enterocolitis.



Conclusions

7.4.1.1. 2003 Report

- No statistically significant difference in the effectiveness of ibuprofen compared to indomethacin in closing the PDA
- Ibuprofen reduces the risk of oliguria
- Ibuprofen may increase the risk of chronic lung disease – based on 3 reports of pulmonary hypertension reported after prophylactic use of ibuprofen
- Ibuprofen does not appear to confer a net benefit over indomethacin for the treatment of PDA

7.4.1.2. 2005 Report

- No statistically significant difference in the effectiveness of ibuprofen compared to indomethacin in closing the PDA
- Ibuprofen reduces the risk of oliguria
- Ibuprofen may increases the risk of chronic lung disease – based on 3 reports of pulmonary hypertension reported after prophylactic use of ibuprofen
- Ibuprofen does not appear to confer a net benefit over indomethacin for the treatment of PDA
- Indomethacin should remain the drug of choice for the treatment of a PDA

7.4.1.3. 2008 Report

- No statistically significant difference in the effectiveness of ibuprofen compared to indomethacin in closing the PDA
- Ibuprofen reduces the risk of oliguria and is associated with lower serum creatinine levels following treatment
- Pulmonary hypertension has been observed in 3 infants after prophylactic use of iburprofen and 1 infant receiving ibuprofen for treatment

- The available data support the use of either drug for the treatment of a PDA. As both drugs are equally effective closing a PDA the clinician needs to weigh the potential side effects of 1 drug vs the other in making a decision

7.4.1.4. 2010 Report

- Ibuprofen is effective in closing a PDA
- Ibuprofen is as effective as indomethacin in closing a PDA and reduces the risk of NEC and transient renal insufficiency
- Ibuprofen appears to be the drug of choice

7.4.1.5. 2011 Report

- Prophylactic use of ibuprofen decreased the incidence of PDA and decreased the need for rescue treatment with COX inhibitors and decreased the need for surgical closure
- In the control group, the PDA closed spontaneously by Day 3 in 58% of the neonates
- Prophylactic treatment exposes many infants to a drug that has concerning renal and gastrointestinal side effects without conferring any short term benefits and is not recommended
- Until long term follow up results are published from the included trials no further trials of prophylactic ibuprofen are recommended.

All the reports stressed the lack of long term studies investigating the longer term outcomes of treatment with ibuprofen. This is best expressed by the following:

"The most urgent research question to be answered is whether ibuprofen compared to indomethacin confers an improved rate of intact survival (survival without impairment) at 18 months corrected age and at the age of school entry." (2008 report)

7.5. Evaluator's conclusions on clinical efficacy

In Europe, the sponsor relied on efficacy data reported in the published literature by submitting a mixed dossier (clinical studies and literature). This was not done in Australia where the submission contained only clinical studies and published studies were included only as literature references.

The submitted efficacy studies were fairly old, being conducted in the range 2000 to 2004 and reflecting medical management applicable at that time in Europe.

This raises difficulties when it comes to conclusive data on efficacy. All the studies submitted in support of efficacy have strong limitations mostly reflecting the small number of patients, age of the studies and the primary objective of most of the studies being safety.

The efficacy data suggests that the success rate of ibuprofen (10/5/5 regimen) in treating PDA is about 50% for the total GA range of 24 to 28 weeks but is probably lower in the lower GA range (24-26 weeks) who may need a higher dose. The results may also be variable depending on the context of the medical management at the treating medical centres. This response rate may be low compared to that reported in the literature (stated in the *Clinical Overview* to be ~75% based on a review of 15 published trials).

It is disappointing that the sponsor did not include a prospective comparative study with indomethacin. The Cochrane review repeatedly found no significant difference between indomethacin and ibuprofen (based on total of 20 published studies).

8. Clinical safety

Comment: The Summary of Clinical Safety is very poorly presented. The document is not indexed and does not contain an aggregated/integrated assessment of the data. Only the efficacy studies (not PK/PD studies) are included in the summary and each study is presented separately with the safety results of each study report repeated with very little discussion or critical assessment. Study IBU/PROPHYL/2000 – prophylactic group is not included despite the trial being prematurely terminated on safety grounds.

8.1. Studies providing evaluable safety data

8.1.1. Pivotal studies that assessed safety as the sole primary outcome

- Study IBU/Survey

8.1.2. Pivotal and/or main efficacy studies

- Study IBU/PROPHYL/2000 (curative group)

8.1.3. Other studies

8.1.3.1. Other efficacy studies

- Study IBU/PROPHYL/2000 (prophylactic group)
- Study Long Term FU
- Study IBU/20mg/2009

8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology

- Study IBU/99/DoseRange
- Study P000241
- Study 9-33/93
- Study IBU/BILICLIN 04
- Study IBU/GER/2003

8.1.3.3. Studies evaluable for safety only

Not applicable.

8.2. Studies that assessed safety as the sole primary outcome

8.2.1. Study IBU/Survey

Comment: This was not a randomised controlled trial, it is a report of the compassionate use program run by the sponsor in 3 countries in Europe. It does not report all safety issues usually reported in a clinical trial but the sole purpose of the study was to review the safety of the product. All AEs were not reported, only those specified AEs relating to ventilation, vascular, digestive, neurological and renal function were reported. The survey results are reported in 3 subsets: total population treated with ibuprofen (early treatment Day 0-1 versus Day 2+); comparative population (ibuprofen versus indomethacin) and subset of patients treated early. The results of the comparative group are reported in this summary.

8.2.1.1. Study design, objectives, locations and dates

This was a retrospective survey of the compassionate use program run by Orphan Europe. The compassionate use program ran from 1 March 2001 to 31 December 2001 during which time

Pedea was supplied to 15 sites in France, Germany and Sweden. A period of equal duration from May 2000 to February 2001 was included to allow comparison with indomethacin.

8.2.1.2. Inclusion and exclusion criteria

All premature newborns were included:

- Either those who had received ibuprofen IV Orphan Europe (Pedea®) as a medical treatment of the PDA, and who were born between March 1st 2001 and December 31st 2001
- Those who had received indomethacin (Indocid-PDA®) as a medical treatment of the PDA, and who were born between May 1st 2000 and February 28th 2001

8.2.1.3. Study treatments

Ibuprofen IV Orphan Europe was provided as a solution for injection containing 5 mg/mL of ibuprofen acid per ampoule. It was presented in boxes containing 4 ampoules of 2 mL See results (8.2.1.12) for actual doses taken.

Details of the indomethacin presentation or treatment regimen are not provided.

8.2.1.4. Safety variables and outcomes

Data was extracted from the patients' hospital records as well as from hospital discharge summaries. The following were recorded:

- Ventilation: any change from spontaneous to CPAP to mechanical ventilation and/or from conventional to HFO ventilation; maximum FiO2 with the 24 h before and after each administration of the drug; need for nitric oxide administration
- Vascular status: hypotensive episodes; lowest mean BP starting within the 24 h before and up to 24 h after each drug administration
- Digestive function: incidence of digestive perforations and/or necrotising enterocolitis
- Neurological function: presence of IVH of grade III or IV (Papile classification) and/or presence of cystic periventricular leukomalacia
- Renal function and homeostasis: weight, urine water excretion, water intake recorded at birth and within 24 h before and after each infusion; maximal values of plasma creatinine and potassium and minimal values of sodium at birth and within 24 h before and after each infusion
- Other parameters: minimal values of platelet count and haemoglobin; deaths; need for surgical ligations of the PDA and the number of ibuprofen courses and back up indomethacin treatment

8.2.1.5. Randomisation and blinding methods

Not applicable.

8.2.1.6. Analysis populations

Two sets of ibuprofen patients were considered:

- Patients from all centres, these patients are referred to as the "total population"
- Patients belonging to a centre which had systematically switched from indomethacin to ibuprofen. These patients are referred to as the "comparative population"

Populations are also split according to the timing of the first dose of PDA treatment:

- Patients who had received the drug on the same day as their birth day or on the following day are referred to as the "early treatment population" (or "Day 0-1" in the tables)

- Patients who had received the first dose of the drug on any of the following days are referred to as the "late treatment population" (or "Day 2+" in the tables)

8.2.1.7. Sample size

A total of 165 patients who had received a total of 605 infusions as early treatment (n=54) or as late treatment (n=111) were included in the analysis.

8.2.1.8. Statistical methods

Descriptive only.

8.2.1.9. Participant flow

Not applicable.

8.2.1.10. Major protocol violations/deviations

Not applicable.

8.2.1.11. Baseline data

From March 2001, 9 of the 15 centres had systematically switched from indomethacin to ibuprofen. The number of patients treated early (46 indomethacin, 46 ibuprofen) or late (65 indomethacin, 62 ibuprofen) was similar among the various centres, showing that they had used ibuprofen under similar circumstances as they did with indomethacin.

A total of 62 preterm neonates had received ibuprofen and 65 indomethacin as a treatment of the PDA from the second day of life and onwards.

Table 20: Study IBU/Survey: Demographic characteristics – comparative group

	Ibuprofen		**Indomethacin**	
	N		**N**	
Sex				
Male	62	35	65	29
Female		27		36
Birth weight (g)				
Median	61	1006	64	1092
Range		590-2400		550-2960
Distribution of BW (g) (%)				
<750	10 (16.4)		8 (12.5)	
750-999	18 (29.5)		23 (35.9)	
1000-1250	18 (29.5)		9 (14.1)	
>1250	15 (24.6)		24 (37.5)	
GA (weeks)				
Median	62	28	65	29
Range		24-36		24-37
Distribution of GA (weeks)				
<27	20		17	
27-29	29		26	
>29	13		22	
Intrauterine growth retardation (%)	8.6		7.8	
APGAR 5 min	49	8	50	9
Median		1-10		4-10
Range				

Sex ratio was 1.29 in ibuprofen and 0.82 in indomethacin which was rather pejorative for ibuprofen, as male preterm newborns have a poorer prognosis.

Table 21: Study IBU/Survey: Maternal events – comparative group.

	Ibuprofen		Indomethacin	
	%	N	%	N
Sample size	100	62	100	65
Rupture of membranes	6.5	4	6.2	4
Placental or umbilical complications	8.1	5	12.3	8
Eclampsia/toxaemia	8.1	5	24.6	16
Chorioamniotitis	6.5	4	4.6	3

The incidence of eclampsia or toxaemia was very different between groups without clear explanation.

Table 22: Study IBU/Survey: Respiratory characteristics at birth – comparative group.

	Ibuprofen		Indomethacin	
	%	N	%	N
Sample size	100	62	100	65
Mechanical	75.8	47	69.2	45
HFO	4.8	3	3.1	2
CPAP	12.9	8	21.5	14
Spontaneous	4.8	3	3.1	2
ND	1.6	1	3.1	2
Maximal FiO_2 (%) – median (range)		45 (21-100)	50 (21-100)	

Rate of spontaneous ventilation at birth was identical in both groups. More mechanical/HFO ventilation in the ibuprofen group than in the indomethacin group and much less CPAP confirmed the worse clinical status of the ibuprofen group despite similar FiO2.

Table 23: Study IBU/Survey: Medical events before first drug administration – comparative group.

	Ibuprofen		Indomethacin	
	%	N	%	N
Sample size	100	62	100	65
HMD	85.5	53	84.6	55
Infection	6.5	4	9.2	6
Hypotension	21	13	10.8	7
Grade III & IV IVH	1.6	1	1.5	1
PVLM	0	0	1.5	1
Renal failure	3.2	2	4.6	3
Bleeding	8.1	5	4.6	3
NEC	0	0	1.5	1

Lowest natraemia, highest kalaemia, highest serum creatinine, lowest platelet counts and haemoglobin were similar in both groups.

Table 24: Study IBU/Survey: Treatments received before PDA drug administration – comparative group.

	Ibuprofen		Indomethacin	
	%	N	%	N
Sample size		62		65

	Ibuprofen		Indomethacin	
	%	N	%	N
Corticosteroids	6.5	4	4.6	3
Surfactant	85.5	53	83.1	54
Inotropics	35.5	22	24.6	16
Diuretics	35.5	22	20	13
Aminosides	90.3	56	90.8	59
Nitric oxide	6.5	4	4.6	3

8.2.1.12. Results for the safety outcomes

Dose

Patients were administered 1 or 2 courses. Two courses were given to 13 (21%) of ibuprofen and 3 (4.7%) of indomethacin patients. The courses given complied with the recommended dosage for both drugs. Indomethacin dosage was 3 consecutive doses of 0.2 mg/kg. The number of infusions was different between the groups: 3 infusions in 55/62 (88.7%) of the ibuprofen patients whereas indomethacin was given as 3 infusions only in 38/65 (59.4%) of cases. Most courses were done over 3 consecutive days in the ibuprofen group, whereas the duration ranged from 1 to 6 days for indomethacin.

Table 25: Study IBU/Survey: Treatment characteristics – comparative group.

	Ibuprofen		Indomethacin	
Number of courses	**%**	**N**	**%**	**N**
1	79	49	95.3	61
2	21	13	4.7	3
Number of infusions 1st course				
1	3.2	2	6.3	4
2	8.1	5	18.8	12
3	88.7	55	59.4	38
>3	0	0	15.7	10
Dose (mg/kg) 1st course				
	Mean	**Median Range**	**Mean**	**Median Range**
1st infusion	9.9	10 4.5-11.6	0.2	0.2 0.1-0.4
2nd infusion	5	5 2.2-5.9	0.2	0.2 0.1-0.2
3rd infusion	4.9	5 1-8.9	0.2	0.2 0.1-0.2

Concomitant medications were similar in both groups. There were some qualitative differences with more methylprednisolone and dexamethasone in the indomethacin group (7.7 vs 4.8% and 4.6 vs 1.6%) versus more hydrocortisone in the ibuprofen group (8.1 vs 1.5%).

Respiratory status

Numbers of "ventilation worsening" were similar in both groups and over repetition of infusions (4/61 and 6/59 for ibuprofen vs 4/64 and 5/62 for indomethacin). Median maximum FiO_2 decreased from 34 to 30 and 26.5 under ibuprofen from 1st to 3rd infusion, whereas it remained at 30% from 1st to 3rd infusion of indomethacin. This evolution profile, based on few

data, should be considered with caution, but underlines that the respiratory status did not worsen noticeably under ibuprofen.

Treatment with nitric oxide occurred in 4 cases on the same day as the 1st infusion of ibuprofen (Day 0) and in 2 cases on the same day than the 1st infusion of indomethacin (Day 0). None of these case reports showed a relationship between the ibuprofen infusion and the onset of refractory hypoxemia.

Renal function and homeostasis

The median body weight gain from Day 0 to Day 2 was higher in the indomethacin group (+47.9 g/kg BW vs +25.6 g/kg BW). Therefore, it is obvious that ibuprofen administration was not associated with significant water retention in preterm infants while indomethacin induced marked water retention.

The clinical significance of this water retention was shown by lower sodium serum concentrations in the indomethacin group on Day 2 and increased incidence of severe hyponatremia on day 2 (28.8% vs 6.8%). Otherwise, serum potassium concentrations were stable and hyperkalaemia was infrequent in both groups. Diuretic administration was similar in both groups.

Changes were not different between groups for: urine water excretion, water intake, output/input ratio. However, oliguria was more frequently observed on Day 1 and 2 in the indomethacin group (24.2% vs 0% and 18.2% vs 0%).

Table 26: Study IBU/Survey: Evolution of renal clinical parameters – comparative group.

	Ibuprofen				**Indomethacin**			
	Median Range N				**Median Range N**			
Day	-1	0	1	2	-1	0	1	2
Weight (g)	977.5 550-2290 44	905 595-2270 41	962.5 610-2250 46	943 646-2180 46	970 560-2960 46	1050 550-2960 47	1005 450-2700 58	1095 590-2740 53
Urine output (ml/kg/h)	3.5 0.3-11.5 42	3.9 0.5-9.3 43	3.1 1.4-11.1 48	3.1 1.1-12 46	2.9 1.1-8.4 30	2.5 0.3-6.3 38	2 0-5.7 43	2.3 0.5-6.7 44
Water out/input ratio	0.6 0-2 37	0.6 0.2-3.2 40	0.5 0.1-3 43	0.6 0.2-1.3 43	0.7 0.2-2.9 28	0.6 0-1.3 36	0.4 0-1.4 39	0.5 0.1-2.3 39

Creatinine plasma concentrations were stable over the ibuprofen treatment. In contrast, changes in plasma creatinine concentration from Day 0 to Day 2 (median +12 µmol/L) were higher in the indomethacin group than in the ibuprofen group (median +3 µmol/L).

Even if plasma creatinine concentration is not an optimal way to assess glomerular filtration rate in neonates, this data showed that indomethacin affected glomerular filtration rate much more than ibuprofen did since identical plasma creatinine concentrations at Day 0 eliminated the problem of the transplacental transfer of creatinine.

Table 27: Study IBU/Survey: Evolution of renal biological parameters – comparative group

	Ibuprofen				**Indomethacin**			
	Median Range N				**Median Range N**			
Day	-1	0	1	2	-1	0	1	2

	Ibuprofen				Indomethacin			
	Median Range N				Median Range N			
Lowest natraemia (mmol/L	137 118-147 57	140 118-151 49	138 124-153 54	138 126-146 44	138 125-151 60	138 122-158 54	135 115-158 55	134 122-155 52
Highest kalaemia (mmol/L)	4.7 3.1-8.4 57	4.5 2.9-6.9 48	4.7 2.9-7.7 54	4.4 2.4-7.6 44	4.8 3.3-8.1 61	4.6 3.3-6.4 53	4.9 3.3-7.9 55	4.6 3.1-8.1 52
Highest creatininaemia (µmol/L)	86 42-159 45	87 47-147 38	86.5 38-129 42	86 44-176 38	87 42-163 37	83 35-180 33	85 46-168 37	97 48-213 38
Lowest platelets (g/L)	189.5 31-479 40	149 16-649 32	189 65-680 26	167.5 39-686 24	196 33-552 47	210 52-308 20	180.5 56-468 20	164 35-502 17
Lowest haemoglobin (g/dL)	14.2 4.1-18.5 38	11.8 4.6-18.4 30	13.9 4.6-16.9 25	14.2 4.4-18.9 22	13.6 9-18.5 47	11.9 7.4-18.6 23	12.1 8.3-20.4 23	10.7 7.9-17 19

Table 28: Study IBU/Survey: Medical events after start of treatment of PDA – comparative group

	Ibuprofen		Indomethacin	
	%	N	%	N
Sample size	100	62	100	65
Confirmed infection	38.7	24	24.6	16
Hypotension	1.6	1	0	0
Calculated hypotension				
1st infusion	45.3	24	17.5	17
2nd infusion	16.3	8	14	13
3rd infusion	11.1	5	9.2	8
Grade III-IV IVH	8.1	5	3.1	2
PVLM	4.8	3	12.3	8
Bowel perforation	1.6	1	0	0
NEC	6.5	4	4.6	3
Renal failure	8.1	5	4.6	3
Bleeding	3.2	2	3.1	2
Death	17.7	11	9.2	6

Deaths

Mortality was higher in the ibuprofen group (17.7%) than in the indomethacin group (9.2%). Ibuprofen patients died in 7/11 cases within the first week of initiation of treatment, confirming the observation that they were more severely ill patients (2/6 patients died within that period in the indomethacin group).

Efficacy

PDA surgery was carried out more frequently in the ibuprofen (20/62) that in the indomethacin group (6/65).

Subset of patients treated early: A total of 46 preterm neonates had received ibuprofen and 46 indomethacin as an early treatment of the PDA.

- The median dose of indomethacin used was lower than in the later time treatment group, as it was 0.1 mg/kg for the 3 injections (instead of 0.2)
- The trend of a higher number of patients needing a second course of treatment was also higher in the ibuprofen than in the indomethacin group, though less pronounced than in the other subset (21.8% vs 8.7% respectively)
- The drug was administered over 3 infusions with a higher proportion of 3 infusions in ibuprofen than in indomethacin group during any courses of treatment
- PDA surgery was carried out nearly as frequently in the ibuprofen (5/46) as in the indomethacin group (3/46)

8.2.1.13. Evaluator commentary

This survey was conducted following the termination of Study IBU/PROPHYL/2000 due to the occurrence of 3 cases of reversible refractory hypoxaemia. These cases were very similar in their respective occurrence and timing. They constituted 3 independent cases (at 3 different centres) of severe refractory hypoxaemia right after administration of the loading dose of the drug (10 mg/kg) which occurred within the first 6 h of life in very premature newborns of less than 28 weeks gestation. Refractory to increased ventilation support (increased ventilation pressures, increased FiO_2, high frequency oscillation ventilation, repeated instillations of exogenous surfactant), the 3 cases recovered rapidly after the administration of nitric oxide. In 2 of the 3 cases, the maintenance doses (5 mg/kg) were administered within 24 h without any further problem and treatment was withdrawn in the other patient.

As the refractory hypoxemia was rapidly reversible after inhaled nitric oxide it suggested a transient pulmonary vasoconstriction and thus it was considered mandatory, following discussion with the French Medicines Agency to obtain more information about this adverse effect.

Refractory hypoxaemia had not been reported in publications on ibuprofen studies nor in studies with indomethacin. However there have been 3 case reports of preterm newborns with refractory hypoxaemia following indomethacin for treatment of PDA.

The result of the survey was that no refractory hypoxaemia was seen that could be related to an ibuprofen infusion.

The recommendation of the clinicians at the sites is that ibuprofen should be avoided in the first 6 h of life in preterm infants (when pulmonary vascular resistances are still particularly elevated) and should always be preceded by an ultrasound and Doppler examination of the heart. The ultrasound examination is directed to exclude both pulmonary hypertension with poor pulmonary perfusion and congenital heart disease depending on patency of the DA.

The survey demonstrates, as do the studies that preterm infants present with known complications: severe IVH, PVL, NEC, bowel perforations. The incidences of these complications did not appear to be different between the ibuprofen and indomethacin treated patients.

The survey was not intended to evaluate the efficacy of ibuprofen. However, the curative ibuprofen therapy appeared less efficient than indomethacin as the respective surgical closures of PDA were 32 % and 9%. This data is not in line with previous published randomised studies that showed that efficacy of ibuprofen and indomethacin to be similar. Some obvious bias is suggested which may explain this discrepancy:

- 4/8 centres were unbalanced with regard to their contribution: more ibuprofen patients in 3 centres, and more indomethacin patients in 1 centre. This clearly suggests a shift in the medical management of PDA

- The rate of surgical closure of PDA in ibuprofen patients depended on the NICU and varied from 0% to 88%. This suggests that local clinical practices and/or unidentified differences in patient characteristics may strongly influence the efficacy of ibuprofen.
- Some baseline characteristics appeared to differ between the 2 groups such as: gestational age and birth weight, incidence of eclampsia/toxaemia, incidence of hypotension, rate of mechanical ventilation, inotropic and diuretic support. Previous prospective trials have suggested that the lower the GA the higher the need for surgical closure of PDA. This close inverse relationship between efficacy of ibuprofen and GA was also found in this survey as the success rate for PDA closure was 70% when GA was below 27 weeks and 80% when GA ranged between 27 and 29 weeks.

8.3. Patient exposure

See Tables 29-31.

Table 29: Estimated cumulative subject exposure to Pedea from clinical trials (29 July 2004 to 30 July 2014)

Study	Pedea	Comparator (Indomethacin)	Placebo	Total
IBU/LT/2004	93	89	0	182
IBU/BILICLIN/2004	34	0	0	34
IBU/20mg/2009	23	0	0	23
IBU/GER/2003	15	0	0	15
IBU/99/DoseRange	40	0	0	40
IBU/PROPHYL/2000	90	9	66	131
IBU/Survey	89	93	0	182
Total	**384**	**89**	**0**	**239**

Table 30: Estimated cumulative subject exposure to Pedea from clinical trials by GA

Study	24-26 weeks	>26 weeks	Total
IBU/LT/04	56	37	93
IBU/BILICLIN/04	5	29	34
IBU/20mg/2009	12	11	23
IBU/GER/2003	14	1	15
IBU/99/DoseRange	20	20	40
IBU/PROPHYL/2000	27	104	131
IBU/Survey	79	86t	165
Total	**73**	**77**	**150**

Table 31: Estimated cumulative subject exposure to Pedea from clinical trials by gender

Study	Male	Female	Total
IBU/LT/04	61	32	93
IBU/BILICLIN/04	18	16	34
IBU/20mg/2009	13	10	23
IBU/GER/2003	9	6	15
IBU/99/DoseRange	23	20	43
IBU/PROPHYL/2000	65	66	131
IBU/Survey	99	66	165
Total	**92**	**58**	**150**

8.4. Adverse events

8.4.1. All adverse events (irrespective of relationship to study treatment)

8.4.1.1. Main/pivotal studies that assessed safety as sole primary outcome

All AEs were not reported in the study IBU/Survey. The only data provided are the medical events recorded after the start of treatment (which reflects the major clinical complications of prematurity) which were similar between treatments. The table below compares the results of the comparative group with the results for the ibuprofen treated patients treated early and late.

Table 32: Study IBU/Survey: Medical events after start of treatment of PDA – comparative group.

	Ibuprofen		Indomethacin		Day 0-1		Day 2+		All	
	%	N	%	N	%	N	%	N	%	N
Sample size	100	62	100	65	100	54	100	111	100	165
Confirmed infection	38.7	24	24.6	16	35.2	19	34.2	38	34.5	57
Hypotension	1.6	1	0	0	7.4	4	1.8	2	3.6	6
Calculated hypotension										
1st infusion	45.3	24	17.5	17	45.3	24	17.5	17	27.3	41
2nd infusion	16.3	8	14	13	16.3	14	14	13	14.8	21
3rd infusion	11.1	5	9.2	8	11.1	8	9.2	8	9.8	13
Grade III-IV IVH	8.1	5	3.1	2	5.6	9	8.1	9	7.3	12
PVLM	4.8	3	12.3	8	5.6	4	3.6	4	4.2	7
Bowel perforation	1.6	1	0	0	3.7	3	2.7	3	3	5
NEC	6.5	4	4.6	3	7..4	8	7.2	8	7.3	12
Renal failure	8.1	5	4.6	3	5.6	7	6.3	7	6.1	10
Bleeding	3.2	2	3.1	2	1.9	3	2.7	3	2.4	4
Death	17.7	11	9.2	6	25.9	17	15.3	17	18.8	31

8.4.1.2. Pivotal and/or main efficacy studies

Study IBU/PROPHYL/2000 (curative group)

In the first 3 days of life (prior to the first ibuprofen dose) there were 6 AEs reported by 2 patients: renal failure in 1 patient and Grade III IVH, nosocomial infection, pulmonary haemorrhage and pulmonary hypertension and renal failure in 1 patient.

Following treatment (up to Day 21) there were 20 AEs reported in 11 patients.

Table 33: Study IBU/PROPHYL/2000 (curative group): Incidence of main AEs (placebo and curative treatment set).

System Organ Class Preferred Term	All N=25
Nervous System Disorders	4 (16.0%)
Intraventricular Haemorrhage Neonatal	1 (4.0%)
Periventricular Leukomalacia	1 (4.0%)
Other	3 (12.0%)
Infections and Infestations	4 (16.0%)
Gastrointestinal Disorders	3 (12.0%)
Necrotising Enterocolitis Neonatal	1 (4.0%)
Small Intestinal Perforation	1 (4.0%)
Other	2 (8.0%)
Renal and Urinary Disorders	2 (8.0%)
Nephrocalcinosis	1 (4.0%)

System Organ Class Preferred Term	All N=25
Oedema Due to Renal Disease	1 (4.0%)
Oliguria	1 (4.0%)
Respiratory, Thoracic and Mediastinal Disorders	2 (8.0%)
Bronchopulmonary Dysplasia	1 (4.0%)
Hypoxia	1 (4.0%)

Five infants developed a Grade III-IV IVH: 1 patient had IVH detected prior to treatment. It did not aggravate further but the patient later developed PVL with hydrocephalus. Two patients had IVH detected early after the curative treatment (Day 4-7) and 2 patients had IVH detected at later time (Day 8-14 and Day 14-21).

8.4.1.3. Other studies

Other efficacy studies

Study IBU/PROPHYL/2000 – prophylactic group

Overall, 65 AEs in 31 infants (47%) were recorded in the curative group versus 79 AEs in 33 infants (51%) in the prophylactic group. The most frequent AEs were respiratory, neurologic, renal, infectious and gastrointestinal disorders. Except for CNS disorders, they were all slightly more frequent in the prophylactic group than in the curative group.

Table 34: Study IBU/PROPHYL/2000 – prophylactic group: Main AEs

System Organ Class Preferred Term	Curative group N = 66	Prophylactic group N = 65	All N = 131
Any Adverse event	31 (47.0%)	33 (50.8%)	64 (48.9%)
Respiratory, Thoracic and Mediastinal Disorders	9 (13.6%)	19 (29.2%)	28 (21.4%)
Hypoxia	6 (9.1%)	12 (18.5%)	18 (13.7%)
Pulmonary Hypertension Pulmonary Haemorrhage	5 (7.6%)	9 (13.8%)	14 (10.7%)
Other	2 (3.0%)	5 (7.7%)	7 (5.3%)
	5 (7.6%)	3 (4.6%)	8 (6.1%)
Nervous System Disorders Intraventricular	15 (22.7%)	10 (15.4%)	25 (19.1%)
Haemorrhage Neonatal Periventricular Leukomalacia	10 (15.2%)	4 (6.2%)	14 (10.7%)
Other	4 (6.1%)	3 (4.6%)	7 (5.3%)
	3 (4.5%)	3 (4.6%)	6 (4.6%)
Renal and Urinary Disorders	6 (9.1%)	10 (15.4%)	16 (12.2%)
Renal failure	2 (3.0%)	7 (10.8%)	9 (6.9%)
Anuria/Oliguria	2 (3.0%)	3 (4.6%)	5 (3.8%)
Oedema due to renal disease	2 (3.0%)	1 (1.5%)	3 (2.3%)
Other	2 (3.0%)	2 (3.1%)	4 (3.1%)
Infections and Infestations	7 (10.6%)	9 (13.8%)	16 (12.2%)
Gastrointestinal Disorders	6 (9.1%)	8 (12.3%)	14 (10.7%)
Intestinal perforation	1 (1.5%)	5 (7.7%)	6 (4.6%)
Necrotising Enterocolitis Neonatal	2 (3.0%)	5 (7.7%)	7 (5.3%)
Other	4 (6.1%)	2 (3.1%)	6(4.6%)

The incidence of grade I-II IVH was similar in both treatment groups but grade III-IV IVH were twice as frequent in the curative group (23%) as in the prophylactic group (11%) however, the difference did not reach statistical significance (p=0.10).

The number of infants who developed a NEC, whether early or late, was significantly higher in the prophylactic group (17%) than in the curative group (5%) (p=0.025).

There were 3 cases of pulmonary hypertension (PHT) with refractory hypoxaemia which prompted the discontinuation of the trial. A systematic search of this type of AE and of the use of inhaled nitric oxide (NO), a selective vasodilator, was subsequently conducted, regardless of their chronology. Overall, hypoxaemia/PHT was recorded in 24 infants of whom 17 received NO. This appeared to occur more frequently in the prophylactic group but mainly after the treatment period when other causes could be identified.

Table 35: Study IBU/PROPHYL/2000 – prophylactic group: Incidence of hypoxaemia.

	Curative group N=66	Prophylactic group N=65	All N=131	Comparative Test
Use of nitric oxide (NO)	7 (10.6%)	10 (15.4%)	17 (13.0%)	p=0.45
Hypoxaemia and/or PHT	9 (13.6%)	15 (23.1%)	24 (18.3%)	p=0.18
Started				
During Day 1 to 3	6 (9.1%)	7 (10.8%)	13 (9.9%)	
During Day 4 to 7	2 (3.0%)	5 (7.7%)	7 (5.3%)	
After Day 7	1 (1.5%)	3 (4.6%)	4 (3.1%)	

A detailed analysis of these cases, especially the early occurrences identified a number of predisposing factors in most of the cases but it confirmed that the refractory hypoxaemia occurring within 1 hour of the infusion differed from the other cases identified and might indeed by drug related.

Study Long Term FU

Only treatment related AEs were reported.

Study IBU/20mg/2009

Overall 127 AEs were reported (122 TEAE) in 23 patients.

Table 36: Study IBU/20mg/2009: Predefined AEs according to centre

AE Summary	Centres			All patients
	1	2	3	
	N=9	N=12	N=2	N=23
Number of AEs				
1	1 (11.1%)	0	0	1 (4.3%)
2	0	4 (33.3%)	2 (100.0%)	6 (26.1%)
3	2 (22.2%)	2 (16.7%)	0	4 (17.4%)
4	0	2 (16.7%)	0	2 (8.7%)
5	1 (11.1%)	1 (8.3%)	0	2 (8.7%)
6	3 (33.3%)	2 (16.7%)	0	5 (21.7%)
8	1 (11.1%)	1 (8.3%	0	2 (8.7%)
11	1 (11.1%)	0	0	1 (4.3%)
Number of AEs				
N	9	12	2	23
Mean (SD)	5.4 (3.0)	3.9 (2.0)	2.0 (0.0)	4.3 (2.5)
Median	6.0	3.5	2.0	4.0
Range	1 - 11	2 - 8	2 - 2	1 - 11

AE Summary	Centres			All patients
	1	2	3	
	N=9	N=12	N=2	N=23
Anaemia	9 (36.0%)	12 (42.9%)	2 (50.0%)	23 (40.4%)
Hyponatraemia	2 (8.0%)	0	0	3 (5.3%)
Hypoxia	1 (4.0%)	1 (3.6%)	0	4 (7.0%)
Intraventricular haemorrhage	3 12.0%)	3 (10.7%)	0	3 (5.3%)
Necrotising colitis	1 (4.0%)	0	0	1 (1.8%)
Oliguria	1 (4.0%)	0	0	2 (3.5%)
Pulmonary hypertension	0	1 (3.6%)	0	2 (3.5%)
Renal failure	1 (4.0%)	2 (7.1%)	1 (25.0%)	2 (3.5%)
Retinopathy of prematurity	1 (4.0%)	0	0	1 (1.8%)
Sepsis	5 (20.0%)	0	1 (25.0%)	12 (21.1%)
Thrombocytopenia	1 (4.0%)	6 (21.4%)	0	4 (7.0%)
		3 (10.7%)		

Studies with evaluable safety data: dose finding and pharmacology studies

Study IBU/DoseRange (-27 weeks)

There were 12 AEs reported in 8/22 patients, half of them suggesting an effect of ibuprofen on renal function.

Table 37: Study IBU/DoseRange (-27 weeks) AEs according to the dose regimen

Initial ibuprofen dose (mg/kg)	5 (n=7)	10 (n=7)	15 (n=6)	20 (n=2)	T	Relation to treatment
Total number of infants presenting an AE	1	5	2	0	8	
Total number of AEs	2	7	3	0	12	
RENAL & URINARY DISORDERS						
Excessive weight gain		5				Probable
Oliguria		1				Probable
GASTROINTESTINAL DISORDERS						
Enteropathy		1				Possible
Glucose intolerance			1			Not related
NERVOUS SYSTEM DISORDERS						
Intraventricular haemorrhage	1					Not related
INFECTIONS & INFESTATIONS						
Infection			1			Not related
RESPIRATORY, THORACIC & MEDIASTINAL						
Pulmonary interstitial emphysema						
Pulmonary haemorrhage	1		1			Not related

AEs affecting the renal system were only reported in the 10 mg/kg group. Excessive weight gain was initially defined as >20 g/kg/day body weight but was later increased to more than 30 g/kg/day. These AEs were reported as mild to moderate and were reported on the 2nd day of treatment in 2 cases, on the 3rd day in 1 case and after the end of the treatment course in 2 cases.

Study IBU/DoseRange (+27 weeks)

There were 19 AEs reported in 14/21 newborns, most of them suggesting an effect of ibuprofen on renal function.

Table 38: Study IBU/DoseRange (+27 weeks) AEs according to the dose regimen.

Initial ibuprofen dose (mg/kg)	5 (n=2)	10 (n=8)	15 (n=11)	Relation to treatment
Total number of infants	2	5	7	14
Total number of AEs	3	5	11	19
RENAL & URINARY DISORDERs				
Excessive weight gain		2	5	Probable
Oliguria			2	Probable
GASTROINTESTINAL DISORDERS				
Gastric bleeding		1		Probable
NERVOUS SYSTEM DISORDERS				
Intraventricular haemorrhage (neonatal)	1	1	1	Possible
HEPATOBILIARY DISORDERS				
Jaundice (neonatal)		1	3	Not Related
INFECTIONS & INFESTATIONS				
Septicaemia	1			Not Related
RESPIRATORY, THORACIC & MEDIASTINAL DISORDERS				
Apnoea & bradycardia	1			Not Related

AEs affecting the renal system were more common in the 15 mg/kg group (6/11 patients) than in the 10 mg/kg group (2/8 patients). Excessive weight gain was initially defined as >20 g/kg/day body weight but was later increased to more than 30 g/kg/day. The AEs were rated as mild to moderate and were usually reported on the 2nd day of treatment.

AEs reported in the pharmacology studies are provided. No clinically significant safety issues were identified in the studies in heathy adult volunteers.

8.4.2. Treatment related adverse events (adverse drug reactions)

Only AEs were reported in most of the studies. The relationship of AE to drug was not recorded. It is stated on 1 CSR that:

> *The judgment of the relation to drug was not taken into account since the potential complications of PDA and those of the pharmacological intervention with NSAIDs are well known to be similar (oliguria, NEC, IVH, PVLM).*

8.4.2.1. Study IBU/LT/2004

The incidence of AEs considered related to COX-inhibitors was significantly higher in the indomethacin group compared with the ibuprofen group (37.1% vs 18.3%, p=0.005). Details of the AEs reported (defined as an event complicating the patient's clinical course that occurred within 3 days after the end of the COX inhibitor treatment) are not provided.

The Survey reports on the known complications of prematurity.

Table 39: Study IBU/LT/2004: Proportions of patients with significant morbidity of prematurity.

	Indomethacin		Ibuprofen		all		p value
	n/N	%	n/N	%	n/N	%	
IVH Grade 3 or more	10/89	11.2	9/93	9.7	19/182	10.4	0.811
Cystic PVL	7/78	9.0	5/82	6.1	12/160	7.5	0.558
Renal failure (creatinine ≥ 1.5 mg/dL)	5/89	5.6	4/93	4.3	9/182	4.9	4.9
Oliguria*	3/88	3.4	1/93	1.1	4/181	2.2	0.357
Pulmonary haemorrhage	1/89	1.1	4/93	4.3	5/182	2.7	0.369
Refractory Hypoxaemia with PPHN	3/89	3.4	6/93	6.5	9/182	4.9	0.498
NEC Grade 2b or more	4/89	4.5	5/93	5.4	9/182	4.9	1.000
Gastrointestinal perforation**	7/89	7.9	7/93	7.5	14/182	7.7	NT
Retinopathy of prematurity Grade 2 or more	7/78	9.0	6/81	7.4	13/159	8.2	0.778

* Oliguria was defined as a diuresis lower than 1 mL/kg/hr over at least 12 hours – recorded during the time span from birth until 1 day after the end of COX-inhibitor treatment; ** 3 patients in the indomethacin group and 1 in the ibuprofen group had a GI perforation during an episode of NEC Therefore these 4 patients are not reflecting separate gastrointestinal perforation; NT = not tested

8.4.2.2. IBU/20mg/2009

In this most recent study, treatment related AEs are reported briefly as "Twenty two infants out of 23 (96%) presented a total of 57 drug related AE (Table 14.3.3.1S)." No further details are provided.

> *Comment: This table could not be located in the CSR or appendices included in the submission despite manual searching as the CSR is not indexed electronically and there was no hyperlink on the table reference. The sponsor should indicate the location of the table and if the relevant appendix was not provided in the submission it should be provided. A table is provided of the Severe SAEs which were considered treatment related (again the Table referenced could not be located).*

Table 40: Study IBU/20mg/2009: Severe treatment related SAEs.

SOC Preferred Term	Safety population N=23
Gastrointestinal disorders Meconium Ileus	1 (4.3%) 1 (4.3%)
Infections and infestations Sepsis	1 (4.3%) 1 (4.3%)
Nervous system disorders Intraventricular haemorrhage	1 (4.3%) 1 (4.3%)
Respiratory, thoracic and mediastinal disorders Apnoea Hypoxia Pulmonary hypertension	3 (13.0%) 1 (4.3%) 2 (8.7%) 1 (4.3%)

8.4.3. Deaths and other serious adverse events

8.4.3.1. Main/pivotal studies that assessed safety as sole primary outcome

In the IBU/Survey, the mortality was higher in the early treatment group (25.9%) than in the late group (15.3%). Half the deaths (7/14) occurred within the first 4 days of treatment initiation in the early treatment group, confirming that these were more severe patients (by comparison 4/17 patients died within the first 4 days in the late treatment group).

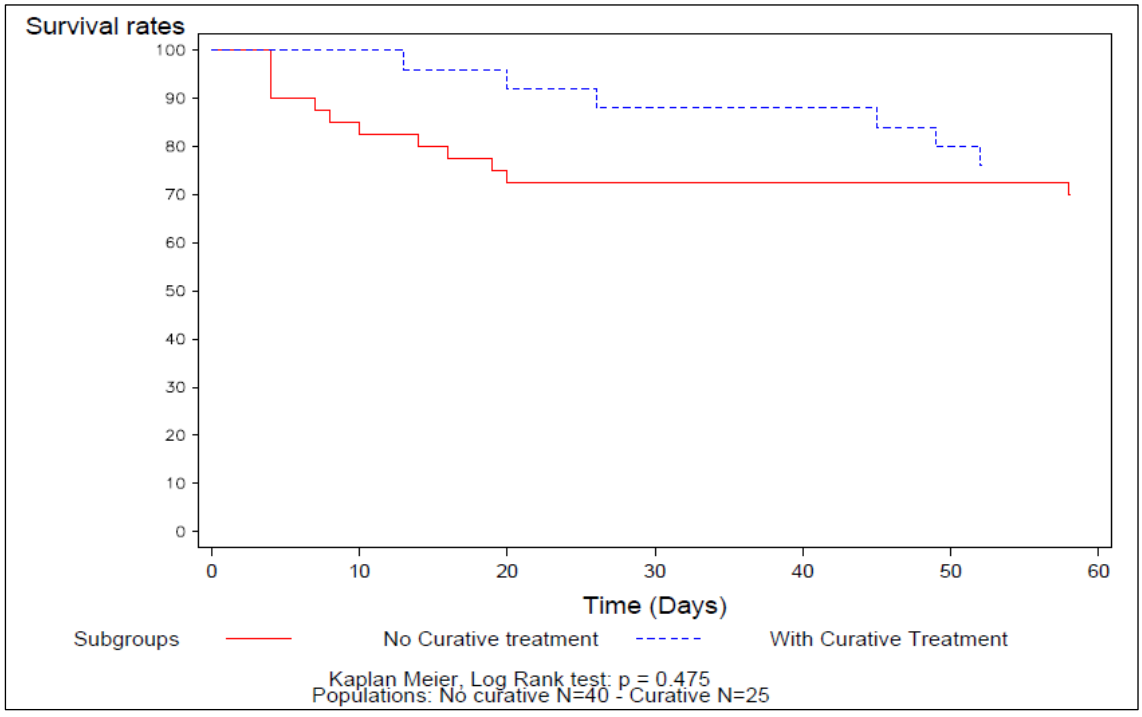
Mortality was higher in the ibuprofen group (17.7%) than in the indomethacin group (9.2%). Ibuprofen patients died in 7/11 cases within the first week of initiation of treatment, confirming the observation that they were more severely ill patients (as 2/6 patients died within that period in the indomethacin group).

8.4.3.2. Pivotal and/or main efficacy studies

Study IBU/PROPHYL/2000 (curative group)

Six patients died before 36 weeks of PCA. The details of the deaths are not provided in the CSR. The survival curve for all infants is presented in the following figure. On the same figure, the survival curve for the 40 newborn from the same trial arm that did not receive ibuprofen (because they had no PDA) and were alive on day 3 has also been presented. Although mortality appeared higher in the latter group during the first weeks, in the long term, survival was similar in both groups.

Figure 7: Study IBU/PROPHYL/2000 (curative group): Survival Curve.



8.4.3.3. Other studies

Other efficacy studies

Study IBU/PROPHYL/2000 – prophylactic group

Overall, 37 infants died before 36 weeks of PCA: 19 (29%) in the curative group and 18 (28%) in the prophylactic group, which showed that survival was very similar with both therapeutic approaches. Causes of death were often multiple and very similar in both groups.

Table 41: Study IBU/PROPHYL/2000 – prophylactic group: Causes of deaths.

	Curative group N = 66	Prophylactic group N = 65
Number of deaths	19 (28.8%)	18 (27.7%)
Respiratory	8	9
CNS	9	8
Sepsis	4	3
Renal	2	3
Digestive	2	3
Cardiac	2	1

Study Long Term FU

Overall there were 10 (11.2%) deaths in indomethacin group and 11 (11.8%) in ibuprofen group. No further details are provided.

Study IBU/20mg/2009

Three deaths were reported during the study:

- 1 patient (GA 25 weeks) who received a full course of ibuprofen developed a Grade 4 IVH on 9 days after drug treatment began and 15 days after drug treatment began the patient experienced refractory hypoxaemia. The patient died the next day from severe respiratory insufficiency with refractory hypoxia. Causality was considered "unknown".
- 1 patient (GA 24 weeks) who received a full course of ibuprofen (20/10/10) plus a second course of lower dose (10/5/5) had persistence of a large PDA 3 weeks later. Two months later the patient died of multi-organ failure with severe hypoxaemia. Autopsy identified closure of the ductus arteriosus and death most likely due to hepatic overload with autolytic suppression due to intra-hepatic cholestasis.
- 1 patient (GA 25 weeks) experienced non-serious arterial pulmonary hypertension (with respiratory aggravation, increased FiO^2 to 50%, SaO_2=82%) 3 hours after the 2nd dose of study drug. The patient received the 3rd dose without any recurrence of the event. On the same day the patient experienced pulmonary emphysema. The patient received a second course of ibuprofen 3 days later for PDA but after the second dose experienced isosystemic/suprasystemic arterial pulmonary hypertension (with FiO_2=50% and SaO_2=90%). The patient did not receive the 3rd dose of study drug and received inhaled nitric oxide (10 ppm) as corrective treatment but died the next day due to pulmonary emphysema and arterial pulmonary hypertension.

Studies with evaluable safety data: dose finding and pharmacology

Study IBU/DoseRange (-27 weeks)

Two patients died during the study:

- 1 patient presented Grade 4 IVH and pulmonary interstitial emphysema after 2nd dose of ibuprofen. The PDA remained even after IV indomethacin which led to haemodynamic impairment and eventually to death. Study drug was discontinued after the first maintenance dose
- 1 patient developed severe infection 4 days after the ibuprofen course which eventually led to death at Day 9, and was considered unrelated to study drug.

Study IBU/DoseRange (+27 weeks)

Only 1 patient died during the trial period – of severe uncontrolled septicaemia with anuria and thrombocytopenia. The death occurred the day after the 1st ibuprofen infusion and was considered unrelated to the study drug.

Other SAEs

In the context of the patient population in most of the studies all AEs were considered serious.

8.4.4. Discontinuations due to adverse events

Discontinuations due to AEs are not discussed in the CSRs or summaries.

Comment: The sponsor should provide a comment on why this was not included.

8.5. Evaluation of issues with possible regulatory impact

8.5.1. Liver function and liver toxicity

Two studies were conducted which investigated the effect of ibuprofen on bilirubin (IBU/BILICLIN/04 and IBU/20mg/2009).

Ibuprofen was not found to lead to significant worsening of the level of unbound bilirubin.

Liver function was not reported in all the efficacy studies. Where recorded it was generally only measured at inclusion and at end of treatment. No clinically significant changes were reported as potentially due to ibuprofen and particularly none reported increased bilirubin displacement from albumin.

8.5.2. Renal function and renal toxicity

8.5.2.1. Main/pivotal studies that assessed safety as the sole primary outcome

IBU/Survey

The median body weight gain from Day 0 to Day 2 was higher in the indomethacin group (+47.9 g/kg BW vs +25.6 g/kg BW). Therefore, it is obvious that ibuprofen administration was not associated with significant water retention in preterm infants while indomethacin induced marked water retention.

The clinical significance of this water retention was shown by lower sodium serum concentrations in the indomethacin group on Day 2 and increased incidence of severe hyponatremia on Day 2 (28.8% vs 6.8%). Serum potassium concentrations were stable and hyperkalaemia was infrequent in both groups. Diuretic administration was similar in both groups.

Changes were not different between groups for: urine water excretion, water intake, output/input ratio. However, oliguria was more frequently observed on Day 1 and 2 in the indomethacin group (24.2% vs 0% and 18.2% vs 0%).

Table 42: Evolution of renal clinical parameters

	Ibuprofen				**Indomethacin**			
	Median Range N				**Median Range N**			
Day	-1	0	1	2	-1	0	1	2
Weight (g)	977.5 550-2290 44	905 595-2270 41	962.5 610-2250 46	943 646-2180 46	970 560-2960 46	1050 550-2960 47	1005 450-2700 58	1095 590-2740 53

	Ibuprofen				Indomethacin			
	Median Range N				Median Range N			
Urine output (ml/kg/h)	3.5 0.3-11.5 42	3.9 0.5-9.3 43	3.1 1.4-11.1 48	3.1 1.1-12 46	2.9 1.1-8.4 30	2.5 0.3-6.3 38	2 0-5.7 43	2.3 0.5-6.7 44
Water out/input ratio	0.6 0-2 37	0.6 0.2-3.2 40	0.5 0.1-3 43	0.6 0.2-1.3 43	0.7 0.2-2.9 28	0.6 0-1.3 36	0.4 0-1.4 39	0.5 0.1-2.3 39

8.5.2.2. Pivotal and/or main efficacy studies

Study IBU/PROPHYL/2000 curative group

During ibuprofen treatment none of the patients presented an abnormal daily creatinine increase. In only 1 infant a transient increase in creatinine was seen (from 38 up to 82 µmol/L) 1 week after the first injection of ibuprofen. No other clinical significantly changes were reported during the study.

8.5.2.3. Other studies

Other efficacy studies

Study IBU/PROPHYL/2000 prophylactic group

Daily increases in creatinine indicative of renal failure were more frequent in the prophylactic group as shown in table below.

Table 43: Study IBU/PROPHYL/2000 prophylactic group - Incidence of creatinine increase

	Curative group N=66	Prophylactic group N=65	All N=131	Comparative Test
Period D1-3	N = 48 3 (6.3%)	N = 51 10 (19.6%)	N = 99 13 (13.1%)	p=0.073
Period D4-7	N = 40 2 (5.0%)	N = 41 10 (24.4%)	N = 81 12 (14.8%)	p=0.026

The overall conclusion was that slight transient renal impairment was indicated by a tendency towards less weight loss but above all by significant decrease in urine output and serum sodium, which did not persist after the end of treatment. Overall, the incidence of renal effects as defined by a renal AE reported by the investigator and/or urine output < 1 mL/kg/h and/or daily increase in creatinine > 45µmol/L and/or administration of a diuretic and/or serum sodium < 130mmol/L was 51% (33/65) for ibuprofen versus 32% (21/66) for the placebo (p=0.034).

Table 44: Study IBU/PROPHYL/2000 prophylactic group – Renal parameters during the first 3 days

Follow Up During the First 3 Days	Placebo N=66	Ibuprofen N=65	All N=131	Test
Sodium (mmol/L)				
At day 1				T-test p=0.054 Wilcoxon p=0.125
N	59	61	120	
Mean (SD)	137.1 (3.40)	135.9 (3.26)	136.5 (3.37)	
Min	127.0	126.0	126.0	

Follow Up During the First 3 Days	Placebo N=66	Ibuprofen N=65	All N=131	Test
Median	137.0	136.0	136.0	
Max	144.0	142.0	144.0	
At day 2				
N	58	57	115	T-test p=0.003 Wilcoxon p=0.004
Mean (SD)	138.1 (5.58)	134.9 (5.78)	136.5 (5.88)	
Min	122.0	115.0	115.0	
Median	137.0	135.0	136.0	
Max	151.0	147.0	151.0	
At day 3				
N	60	57	117	T-test p=0.003 Wilcoxon p=0.007
Mean (SD)	142.4 (6.54)	139.0 (5.60)	140.7 (6.32)	
Min	130.0	125.0	125.0	
Median	142.0	138.0	141.0	
Max	161.0	149.0	161.0	
Creatinine (µmol/L)				
At day 1				
N	53	59	112	T-test p=0.752 Wilcoxon p=0.757
Mean (SD)	63.4 (16.64)	64.6 (21.55)	64.0 (19.31)	
Min	37.0	21.0	21.0	
Median	65.0	63.0	63.5	
Max	112.0	155.0	155.0	
At day 2				
N	48	52	100	T-test p=0.140 Wilcoxon p=0.245
Mean (SD)	87.3 (19.40	93.9 (24.50)	90.8 (22.33)	
Min	40.0	46.0	40.0	
Median	84.0	88.5	87.0	
Max	139.0	154.0	154.0	
At day 3				
N	57	54	111	T-test p=0.005 Wilcoxon p=0.009
Mean (SD)	92.4 (20.47)	104.9 (25.23)	98.5 (23.64)	
Min	50.0	58.0	50.0	
Median	90.0	100.0	95.0	
Max	159.0	183.0	183.0	

1 Patient excluded

Study Long Term FU

Five patients treated with indomethacin (5.6%) developed an episode of acute renal failure as defined by a creatinine above 1.5 mg/dL, from the 9th to the 16th day of life, compared with 4 patients who received ibuprofen (4.3%) which occurred in the first 4 days of life.

Table 45: Study IBU/Long Term FU: Incidence of renal failure

prob. Fisher (without missing data) = 0.7431		Indomethacin		Ibuprofen		All	
		N	%	N	%	N	%
Non Missing	No	84	94.4	89	95.7	173	95.1
	Yes	5	5.6	4	4.3	9	4.9
	All	89	100.0	93	100.0	182	100.0

Only 1 ibuprofen treated patient reported with oliguria (defined as a diuresis lower than 1 mL/kg/h) over at least 12 h – recorded during the time span from birth until 1 day after the end of treatment versus 3 patients who received indomethacin. In either group, no patient with oliguria also reported an episode of renal failure.

Table 46: Study IBU/Long Term FU: Incidence of oliguria

prob. Fisher (without missing data) = 0.3574		Indomethacin		Ibuprofen		All	
		N	%	N	%	N	%
Missing		1	100.0		-	1	100.0
	All	1	100.0		-	1	100.0
Non Missing	No	85	96.6	92	98.9	177	97.8
	Yes	3	3.4	1	1.1	4	2.2
	All	88	100.0	93	100.0	182	100.0

IBU/20mg/2009

Renal function and homeostasis was assessed by measuring the following parameters daily – weight, fluid intake, urinary output, creatinine, sodium and potassium levels. No consistent, clinically significantly changes were found during the study.

Studies with evaluable safety data: dose finding and pharmacology

IBU/99/DoseRange (-27 weeks)

No major effect on renal function was reported but further data analysis showed changes suggesting mild to moderate changes (excessive weight gain and oliguria) usually associated with slight variations on natraemia and creatininaemia. These effects were more frequent at the 10 mg/kg dose regimen.

Table 47: Study IBU/99/DoseRange (-27 weeks): Effects on renal function

Initial ibuprofen dose (mg/kg)	5 (n=7)	10 (n=8)	15 (n=11)	20 (n=2)
Reported AEs				
Oliguria	0	5	0	0
Weight gain	0	1	0	0
Total patients	0	5 (71%)	0	0
Calculated daily weight gain > 30g/kg				
Total patients	3 (43%)	7(100%)	4(66%)	2 (100%)
24-hour urine output				
< 1.0 ml/kg/h	0	0	0	0
≤ 1.4 ml/kg/h	1 (14%)	0	1 (17%)	0
Slight changes in Na and/or creatinine*				
Total patients	3 (43%)	6 (85%)	3 (50%)	1 (50%)
Overall				
Total patients	4 (57%)	7 (100%)	5 (83%)	2 (100%)

* Na decrease > -10 meq/L or creat increase > 10 mmol/L or Na <130 meq/L or creat > 140 mmol/L

IBU/99/DoseRange (+27 weeks)

No major effect on renal function was reported but further data analysis showed changes suggesting mild to moderate changes (excessive weight gain and oliguria) usually associated

with slight variations on natraemia and creatininaemia. These effects were more frequent at the highest dose regimen.

Table 48: Study IBU/99/DoseRange (+27 weeks): Effects on renal function

Initial ibuprofen dose (mg/kg)	10 (n=8)	15 (n=11)
Reported AEs		
Oliguria	2	5
Weight gain		2
Total patients	2 (25%)	6 (55%)
Calculated daily weight gain > 30g/kg		
Total patients	4 (50%)	6 (55%)
24-hour urine output		
< 1.0 ml/kg/h	0	0
≤ 1.4 ml/kg/h	1 (12%)	4 (36%)
Slight changes in Na and/or creatinine		
Total patients	2 (25%)	6 (55%)
Overall		
Total patients	5 (62%)	9 (82%)

8.5.3. Other clinical chemistry

8.5.3.1. Glucose

Study IBU/99/DoseRange (+27)

Since the Pedea ibuprofen solution contains trometamol, an alkalinising agent which may induce hypoglycaemia at high doses, blood glucose and pH were measured before and 30 minutes after the loading dose. Median blood glucose decreased from 5.5 to 5.1 mmol/L (in 15 patients with available data) but without apparent dose relationship. Median blood pH did not change (in 11 patients with available data).

Study IBU/20mg/2009

All patients remained within a range of 3.5 mmol/L and 11.6 mmol/L, which corresponds to acceptable ranges for preterm newborns.

8.5.4. Haematology and haematological toxicity

In most of the studies haematology parameters were measured at inclusion and at end of treatment. No consistent, clinically significant changes were found in any of the studies.

8.5.5. Vital signs and clinical examination findings

Overall, no consistent clinical relevant changes in vital signs and physical examination were found that could be related to ibuprofen. Not all CSRs report on the individual parameters.

8.5.5.1. Study IBU/99/DoseRange

Blood pressure and heart rate

Blood pressure measurements were not standardised with regard to the ibuprofen infusions.

In the -27 week group, analysis of the measurements taken indicated that patients in the 15 and 20 mg/kg groups had initially higher BP values, which is consistent with a better clinical condition as suggested by their ventilation requirements. Slight increases in both systolic and diastolic BP as well as in mean BP were recorded over the treatment period in all dose level groups, which is consistent with an improvement of the haemodynamic conditions.

In the +27 week group, patients from the 15 mg/kg group had initially higher BP values, which is consistent with a better clinical condition as suggested by their ventilation requirements. A

slight and transient BP increase was recorded over the treatment days in this group. In patients from the 10 mg/kg group BP values rose only after the treatment days and eventually reached the levels of the other group. Whether the trend observed in the highest dose level group indicates a pharmacological effect of the drug is difficult to establish in such a small sample.

Variations in heart rate however remain difficult to interpret, because of often single value per patient and time point: nevertheless these variations tended to decrease which was consistent with the improvement in the patients' haemodynamic conditions.

Cerebral Echo-Doppler assessment

Cerebral Echo-Doppler was performed before and 3 h after the loading dose of ibuprofen in order to evaluate any potential deleterious effect of the drug on cerebral blood flow. Velocities in the anterior or mean cerebral artery showed only minor changes regardless of the dose.

8.6. Other safety issues

8.6.1. Safety in special populations

No studies submitted

8.6.2. Safety related to drug-drug interactions and other interactions

No studies submitted.

8.6.3. Long Term Safety

The Long Term FU survey reported on some long term follow up conducted at discharge from hospital and at 24 months.

8.6.3.1. Neuromotor development at 2 years

The proportions of patients who developed cerebral palsy (CP) was similar with both treatments (12.5% of indomethacin treated and 10% in ibuprofen treated infants) and the detail of the abnormalities (topography of the palsy) was also similar. The results suggest that a HsPDA or its treatment did not constitute independent predictive factors of cerebral palsy.

Table 49: Study Long Term FU: Incidence and topography of cerebral palsy.

prob. Fisher (without missing data) = 1.0000		Indomethacin		Ibuprofen		All	
		N	%	N	%	N	%
Missing		6	35.3	12	52.2	18	45.0
	Death	11	64.7	11	47.8	22	55.0
	All	17	100.0	23	100.0	126	100.0
Non-missing	None	63	87.5	63	90.0	126	88.7
	Hemiparesis/hemiplegia with unilateral impairment of arm and leg on the same side.			1	1.4	1	0.7
	Diplegia with primarily motor impairment of the legs and usually with some relatively limited involvement of the arms	5	6.9	4	5.7	9	6.3
	Triplegia with 3 limb involvement	1	1.4			1	0.7
	Quadriplegia/tetraplegia with involvement of all four limbs and functional compromise of the whole body	3	4.2	2	2.9	5	3.5
	All	72	100.0	70	100.0	142	100.0

A predictive index, the early motor pattern profile (EMPP) at the age of 12 months was evaluated as the risk assessment for the later development of CP was similar in both patient populations.

The Griffith score for neurodevelopment (corrected age of 20 months) was not statistically different between the treatment groups (p=443).

Neuorsensory assessment at 2 years did not show any statistical difference between the treatment groups for hearing loss.

Retinopathy of prematurity (ROP) occurred in 42.8% of indomethacin treated infants versus 19.7% of ibuprofen treated infants (p=0005). The proportion of patients who presented with retinopathy graded more than 2 were 9.0% (indomethacin) and 7.4% (ibuprofen). One patient in each treatment group subsequently developed blindness. The ibuprofen treated patient had received cryotherapy for a bilateral ROP grade 3. The indomethacin treated patient presented with a right sided vitreous haemorrhage and a left sided retinal detachment during the primary hospital stay. Both events were not associated with ROP but with bilateral hypoplasia of the optic nerve and visual evoked potentials (VEP) showing bilateral latency delay.

Table 50: Study Long Term FU: Proportion of patients with significant neurosensory impairments.

	Group				All		
	Indomethacin		Ibuprofen				
	n/N	%	n/N	%	n/N	%	p-value
Bayley score < 70	not assessed		12/49	24.5	12/49	24.5	no test
Griffith score < 88	30/78	38.5	20/43	46.5	50/12	41.3	0.443
Development of blindness	1/76	1.3	1/80	1.3	2/156	1.3	0.734
Need for hearing amplification	0/76	0.0	2/80	2.5	2/156	1.3	0.497
Absence of free-walking at the age of 24 months	5/75	6.7	4/79	5.1	9/154	5.8	0.741

8.6.3.2. Respiratory follow up

The generally accepted definition of bronchopulmonary dysplasia is the need for supplemental oxygen at 36 weeks of GA. There was no statistically significant difference between treatment groups (34.5% ibuprofen vs 37.8% indomethacin, p=0.75). It was also found that the frequency of complete antenatal steroid application (62 patients in both groups) and surfactant therapy for severe respiratory distress syndrome (73% indomethacin and 72% ibuprofen) did not differ between the 2 groups. Similar numbers of infants were under CPAP or PPV in the 2 treatment groups at a chronological age of 36 weeks.

Persistent pulmonary hypertension of the newborn (PPHN) was reported for 3 patients in the indomethacin and 6 patients in the ibuprofen group, 1 and 3 of whom received nitric oxide treatment. It was noted however, that these episodes of PPHN occurred either before any COX inhibitor for the 3 other patients and therefore was not related to the PDA intervention.

In the long term, more than 30% of surviving patients in either population had to be re-hospitalised because of respiratory diseases during the first 24 months after the initial hospital discharge. The number and duration of the hospital admissions were similar for patients who received indomethacin and ibuprofen.

8.7. Post marketing experience

Comment: The post marketing section of the Summary of Clinical Safety includes a summary of the 9 PSURS which have been submitted in Europe with no integration of the data or overall summary as each PSUR is reported separately.

Pedea was granted marketing authorisation in the EU on 29 July 2004.

8.7.1. Patient exposure

See Table 51.

Table 51: Patient exposure.

PSUR Reporting period	No of boxes	Cumulative total boxes	Cumulative total patients
29/07/2004 to 29/01/2005	2,300		2,300
30/01/2005 to 29/07/2005	2,500	4,500	3,900
30/07/2005 to 29/01/2006	2,900	7,100	5,600
30/01/2006 to 29/07/2006	3,500	10,600	8,400
30/07/2006 to 29/07/2007	7,900	19,100	15,200
30/07/2007 to 29/07/2008	8,600	26,700	21,300
30/07/2008 to 29/07/2008 addendum	2,800	29,500	23,600
30/07/2008 to 29/07/2011	39,784 (patients)		63,147
30/07/2011 to 29/07/2014	42,027	115,195	

1 box ~ 1 treatment course

Overall, the most commonly reported spontaneous AEs appear to be gastrointestinal disorders (in each report they contribute 23 to 59% of all reports) and renal disorders.

Based on the PSUR data (and post marketing studies) the sponsor has made the following changes to the SmPC in Europe:

- In 2005 (PSUR #3), the SmPC was updated to include details of potential interactions with antiseptics or disinfectants and with aminoglycosides. The following statements was added:

  Chlorhexidine must not be used to disinfect the neck of the ampoule as it is not compatible with the Pedea solution. Therefore, for asepsis of the ampoule before use, ethanol 60% or isopropyl alcohol 70% is recommended. When disinfecting the neck of the ampoule with an antiseptic, to avoid any interaction with the Pedea solution, the ampoule must be completely dry before it is opened.

- In section 4.4 of the SPC (special warning and precautions for use):

  As ibuprofen may decrease the clearance of aminoglycosides, strict surveillance of their serum levels is recommended during co-administration with ibuprofen.

- In section 4.5 (Interactions) of the SPC:

  Aminoglycosides: since ibuprofen may decrease the clearance of aminoglycosides, their co-administration may increase the risk of nephrotoxicity and ototoxicity

- In 2006 (PSUR #4), acute renal failure was added to Section 4.8 Undesirable effects

- In 2012 (PSUR #8), the post marketing cases of pulmonary hypertension were added to Section 4.4

8.8. Evaluator's overall conclusions on clinical safety

The Australian submission comprised substantially less safety data than the EU MAA submission as it comprised the limited clinical studies and did not include the literature (published studies) which was submitted in Europe. This limited the evaluable safety data. Additionally, the Summary of Clinical Safety was particularly poorly written and did not include a full assessment of the data in the submission.

A substantial amount of data comprises comparison of ibuprofen versus indomethacin but no direct comparative studies are provided except as part of the Long Term FU study, however, this survey is not conclusive due to the retrospective and non-formal study design, small sample size, and the sequential nature of the treatment cohorts (indomethacin followed by ibuprofen).

The Summary of Clinical Safety focusses on renal, digestive and neurological side effects to support claims of better tolerance than indomethacin. However, in the absence of comparative data, the claims are based solely on retrospective data and hence not very convincing.

In the context of the clinical presentation of PDA in very preterm infants, it is difficult to separate the AEs which could be due to the drug and the consequences of prematurity and PDA, all of which lead to significant mortality and morbidity. With these reservations, the data collected in the studies does comprise a reasonable number of patients all treated in highly monitored, specialised neonatal intensive care units.

In many of the studies there was not a standardised measurement of safety parameters but the sponsor has collected the measurements taken. This is acceptable given the patient population but unfortunately there is very poor presentation and analysis of the data and little in the way of discussion.

In both clinical studies and post marketing data, the main AEs appear to be related to the known complications of prematurity, particularly IVH and gastrointestinal events (NEC, intestinal or gastric perforation) and renal disorders.

The issue of refractory hypoxaemia which led to premature termination of the study IBU/PROPHYL/2000 appears to be isolated and related to the use of ibuprofen as a prophylactic treatment. This is not being sought as an indication and indeed the proposed PI contains an appropriate warning that the product should not be used prophylactically within 6 hours of birth without confirmation of the PDA.

The most commonly reported AEs in the clinical studies and in the post marketing reports were consistently renal and gastrointestinal.

No new safety issues appear to have arisen during the 11 years of marketing experience in Europe.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

See Table 52.

Table 52: First round assessment of benefits.

Indication: Treatment of PDA	
Benefits	**Strengths and Uncertainties**
Treatment with ibuprofen in dose regimen of 10-5-5 mg leads to closure of PDA in about 50-80% of preterm infants with GA <32 weeks	Strength is placebo controlled trials Uncertainties are small numbers, poor trial design (uncontrolled trials) and use of surveys. Uncertainty is variable results reported in different trials and surveys Uncertainty is also lack of prospective comparative trial with indomethacin (current approved) Uncertainty also by complications of

Indication: Treatment of PDA	
Benefits	**Strengths and Uncertainties**
	comorbidity and know complications of prematurity of all patients.

9.2. First round assessment of risks

See Table 53.

Table 53: First round assessment of risks.

Risks	Strengths and Uncertainties
AEs related to renal function, that is, excessive weight gain, oliguria and increased creatinine	Most studies consistently found minor and transient changes in renal function.
Gastrointestinal AEs	Most common AEs in trials and post marketing. Unproven if related to ibuprofen or not as it is common complication of prematurity.
Refractory pulmonary hypoxaemia	3 isolated cases led to premature termination of study of prophylactic use and there have also been cases reported post marketing. Causal link has not been proven or disproven

9.3. First round assessment of benefit-risk balance

The submission is less than ideal and is disappointing in that it did not include the literature component submitted in Europe. The efficacy is therefore based on a limited number of patients and treatment regimens that were not primarily investigating the treatment as requested in the proposed indication (eg prophylactic treatment during the first day vs curative treatment after the first 6 days). However, in the studies submitted the outcomes were consistently positive although variable in the different studies. Overall, Pedea did lead to closure of the PDA in the majority of cases. No studies comparing Pedea to the currently accepted treatment of indomethacin were submitted. The retrospective survey indicated that the efficacy is possibly comparable but no conclusive statement can be made.

The safety of the product is based on a reasonable number of patients and supported by 10 years of post-marketing data and does not indicate any significant safety issues, especially given the use of the product in highly monitored environment of a NICU.

Therefore despite reservations about the quality of the submission and the uncertainties of the clinical data submitted, based on the clinical data submitted in Module 2 and 5 the benefit-risk balance of Pedea for the proposed usage is favourable.

10. First round recommendation regarding authorisation

Based on the clinical data provided in the submission, approval of Pedea is recommended but it is recommended that the proposed indication should be slightly amended.

The sponsor has requested treatment of babies less than 32 weeks however in all the efficacy clinical trials the data is for premature patients less than 29 weeks. In the 2 surveys (IBU/Survey and Long Term FFU there were only a few (unstated) infants in the range >29 weeks. However, the decisive feature is the haemodynamically significant PDA rather than the GA and therefore it may be acceptable to raise the GA to 34 weeks but it would need to be emphasised that the treatment should be under the supervision of a specialist neonatologist

(this would allow for treatment not in a NICU). This should be included in the Pedea PI also to ensure that there is no inference of comparative safety of Pedea vs indomethacin based on not having this statement in the PI.

It is noted that the approved PI for indomethacin in Australia includes the types of clinical evidence required (respiratory distress, a continuous murmur, hyperactive precordium, cardiomegaly and pulmonary plethora on chest ex-ray). In the clinical trials submitted, haemodynamically significant PDA was defined by functional blood flow or echocardiographic features rather than clinical features. If this is defined in the clinical trials section, then it may not be necessary to include clinical features in the indication.

It is therefore recommended that the indication be slightly modified to be:

Pedea is indicated for the treatment of haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age. Pedea should only be used in a hospital under the supervision of a specialist neonatologist.

11. Clinical questions

11.1. Pharmacokinetics

1. Please correct the sentence in the Summary of Clinical Pharmacology and Clinical Expert Report. Please explain the significance of study 9-33/93 and why it was included in the submission

11.2. Safety

2. Please identify where Table 14.3.3.1S and Table 14.3.3.9S are located in the submission. If not included please provide.
3. Please provide comment on why discontinuations due to AEs were not included.

12. Second round evaluation of clinical data submitted

The sponsor provided responses to the clinical questions asked and provided a revised PI and CMI.

12.1. Question 1

Please correct the sentence in the Summary of Clinical Pharmacology and Clinical Expert Report.

12.1.1. Evaluation of response

The sponsor has responded to the wrong comment. They have responded to the comment on Page 26 (Section 4.2.2). This was not an issue as is stated in the comment. While the old bioequivalence limits were set for the study the results of Study IBU/00/BIOEQ/FR-P000241 met the current bioequivalence criteria.

The question raised related to the comment on Page 25 (Section 4.2) relating to Study 9-33/93 and the incomplete sentence in both the *Summary of Clinical Pharmacology* and *Clinical Expert Report*. This has been responded to under Question Clin-1.1.1b.

12.2. Question 2

Please explain the significance of Study 9-33/93 and why it was included in the submission.

12.2.1. Evaluation of response

The Sponsor acknowledged that the results of the study and their significance had not been properly presented. The original paragraph has been corrected and the corrected information states that Study 9-33/33 was included in the submission to provide some supporting information on the PK of ibuprofen in heathy adults (half-life of 5.79 ± 6.65 min, and an elimination half-life of 58.05 ± 11.40 min). The study also confirmed the safety of ibuprofen injection as there were no adverse events recorded during the study. "The 9-33/93 study evidenced that ibuprofen injections at a mean dose of around 5.9 mg/kg (ie within the recommended dose range in neonates comprised between 5 and 10 mg/kg) was safe in healthy adults." As a first study in a clinical development plan, this is a reasonable approach.

12.3. Question 3

Please identify where Table 13.3.3.15 and Table 14.3.3.9s are located in the submission. If not included, please provide.

12.3.1. Evaluation of response

The Sponsor provided the location of the two tables. It is verified that the information provided in the CSR (and the CER) is correct.

12.4. Question 4

Please provide comment on why discontinuations due to AEs were not included.

12.4.1. Evaluation of response

The Sponsor acknowledges that the discontinuations due to AEs were not included in the submission as they combined discontinuations due to AEs with discontinuation due to disease progression (lack of efficacy). They have provided a detailed response which included a table and narratives for all patients discontinued in the three Orphan Europe sponsored trials – IBU/20mg/2009, IBU/Prophy/2000 and IBU/20/2009.

Table 54: List of discontinuations from Orphan Europe sponsored studies

Study ID	PEDEA doses received (mg/kg)	Reason for discontinuation
IBU/99/DoseRange (-27w)	5 + 2.5	**Intraventricular haemorrhage (possibly related) and pulmonary interstitial emphysema (possibly related)**
	15 + 7.5 + 7.5	**Refractory hypoxaemia (possibly related)** and severe infection (not related)
IBU/20mg/2009	20 + 10 + 10 then 20 + 10	Closure achieved. Third injection of back up course was not necessary (no AEs)
	20 + 10 + 10 then 20 + 10	**Pulmonary hyper-tension with refractory hypoxaemia (related)**
	20 + 10	**Renal failure (related)**
IBU/PROPHYL/2000	10	Clinical deterioration
	10	Clinical deterioration

Study ID	PEDEA doses received (mg/kg)	Reason for discontinuation
	10 + 5	Clinical deterioration
	10	Clinical deterioration
	10 + 5	**Pulmonary hypertension with refractory hypoxaemia (possibly related)**

In total, for these three studies, there were 5 discontinuations due to AEs: three cases of pulmonary hypertension with pulmonary hypoxaemia, one case each of renal failure and intraventricular haemorrhage.

It is noted by the sponsor that:

> *The three cases of pulmonary hypertension with refractory hypoxaemia have prompted the discontinuation of the IBU/Prophyl/2000 trial, even though this occurrence was considered to be serious enough to prompt the cessation of treatment in only one of the three cases (patient #164). These three cases of pulmonary hypertension had occurred in patients less than 28 weeks of gestational age, treated prophylactically within six hours of birth. This led to the abandonment of any further investigation into prophylactic PEDEA use. To date, PEDEA should not be given within six hours of birth, and should not be used prophylactically at any gestational age.*

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of Pedea in the proposed usage are unchanged from those identified in first round.

13.2. Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of Pedea in the proposed usage are unchanged from those identified in first round.

13.3. Second round assessment of benefit-risk balance

After consideration of the responses to the clinical questions, the benefit-risk balance is unchanged from that identified in first round.

14. Second round recommendation regarding authorisation

The recommendation regarding authorisation is unchanged from that outlined in first round.

15. References

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