Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for ibuprofen

Proprietary Product Name: Pedea

Sponsor: Emerge Health Pty Ltd

November 2017

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 AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
ABR	Auditory Brainstem Responses
ACM	Advisory Committee on Medicines
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
CMI	Consumer Medicines Information
CNS	Central nervous system
CO	Cardiac output
COMP	Committee for Orphan Medicinal Products
COX	Cyclooxygenase
CP	Cerebral palsy
CRIB	Clinical risk index for babies

Abbreviation	Meaning
CPAP	Continuous positive airway pressure
CSR	Clinical study report
CYP	Cytochrome P450
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
LVERSUS	Left ventricular diameter in systole
NIRS	Near Infrared spectroscopy
NSAIDs	Nonsteroidal anti-inflammatory drugs
MED	Minimal effective dose

Abbreviation	Meaning
NEC	Necrotising enterocolitis
PaO2	Partial arterial pressure of oxygen
PaCO2	Partial arterial pressure of carbon dioxide
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

Abbreviation	Meaning
Tmax	Time to reach Cmax
TB	Total bilirubin
UB	Unbound bilirubin
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

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	8 March 2017
Date of entry onto ARTG	14 March 2017
Active ingredient:	Ibuprofen
Product name:	Pedea
Sponsor's name and address:	Emerge Health Pty Ltd Suite 3, Level 1 2 Theatre Place Canterbury VIC 3126
Dose form:	Intravenous (IV) infusion
Strength:	10 mg / 2 mL
Container:	Glass ampoule
Pack size:	4 x 2 mL ampoules per carton
Approved therapeutic use:	Pedea is indicated for the treatment of haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age
Route of administration:	IV infusion
Dosage:	Proposed dosage is that treatment 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 IV injections of Pedea given at 24 h intervals. The first injection should be given after the first 6 h 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 1st or 2nd dose, the next dose should be withheld until urine output returns to normal levels. If the ductus arteriosus does not close 48 h after the last injection or if it re-opens, a second course of 3 doses, as above, may be given.
ARTG number:	273093

Product background

This AusPAR describes the application by Emerge Health Pty Ltd to extend the indications for ibuprofen (tradename: Pedea). Ibuprofen is a non-steroidal anti-inflammatory drug first marketed in Australia in 1969. It is registered for use in many tablet, capsule, and oral solution formulations, where it is used for the temporary relief of pain in the patient population 6 months or older. Pedea is proposed for a novel use and novel population in the orphan indication of hemodynamically significant patent ductus arteriosus (PDA) in preterm newborn infants less than 34 weeks of gestational age. The proposed new 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 over-the-counter [OTC] products) are approved in Australia (in respect of 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. None of these, however, is approved for the PDA indication proposed in the preterm newborn population. For example, indications for oral ibuprofen (Brufen) are:

- *Rheumatoid arthritis*
- *Osteoarthritis*
- *Juvenile rheumatoid arthritis*
- *Primary dysmenorrhoea*
- *Pyrexia*
- *Brufen is also indicated for the relief of acute and/or chronic pain states in which there is an inflammatory component.*

A different formulation of ibuprofen for IV injection is also approved in adults 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.*

However, Caldolor is only approved in the adult population for the above indications; it is not approved for the PDA indication, and nor is it approved in the preterm newborn population proposed. The Caldolor formulation also differs from Pedea, as Caldolor contains arginine, an excipient not found in Pedea.

The current approved dose for Brufen in adults is 1200-1600 mg daily in three or four divided doses, with a maximum of 2400 mg daily. The dose in children (6 months to 12 years) is 20-40 mg/kg daily. The approved dose for Caldolor in adults is 400 mg every 4 to 6 h for fever, and 400-800 mg every 6 h for analgesia (maximum 3200 mg daily).

The DA is a blood vessel that connects the pulmonary artery with the aorta during fetal life, shunting the majority of right ventricular output directly to the descending aorta and bypassing the pulmonary vascular bed. At birth, the ductus constricts in response to rising oxygen saturation and falling prostaglandin levels, redirecting blood flow to the lungs. Complete spontaneous closure is usually achieved within 48 hours in full term infants.

About 70-80% of infants under 1,250 g birthweight have a PDA. The incidence of PDA in preterm newborns is inversely correlated to gestational age and birth weight. The current

treatment options include supportive therapy, medical treatment (including indomethacin) and surgery.

Associated risks of prematurity include respiratory (bronchopulmonary dysplasia), gastrointestinal (necrotising enterocolitis) and neurological (intraventricular haemorrhage, cerebral palsy) complications.

Indomethacin IV Mylan is currently available in Australia with the indication:

> *Indomethacin IV Mylan is indicated for the closure of patent ductus arteriosus in premature babies. Clear-cut clinical evidence of a haemodynamically significant patent ductus arteriosus should be present, such as respiratory distress, a continuous murmur, a hyperactive precordium, cardiomegaly and pulmonary plethora on chest x-ray. Indomethacin IV Mylan should only be used in a hospital under supervision of a specialist neonatologist.*

Pedea was granted orphan drug designation in Australia on 29 May 2013. In Europe, the sponsor obtained orphan designation in February 2001 and marketing approval on 22 April 2004. The approved indication in Europe is:

> *Treatment of a haemodynamically significant patent ductus arteriosus in preterm newborn infants less than 34 weeks of gestational age.*

At time of submission to TGA, no submission had been made by the sponsor in the US. No information was provided regarding regulatory status in Canada or New Zealand.

To support the initial approval of Pedea in the EU, Orphan Europe submitted a mixed submission including both clinical study data and published literature to support clinical efficacy and safety. The Australian application relies solely on the clinical trial data, with the literature included as supportive evidence only.

Ibuprofen for this indication has not been previously considered by the ACM.

Regulatory status

The international regulatory status at the time of submission is listed in Table 1.

Table 1: International regulatory status at the time of submission to TGA.

Country	Action – Date	MA number	Trade Name	MAH	Launch date
Argentina	A – 25-Apr-2011	56245	Pedea	Conifarma SA (Stellium)	Marketed 2011
Austria	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	01/09/2004
Belarus	A – 24-Aug-2010	9407/10	Pedea	Nycomed Austria	Marketed 2010
Belgium	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Bulgaria	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	09/2005
Columbia	A – 19-Nov-2010	INVIMA 2010M-0011597	Pedea	Orphan Pharma	Marketed 2010
Croatia	A –1-Jul-2013	EU/1/04/284/001	Pedea	Orphan Europe	Marketed 2013
Cyprus	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Czech Republic	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	01/09/2004
Denmark	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	13/09/2004
Ecuador	A – 14-Nov-2011	30032-11-11	Pedea	Orphan Pharma	Marketed 2011
El Salvador	A-12-Sept-2013	F085912092013	Pedea	Orphan Pharma	
Estonia	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Finland	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
France	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	04/10/2004
Germany	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	01/09/2004
Greece	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Hungary	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	01/09/2004
Iceland	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004

Table 1 (continued): International regulatory status at the time of submission to TGA.

Country	Action – Date	MA number	Trade Name	MAH	Launch date
Iran	A – 21–Sept-2014	IRC: 1228229480	Pedea	Orphan-Europe	Not marketed
Ireland	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Italy	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	28/05/2005
Kazakhstan	A - 19-Feb-2009	RK-LS-5- n°013629	Pedea	Nycomed Austria GmbH	Marketed 2009
Kuwait	A- 01-May-2014	6726/MAY14 COM/1511	Pedea	Bader Sultan & Bros	
Latvia	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	Marketed 2004
Lichtenstein	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	Not marketed
Lithuania	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Luxembourg	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Malta	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Mexico	A – 04- Nov- 2013	133300C1050657	Pedea	Avalar	
Netherlands	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Norway	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Peru	A – 16-Apr-2013	E-23014	Pedea	Orphan Pharmau	Marketed 2013
Poland	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	01/09/2004
Portugal	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Romania	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	Not marketed
Russia	A – 16-Oct-20008	LRS 008162/08-161008	Pedea	Aanora	Marketed 2009
Slovakia	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	01/09/2004
Slovenia	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	01/09/2004
South Africa	A – 15-Aug-2008	A40/3 1/0174	Pedea	Equity Pharmaceutical	Marketed 2008
South Korea	A – 22-Jun-2011	N° product licence: 105	Pedea	Manufacturer :OE Importer : SAMOH	Marketed 2011

Table 1 (continued): International regulatory status at the time of submission to TGA.

Country	Action – Date	MA number	Trade Name	MAH	Launch date
Spain	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	20/06/2005
Sweden	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
United Kingdom	A – 29-Jul-2004	EU/1/04/284/001	Pedea	Orphan Europe	18/09/2004
Ukraine	A – 20-Apr-2007	UA/6243/01/01	Pedea	Nycomed Austria GmbH	09/2007

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug product

Pedea is a sterile, clear colourless solution containing a 5 mg/mL ibuprofen solution for injection (10 mg/2 mL) filled in 2 mL colourless One-Point-Cut (OPC) glass ampoules and supplied in packs of 4 x 2 mL ampoules.

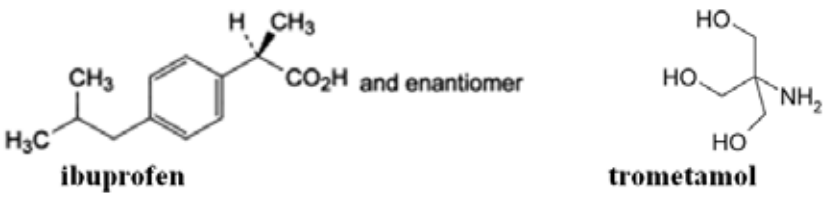
[Various Pedia vitamin tablets are sponsored by Vitex Pharmaceuticals Pty Ltd (Pedia-Cal Pedia-Haem and Pedia C/Zn) but are unlikely to be confused with an injection dosage form.]

There are pharmacopoeial monographs for ibuprofen drug substance but no monographs for ibuprofen injection.

Ibuprofen is practically insoluble in water, but it is solubilised in Pedea using a slight molar excess of the base trometamol which forms a salt with ibuprofen. (The currently registered ibuprofen injection Caldolor contains arginine as a solubilising agent.) Trometamol is used as an excipient in over 200 registered injectable products however these are limited to biological medicines and imaging products. The same Pedea formulation has been used in all clinical trials provided with this application.

Pedea is also formulated with sodium chloride and the pH adjusted to pH of 8.0 (slightly alkaline) with hydrochloric acid or sodium hydroxide. Pedea is isotonic. The injection contains no antimicrobial preservative.

Figure 1: Chemical structures of ibuprofen and trometamol.



ibuprofen trometamol

The adequacy of endotoxin removal for empty ampoules is currently being clarified.

The stability data provided support a shelf life of 2 years when stored below 30°C. Do not freeze.

Administration

The proposed dosage is 10mg/kg IV infusion for the first injection and then 5 mg/kg for the 2nd and 3rd injections with each dose administered at 24 hour intervals. This means that the daily doses are likely to be up to 25 mg (that is, up to three ampoules), based on preterm infant weights up to about 2.5 kg.

Pedea is 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 Pedea infusion solution has a pH of 8.0. The currently proposed PI does not emphasise the alkaline nature of the infusion solution, and contains only limited information on compatibility of mixtures. The UK registered Pedea product contains stronger compatibility warnings. Revision has been proposed.

Bioavailability

As Pedea is only proposed for IV administration, no bioavailability data have been reviewed. The submission did include a single dose, bioequivalence study (IBU/00/BIOEQ/FR) in 18 healthy male volunteers comparing Pedea and an intramuscular ibuprofen lysine formulation (IMBUN) which is not available in Australia. In this study, both treatments were given IV over 15 minutes. Bioequivalence is claimed with respect to both R- and S-ibuprofen.

Quality summary and conclusions

At time of this report, details of endotoxin removal from empty ampoules were being clarified.

Revisions to the labelling and the quality aspects of the PI were also being negotiated.

These aspects should be finalised prior to the ACM meeting. If resolved, registration would be recommended with respect to chemistry and quality control aspects.

III. Nonclinical findings

Introduction

Emerge Health has applied to extend the indications of ibuprofen and register Pedea, a 5 mg/mL solution of ibuprofen for injection for the treatment of haemodynamically significant PDA in preterm newborn infants less than 34 weeks of gestational age. The proposed dosing regimen involves IV injections given at 24 hour intervals. The dose should be adjusted to the body weight as follows: 1st injection (after the first 6 hours of life) 10 mg/kg; 2nd and 3rd injections 5 mg/kg. If the DA does not close 48 hours after the last injection or if it re-opens, a second course of 3 doses, as above, may also be given.

The pharmaco-toxicological profile of ibuprofen has been previously characterised and there is extensive clinical experience with its use. Therefore, a reduced animal testing program, as presented, is appropriate: nonclinical data submitted in support of this application included an acute IV study in adult and juvenile rats, a local tolerance study in

rabbits and an in vitro study on the effects of ibuprofen and indomethacin on unconjugated bilirubin in rat astrocytes. All submitted studies were GLP compliant. A range of pharmacology, pharmacokinetic and toxicology literature papers were also submitted to support the potential efficacy and safety of ibuprofen for this indication.

Efficacy

The sponsor submitted published literature that demonstrated that administration of ibuprofen can cause premature closure of the DA in many species. Ibuprofen causes a dose related constriction of the DA which elicits an ischaemic state which allows the appropriate anatomical remodelling to occur. While there is substantial clinical data to support the efficacy of ibuprofen to close the DA in pre-term neonates, this is also supported by the nonclinical literature.

Safety

Bilirubin displacement

Ibuprofen, like other NSAIDS, binds to serum albumin at the same site as bilirubin, and there is clinical concern that the displaced free bilirubin may cross the blood-brain barrier and cause bilirubin-induced neurotoxicity in neonates.

A newly submitted in vitro study in astrocytes isolated from Wistar rats confirmed displacement of bilirubin from human serum albumin (HSA) by various NSAIDS including ibuprofen, indomethacin and sulfisoxazol. Various effects on astrocytes were observed across the experiments including an increase in cell death by necrosis, a moderate increases in apoptosis and stimulated production of TNF-alpha. of the occurrence of these effects were not related to the presence of bilirubin.. The presence of bilirubin at the molar ratio of 1, ibuprofen 200 mg/L, significantly enhanced the apoptosis at all incubation times. In contrast, indomethacin did not significantly enhance the apoptosis produced by bilirubin at either molar ratio. Neither ibuprofen nor indomethacin increased the release of glutamate, indicating that these drugs do not have any effect on the excitotoxicty induced by bilirubin. Cell death was enhanced in 5DIV as compared to 10DIV astrocytes, which the author suggested as indicative of a higher vulnerability of immature cells.

This study is consistent with the finding of an in vitro study using infant blood serum,[1] which showed that ibuprofen at a concentration similar to that used clinically for treatment of PDA (750 µM/L, that is, 154.7 µg/mL) increased the amount of displaced bilirubin fourfold at a bilirubin to albumin molar ratio (B:A) of 1:2. However, it is noted that this study did not provide values for free bilirubin concentration and therefore it is unknown if bilirubin levels were high enough to risk encephalopathy in infants.[2]

There is clinical literature[3] to suggest that ibuprofen for PDA management at the recommended initial dosage of 10 mg/kg administered IV may not be associated with a significant bilirubin displacing effect in the presence of existing mild to moderate unconjugated hyperbilirubinemia in very premature infants. Nevertheless, as a precautionary measure it is appropriate that the draft PI advises against ibuprofen use for this indication in the presence of marked hyperbilirubinemia.

[1] Cooper-Peel C, et al. Does ibuprofen affect bilirubin albumin binding in newborn infant serum? *Pharmacol. Toxicol.* 76: 297-299 (1996).
[2] Cooper-Peel C, et al. Does ibuprofen affect bilirubin albumin binding in newborn infant serum? *Pharmacol. Toxicol.* 76: 297-299 (1996).
[3] Amin SB, Miravalle N. Effect of ibuprofen on bilirubin-binding affinity in premature infants. *J. Perinat. Med.* 39: 55-58 (2011).

Acute toxicity

No repeat dose toxicity studies were conducted, which is acceptable in light of the well-established pharmaco-toxicological profile of ibuprofen, the current dosage regimen and the proposed indication. Acute IV administration of ibuprofen to weaned (3 weeks old) and adult (>6 weeks old) rats, caused passivity, reduced spontaneous locomotor activity, absence of startle response and reactivity, abnormal gait, ptosis, piloerection, dyspnoea at 30 minutes, and bent back at 3 hours, at doses of 167 mg/kg and above. In weaned rats, death was observed in all animals at 420 mg/kg body weight (BW) due to central nervous system (CNS) depression. In adult rats, death due to CNS depression was observed in 1 animal at 167 mg/kg BW and in most animals at 420 mg/kg BW. A slight reduction in bodyweight was also observed in treated animals. The maximum non-lethal dose was 265 mg/kg in both weaned and adult rats. This corresponds to 12 times the total maximum recommended human dose on a mg/kg basis, 16 times the 'instantaneous' plasma concentration at which transient CNS depression was observed (approximately 500 µg/mL), and approximately 45 times the 'instantaneous' plasma concentration (approximately 180 µg/mL) reported to be effective in therapeutic use.[4]

The US FDA has suggested[5] that the appropriate rat age corresponding to pre-term humans is 0 to 4 days whereas 3 week old rats (as used in the current in the acute toxicity study) correspond to human infants (1-23 months). Despite such limitations, the submitted acute toxicity study has confirmed the acute CNS depression hazard of IV ibuprofen. Further repeated dose animal experiments would not add further value as any other potential chronic effects of ibuprofen on gastrointestinal, cardiovascular and renal systems are already well established from previous clinical and nonclinical data, and suitable precautions and monitoring are emphasised in both the PI and RMP documents. Given the many issues facing a pre-term neonate there is already close monitoring of the function of all major organ systems in a hospital setting.

Local tolerance

In a local tolerance study in rabbits, haematoma and erythema were observed in the area surrounding the injection site following 5 daily injections by the intra-arterial (20 mg/kg), IV (20 mg/kg) or perivenous (0.5 mL) routes of administration. Local effects following IV, intra-arterial and perivascular injection were similar in treated and control groups and are therefore related to the injection rather than the solutions administered (control, vehicle or ibuprofen). Haematoma and erythema were observed in animals of the control and vehicle groups on days 1-5, and in the ibuprofen group on days 4 and 5 of treatment These results suggest that ibuprofen has an initial beneficial effect due to its anti-inflammatory properties. Furthermore, there was no evidence of organ related toxicity at necropsy after 5 daily injections. Therefore, there is low concern for adverse local reactions following IV bolus injection of Pedea.

Excipients

Pedea contains trometamol (2-amino-2-hydroxymethyl-1,3-propanediol, also known as TRIS or THAM) at a concentration of 7.56 mg/2 mL. The maximum single dose IV dose will be 7.56 mg/kg and the maximum total dose of trometamol will be 15.12 mg/kg. There are

[4] Rat calculation: maximum non-lethal dose of 265 mg/kg bodyweight; blood volume 6% for 250g animal; haematocrit 46 = plasma volume 32.4 mL/kg; 'instantaneous' plasma concentration of 8200 mg/L. Human neonate calculation: Plasma volume 41.5 mL/kg; max dose of 20 mg/kg BW would give instantaneous concn of 500mg/L. Protein binding of ibuprofen for human neonate and rat is similar at 95%.

[5] Barrow PC: Toxicology testing for products intended for pediatric populations. In: Sietsema WK, Schwen R, eds. Non clinical safety assessment: practical considerations for successful registrations. FDAnews; May 2007, p. 413.

no toxicological concerns for this excipient as results from the trometamol vehicle were no different from the saline control in the acute toxicity study at five times the therapeutic dose. Furthermore, IV trometamol has been used clinically for the treatment of metabolic acidosis for many years at concentrations ten times more than the Pedea formulation.

Nonclinical summary and conclusions

- Given the well-established nonclinical and clinical data with ibuprofen an abridged nonclinical data package was consisting of an acute IV study in adult and juvenile rats, a local tolerance study in rabbits and an in vitro study on the effects of ibuprofen and indomethacin on unconjugated bilirubin in rat astrocytes. All submitted studies were GLP compliant. Published literature was provided as supportive material.
- In the acute IV toxicity study in adult and weaned rats, central nervous system depression was observed, which resulted in death at higher doses (420 mg/kg BW) in both age groups. Clinical signs of toxicity were similar in rats of both age groups and included passivity, reduced spontaneous locomotor activity, absence of startle response and reactivity, abnormal gait, ptosis, piloerection, dyspnoea. The maximum non-lethal dose was 265 mg/kg in both weaned and adult rats (12 times the maximum recommended human dose on a mg/kg basis).
- In a local tolerance study, ibuprofen was well tolerated following IV, intra-arterial or perivenous injection for 5 days in rabbits using the proposed commercial formulation. Local effects were related to the injection rather than the solution administered and therefore there is low concern for adverse local reactions following injection of Pedea. Moreover, there was no evidence of organ related toxicity at necropsy after 5 daily injections.
- An in vitro study further investigated the known bilirubin displacement effects of ibuprofen in cultured rat astrocytes. Ibuprofen potentiated the effects of bilirubin induced necrosis and apoptosis of astrocytes and variably increased the release of TNFα at high bilirubin to albumin ratios but had no effect on the excitotoxicity induced by bilirubin. While the direct clinical relevance of these results is unclear the draft Product Information appropriately advises against ibuprofen use for this indication in the presence of marked hyperbilirubinemia.
- There are no toxicological concerns for the presence of the trometamol (TRIS, THAM) excipient in the Pedea formulation as results from the trometamol vehicle were no different from the saline control in the acute toxicity study at five times the therapeutic dose. Furthermore, IV trometamol has been used clinically for the treatment of metabolic acidosis for many years at concentrations ten times more than the Pedea formulation.
- There are no nonclinical objections to the registration of ibuprofen (Pedea) for the treatment of haemodynamically significant PDA in preterm newborn infants less than 34 weeks of gestational age.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Information on the condition being treated

Although major advances in the care of preterm infants have been made, preterm birth remains the leading cause of perinatal and infant morbidity and mortality in modern countries. Eight to nine percent of births still occur before 37 weeks gestation and among them (1-2%) those occurring before 32 weeks account for half of perinatal deaths. The immaturity of several organs (lungs, digestive tract, kidneys and brain) cause life-threatening complications in the preterm infant. The duration of hospitalisation for a child born before 32 weeks gestation varies widely, but is rarely less than 10 weeks. With the current techniques of management of the preterm, survival has dramatically improved (approximately 80% born at 26-27 weeks). Neurodevelopmental prognosis in survivors depends on gestational age (GA) at birth. The prognosis is favourable in 70% of infants born at 26 weeks.

The DA is a blood vessel that connects the pulmonary artery with the aorta during foetal life. Since the lungs are unexpanded before birth, only a small part of the blood leaving the right ventricle flows through the pulmonary vascular bed, the most important part is ejected directly into the descending aorta through the DA. By 6 weeks of gestation, the DA shunts most of the right ventricle output from high resistance pulmonary circulation to descending aorta and low resistance placental circulation, where gas exchange occurs.

Patency of the DA during gestation is an active process involving local and circulating prostaglandins (PG). PGE1 and PGE2 stimulate prostanoid receptors mediating smooth muscle cells relaxation. The ductus is exposed to locally released PG (mainly PG12) and circulating PG (mainly PGE2) with concentrations increasing toward term. The placenta is the main source of production and the lungs the main sites of PG catabolism.

Prostaglandin synthease or "cyclooxygenase (COX)" converts arachidonic acid to PG. Two main isoforms are recognised: a constitutive isoform (COX 1) and an inducible isoform (COX 2). The foetal DA primarily expresses COX 1. As gestation proceeds the ductus matures, becomes less sensitive to the dilatory effects of PG and more sensitive to constricting factors such as arterial oxygen tension (PaO2). During the transition from intra to extra uterine life, the ductus constricts, thereby redirecting blood flow from pulmonary artery towards the lungs. In the full term neonate, the physiological closure of the ductus is achieved within 24 h after birth in 20% of cases. This rate reaches 80% and 100% respectively 48 and 96 h after birth.

In premature infants, spontaneous closure is delayed, resulting in persistent patency of the DA. This leads to increased morbidity in the neonate through exacerbation of co-existent respiratory distress syndrome (RDS) and impairment of perfusion of various organs (brain, kidney, digestive tract). The ductus frequently remains open for many days. After birth, pulmonary vascular resistance falls when ventilation starts, and systemic vascular resistance is high and results in systemic arterial blood pressure becoming higher than that in the pulmonary artery. When the DA persists, an open connection between the 2 circulations enables a left to right shunt.

About 70-80% of infants under 1,250 g birthweight have a PDA. The risk of PDA is increased in the presence of RDS and in addition the effect of exogenous surfactant on pulmonary vascular resistance leads to an earlier clinical presentation of the left to right shunt in preterm infants. The consequences of a PDA are: (1) left to right shunt to the pulmonary circulation; (2) increased flow through the lungs with diastolic volume overload; (3) increased flow through the left atrium, left ventricle, and ascending aorta; and (4) aortic backflow with a diastolic steal of blood from the descending aorta and abdominal organs to the pulmonary artery.

The incidence of PDA in preterm newborns generally shows that PDA is inversely correlated to GA and birth weight varying from ~40% for <1000 g to 7% for >1500 to <1750 g (studies from the 1980s). More recent surveys performed in the 1990s suggest similar figures of about 30% in preterm infants weighing <1500 g. In Europe the orphan application estimated the prevalence as 2.13 per 10,000 persons.

In the orphan application an Australian prevalence was estimated at up to 560 infants.

Current treatment options

The current treatment options include supportive therapy, medical treatment and surgery.

Supportive treatment is the first step of treatment and includes: maintaining haematocrit above 40% because lowered oxygen transport capacity and delivery may compromise myocardial oxygenation; provision of electrolytes, glucose and nutritional requirements using parenteral alimentation; and fluid restriction to avoid volume overload and left ventricular failure.

The principle of medical therapy is administration of vasoconstricting agents. NSAIDs interact with vasodilator PG activity at the site of the PDA. Several COX inhibitors have been tried but indomethacin is the one most studied.

Indomethacin is frequently associated with complications such as decreased cerebral, renal and mesenteric blood flow, altered renal function and altered platelet function. In the kidney, indomethacin causes a transient decrease in both glomerular filtration rate and urine output, and is therefore contraindicated in cases of poor renal function. In the gastrointestinal tract, the reduction in mesenteric blood flow induced by indomethacin may aggravate bowel ischaemia secondary to the ductus. In addition, indomethacin in adequate doses inhibits platelets from producing COX products and may prolong the bleeding time. Indomethacin may also reduce cerebral oxygenation and blood flow by 25-60%, which could lead to cerebral ischaemia, although it does not have a negative effect on neurodevelopmental outcome.

Indomethacin is contraindicated in patients with significant renal dysfunction, overt bleeding, shock, proven or suspected necrotising enterocolitis, thrombocytopenia or coagulation defects.

In cases of medical treatment failure or contra-indication, surgical closure of the ductus is performed. Ligation can be done with low morbidity/mortality event in very low birth weight (VLBW) infants. However, respiratory compromise, blood pressure fluctuations, intracranial haemorrhage, infection, chylothorax, and death are still risks associated with surgical closure. Surgery implies a thoracotomy and therefore in many neonatal units, it is restricted to persistent haemodynamically significant PDA (HsPDA) that have resisted one or several medical treatment courses and have not closed spontaneously.

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.

Guidance

The TGA has adopted the following EU Guidelines relevant to this submission:

- Guideline on the Investigation of Medicinal Products in the Term and Preterm Neonate. EMEA/536810/2008, effective from January 2010, adopted by TGA May 2010
- Guideline on Clinical Trials in Small Populations. CHMP/EWP/83561/2005, effective from February 2007, adopted by TGA December 2006
- Guideline on Reporting the Results of Population Pharmacokinetic Analyses CHMP/EWP/185990/06, effective from January 2008, adopted by TGA June 2009
- Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population EMEA/CHMP/EWP/147013/2004 effective from January 2007, adopted by TGA August 2009

It is noted that all these guidelines became effective and adopted in Australia after the studies submitted in the dossier were planned and completed.

Contents 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)

Paediatric data

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

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.

Later studies are stated to comply with GCP, the Helsinki principles and applicable local requirements and that 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.

Pharmacokinetics

Studies providing pharmacokinetic data

Submitted pharmacokinetic studies are shown in Table 2.

Table 2: 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/BILICLIN04	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.

Evaluator's 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 with 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 wide interpatient variability but this is consistent with the numerous factors that affect preterm infants and lead to interference with drug metabolism and elimination.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 3 shows the studies relating to each PK topic and the location of each study summary.

Table 3: 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.

Evaluator's conclusions on pharmacodynamics

Only 3 PD studies were submitted as part of the Australian dossier. These studies were primarily related to assessing 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 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.

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

Clinical trials on ibuprofen were all conducted with the same dose regimen as in the first published study.[6] 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.

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 premature preterm newborns, and therefore, a different target closure rate was chosen to define efficacy in relation to GA: 50% in the < 27 weeks group versus 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.

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] Varvarigou A, et al. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. *JAMA* 275: 539-44 (1996).

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[7] 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.

Efficacy

Studies providing efficacy data

The studies providing evaluable efficacy data are:

- 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.
- 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 versus 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] Varvarigou A, et al. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. *JAMA* 275: 539-44 (1996).

Evaluator's conclusions on 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).

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

- Study IBU/Survey

Pivotal and/or main efficacy studies

- Study IBU/PROPHYL/2000 (curative group)

Other studies

Other efficacy studies

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

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

Studies evaluable for safety only

Not applicable.

Patient exposure

See Tables 4-6 for patient exposure.

Table 4: 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 5: 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 6: 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**

Safety issues with the potential for major regulatory impact

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.

Renal function and renal toxicity

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 versus +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% versus 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% versus 0% and 18.2% versus 0%).

Table 7: 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
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

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.

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 8: 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 9: 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	
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
Mean (SD)	87.3 (19.40	93.9	90.8	

Follow Up During the First 3 Days	Placebo N=66	Ibuprofen N=65	All N=131	Test
		(24.50)	(22.33)	Wilcoxon p=0.245
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 10: 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 11: 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 12: 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 13: 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%)

Other clinical chemistry

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.

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.

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.

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.

Post marketing data

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

Table 14: 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

PSUR Reporting period	No. of boxes	Cumulative total boxes	Cumulative total patients
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 SmPC (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 SmPC:

  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

Evaluator's conclusions on safety

The Australian submission comprised substantially less safety data than the EU Marketing Authorization Application (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.

First round benefit-risk assessment

First round assessment of benefits

See Table 15.

Table 15: 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 comorbidity and know complications of prematurity of all patients.

First round assessment of risks

See Table 16.

Table 16: 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

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 (for example, prophylactic treatment during the first day versus 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 (Neonatal Intensive Care Unit).

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

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 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 versus 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 X-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 PDA 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.

Clinical questions

Pharmacokinetics

- 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.

Safety

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

Second round evaluation

Details of sponsor's responses to clinical questions and evaluator's subsequent comments are contained in Attachment 2.

Second round benefit-risk assessment

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.

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.

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.

Second round recommendation regarding authorisation

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

V. Pharmacovigilance findings

Risk management plan

Summary

- In support of the extended indications, the sponsor submitted EU-RMP version 2 (DLP 30 July 2011) and ASA version 0.1 (7 March 2016).
- The sponsor submitted ASA version 0.2 (25 October 2016) in its Section 31 response.
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below.

Table 17: Summary of Safety Concerns and their associated risk monitoring and mitigation strategies.

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Respiratory function: risk of hypoxemia with pulmonary hypertension, especially if treated with ibuprofen IV within 6 hours of life.	ü	–	ü	–
	*Renal function disorders	ü	–	ü	–
Important potential risks	Cerebral disorders	ü	–	ü	–
	Haematological disorders	ü	–	ü	–
	Gastrointestinal disorders	ü	–	ü	–
	Gestational age under 28 weeks	ü	–	ü	–
	Bilirubin toxicity	ü	–	ü	–
	Known drug interactions with ibuprofen	ü	–	ü	–
Missing information	Unknown food and drug interactions	ü	–	ü	–

R = Routine
A = Additional
*Added on the advice of the clinical evaluator and accepted by the sponsor in its Section 31 response. This Safety Concern is included in ASA version 0.2 (25 October 2016).

New and outstanding recommendations - Round 2

There are no outstanding issues or new recommendations in Round 2.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is: Implement EU-RMP version2 (DLP 30 July 2011) with ASA (version 0.2, date 25 October 2016) and any future updates as a condition of registration.

Other advice to the Delegate

The Delegate may wish to consider further simplification to the wording in the CMI listed under Side Effects.

VI. Overall conclusion and risk/benefit assessment

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

Quality

Pedea is a sterile, clear colourless solution containing a 5mg/mL ibuprofen solution for injection filled in 2 mL colourless OPC glass ampoules and supplied in packs of 4 x 2 mL ampoules. Ibuprofen is practically insoluble in water, but it is solubilised in Pedea using a slight molar excess of the base trometamol which forms a salt with ibuprofen (the currently registered ibuprofen injection Caldolor contains arginine). Trometamol is used as an excipient in over 200 registered injectable products. The same Pedea formulation has been used in all clinical trials provided with this application.

The module 3 evaluator has no objections to the registration of Pedea, pending clarification of the details of endotoxin removal from empty ampoules, and revisions to the labelling and the quality aspects of the Product Information.

Nonclinical

There are no nonclinical objections to the registration of ibuprofen (Pedea) for the treatment of haemodynamically significant PDA in preterm newborn infants less than 34 weeks of gestational age.

Given the well-established nonclinical and clinical data with ibuprofen, an abridged nonclinical data package was submitted, consisting of an acute IV study in adult and juvenile rats, a local tolerance study in rabbits, and an in vitro study on the effects of ibuprofen and indomethacin on unconjugated bilirubin in rat astrocytes.

In the acute IV toxicity study in adult and weaned rats, central nervous system depression was observed, which resulted in death at high doses (420 mg/kg BW) in both age groups. Clinical signs of toxicity were similar in rats of both age groups and included passivity, reduced spontaneous locomotor activity, absence of startle response and reactivity, abnormal gait, ptosis, piloerection, dyspnoea. The maximum non-lethal dose was 265 mg/kg in both weaned and adult rats (12 times the maximum recommended human dose on a mg/kg basis).

In a local tolerance study, ibuprofen was well tolerated following IV, intra-arterial or perivenous injection for 5 days in rabbits using the proposed commercial formulation. Local effects were related to the injection rather than the solution administered and therefore there is low concern for adverse local reactions following injection of Pedea. Moreover, there was no evidence of organ related toxicity at necropsy after 5 daily injections.

An in vitro study further investigated the known bilirubin displacement effects of ibuprofen in cultured rat astrocytes. Ibuprofen potentiated the effects of bilirubin induced necrosis and apoptosis of astrocytes and variably increased the release of TNFα at high bilirubin to albumin ratios but had no effect on the excitotoxicity induced by bilirubin. While the direct clinical relevance of these results is unclear the draft PI appropriately advises against ibuprofen use for this indication in the presence of marked hyperbilirubinemia.

Clinical

The clinical evaluator has recommended approval of Pedea, with the revised indication:

> *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.*

The clinical dossier contained the following data:

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

Pharmacology

Ibuprofen is a chiral molecule, consisting of a racemic mixture of S(+) and R(-) enantiomers. The S(+) isomer is responsible for the clinical activity.

Study IBU/00/BIOEQ/FR established bioequivalence of the Orphan Europe ibuprofen (the formulation proposed for Australia) and the reference ibuprofen lysine (Imbun; the formulation used in most of the published clinical studies) in 18 healthy male volunteers.

Pharmacokinetics

- Ibuprofen is metabolised in the liver via oxidation (cytochrome P450 2C9) and glucuronidation. In addition, there is unidirectional conversion of around 60% of R-ibuprofen to S-ibuprofen.
- Two studies examined pharmacological parameters in 51 preterm infants.
- For S-ibuprofen; estimated mean clearance was 3.8 mL/h/kg, volume of distribution 154 mL/kg, and half-life 35 h.
- For R-ibuprofen, estimated mean clearance was 86 mL/h/kg, volume of distribution 194 mL/kg, and half-life 1.6 h.
- Population pharmacokinetic analysis in a total of 108 preterm infants derived a mean clearance for S-ibuprofen of 3.5 mL/h/kg, volume of distribution 173 mL/kg, and half-life 34.3 h. R-ibuprofen elimination increased during the first week of life while S-ibuprofen elimination changed little.
- No interaction studies were performed. The subjects in the trials received drugs commonly used in the management of preterm infants, such as antibiotics, inotropes, sedatives, steroids, respiratory stimulants, diuretics and bronchodilators.
- Compared to adults and older children, clearance was markedly lower and elimination half-life substantially longer in preterm infants.

Pharmacodynamics

- Ibuprofen inhibits the 2 isoforms of the COX enzyme, leading to reduced prostaglandin synthesis. This is 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.
- Three pharmacodynamic studies investigated the toxic effects of ibuprofen on pulmonary perfusion, left ventricular function, and unbound bilirubin levels. There were no significant changes seen in pulmonary blood flow parameters, oxygen saturation, systolic blood pressure or bilirubin levels.

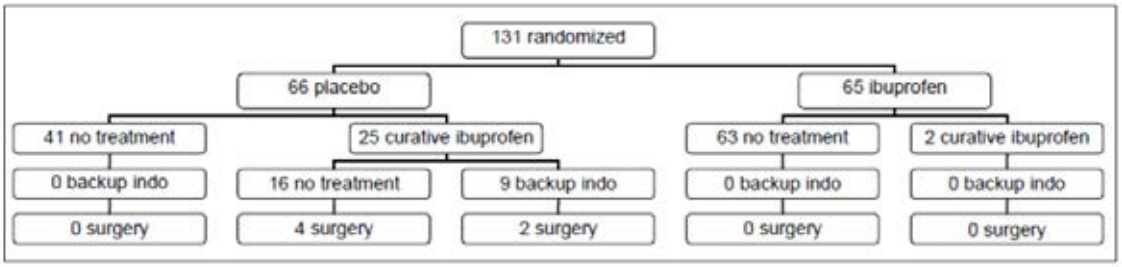
Efficacy

Unless otherwise noted, the studies outlined below were performed in Western Europe during the period 1998-2003, and enrolled premature infants under 30 weeks gestation. Clinical studies all followed the regimen of a loading dose followed by two maintenance doses (each half of the loading dose) at 24 h intervals. This is based on a single published study in 30 infants comparing a three-dose with a single dose regimen. An example regimen is a 10 mg/kg loading dose, followed by two maintenance doses of 5 mg/kg each. This will be referred to as a 10/5/5 dose. This is the dose regimen approved in Europe.

The dose ranging study IBU/99/DoseRange used loading doses of 5, 10, 15, and 20 mg/kg, in infants with echocardiographic evidence of PDA, dependence on mechanical ventilation or nasal CPAP, and gestational age 24-29 weeks. Infants were divided into two groups according to gestational age (24-26 (N=21) and 27-29 (N=22) weeks). Median birth weight was 830 g (range 600-1030) in the 24-26 week group, and 1030 g (670-1580) in the 27-29 week group. Loading dose of ibuprofen was given at 72-120 h postnatal age. Individual group sizes were small, with particularly low subject numbers in the younger age group receiving higher ibuprofen doses. In the older group, probability of PDA closure was higher with the 15/7.5/7.5 regimen (91% versus 75% for the 10/5/5 dose), but with a higher rate of renal adverse effects. Probability of PDA closure was 33% for both the 15/7.5/7.5 and 10/5/5 regimens in the younger age group. An additional study in Europe showed improved benefit for a 20/10/10 regimen in very low birthweight infants. The clinical evaluator concludes that the proposed 10/5/5 dose represents an appropriate compromise between efficacy and safety, but may not be optimal for low gestational age infants.

The main ("curative") efficacy study was a substudy of a ("prophylactic") randomised, placebo-controlled study IBU/PROPHYL/2000 of ibuprofen 10/5/5 in preterm infants under 28 weeks gestational age. After an initial three days of treatment (ibuprofen or placebo, administered in a blinded manner), infants were assessed for the presence of a "significant" PDA (visible on echocardiograph, along with at least 2 out of: LA/aortic root ratio > 1.48; retrograde or absent diastolic flow in the descending aorta; pulsatile flow in the DA; diastolic flow in pulmonary artery > 20 cm/s). Those infants who received placebo initially, then were found to have a PDA, were administered "curative" ibuprofen at the 10/5/5 dose in an open label manner, with no comparator treatment. The primary efficacy outcome for the "curative" substudy was the need for further treatment (with indomethacin or surgery) due to non-closure of PDA. The complete study is outlined below.

Figure 2: Study schema: IBU/PROPHYL/2000.



25 infants were enrolled, with a median gestational age 26 weeks and equal numbers of males and females. Median birth weight was 850 g (range 630-1180). Overall success rate (PDA closure after a single course of treatment) for ibuprofen was 12/25 (48%). Follow-on treatment was surgery (n = 4), indomethacin (n = 7), or indomethacin then surgery (n = 2). Response rate did not seem to be correlated with gestational age. As noted, this was a substudy of the larger study, and was not sufficiently powered to investigate "curative" PDA treatment with ibuprofen.

The larger "prophylactic" study was designed to examine the effect of ibuprofen on the need for surgical treatment of PDA in neonates under 28 weeks gestational age. The study was planned to enrol 220 infants, but was stopped prematurely after enrolment of 131 infants, following three occurrences of refractory hypoxemia (described below) in subjects treated with ibuprofen. Subjects were given prophylactic ibuprofen or placebo commencing within the first six hours of life, and monitored with echocardiograms on days 3, 7, 14, and 21. Six patients in the placebo group underwent surgery, versus none in the ibuprofen group. The overall incidence of detectable PDA was 59% in the placebo group, versus 29% in the ibuprofen group (p = 0.001). 89% of PDAs were detected during the first week of life. Two patients (3%) in the ibuprofen group versus 25 (38%) in the placebo group required "curative" ibuprofen treatment.

Study IBU/LT/2004 was a follow-up study of 182 premature neonates with haemodynamically significant PDA born between 1998-2003 at a single hospital in Berlin who received either ibuprofen (during 2001-2003) (N = 93) or indomethacin (during 1998-2001) (N = 89). Statistics were mostly descriptive. There were significantly more males in the ibuprofen group (66% versus 51%); male sex is classically associated with a poorer prognosis. PDA closure was achieved with a single course of treatment for 77% of indomethacin treated patients versus 58% of ibuprofen treated patients, however the mean duration of treatment was significantly lower with ibuprofen. Surgical treatment was necessary for 27% in the indomethacin group versus 30% in the ibuprofen group (p = 0.743).

Study IBU/20/2009 was primarily a safety study (of bilirubin levels) of ibuprofen 20/10/10 in 23 neonates less than 28 weeks gestational age with haemodynamically significant PDA. Closure of PDA was achieved in 10/23 (44%) after a single dose of ibuprofen.

A number of Cochrane literature reviews have examined the use of ibuprofen for PDA closure in premature infants. The 2010 review was based on 19 studies comparing ibuprofen to indomethacin, involving 956 infants. There was no statistically significant efficacy difference between treatments, with relative risk of failure of PDA closure for ibuprofen versus indomethacin of 0.94 (95% CI 0.76-1.17). Based on 15 studies, the relative risk of necrotising enterocolitis was lower with ibuprofen at 0.68 (95% CI 0.47-0.99); there was less evidence of transient renal insufficiency with ibuprofen; no other differences were seen for common neonatal morbidities.

Safety

The clinical evaluator comments that safety information was poorly presented in the submission, with no aggregated safety assessment performed. The only aggregated safety information available is the table of serious adverse events provided in the draft PI.

Study IBU/Survey was a review of the safety of the 2001 Pedea European compassionate use program, which involved 165 neonates. Infants who had received indomethacin during 2000-2001 were used as a comparator group. Results were:

- incidence of "ventilation worsening" was similar for ibuprofen and indomethacin
- incidence of severe hyponatremia on day 2 was higher for indomethacin (29% versus 6.8%); incidence of oliguria was higher for indomethacin (24% Day 1, 18% Day 2 versus 0% for ibuprofen)
- mortality was higher in the indomethacin group (18% versus 9.2%)
- PDA surgery was more frequent in the ibuprofen group (32% versus 9.2%); however it is noted that surgical rate varied considerably between centres, and there was an imbalance of baseline characteristics such as gestational age and birthweight, between the two groups

Total estimated exposure to Pedea in clinical trials was 384 patients versus 182 for comparator indomethacin, although no direct comparative study was performed. The clinical evaluator comments that the main adverse effects were those related to the known complications of prematurity, such as intraventricular haemorrhage, renal disorders, and gastrointestinal events. PSUR summaries covered 11 years of postmarketing experience in Europe (around 100,000 infants treated); the most commonly reported spontaneous adverse events were gastrointestinal (23 to 59% of all reports) and renal. Post-market reports revealed signals for acute renal failure, pulmonary hypertension, and interaction with aminoglycosides.

There were six deaths in infants who received ibuprofen in the curative arm of the main study. No further details are provided, however the survival rate was similar to that seen for the subjects who did not receive ibuprofen (because they had no PDA).

Across the three studies performed by the sponsor, there were nine discontinuations due to adverse events: three cases of refractory hypoxemia (described below), one intraventricular haemorrhage, one renal failure, and four "clinical deterioration".

Specific adverse events examined were:

- ibuprofen did not lead to significant increase in bilirubin levels
- slight transient renal impairment (increased serum creatinine and decreased urine output) was seen in the prophylactic study; this did not persist after the end of treatment; none of the infants in the curative study had abnormalities of serum creatinine
- Pedea had no significant effect on blood glucose or pH
- no significant effect for ibuprofen was seen on blood pressure, heart rate, or cerebral blood flow
- comparing indomethacin and ibuprofen patients at two years in the follow-up study, incidence of cerebral palsy was similar for indomethacin (13%) and ibuprofen (10%), and there was no statistically significant difference between the two groups in Griffith score for neurodevelopment or the incidence of hearing loss

- incidence of bronchopulmonary dysplasia (defined as need for supplemental oxygen at 36 weeks gestational age) was similar for ibuprofen (35%) and indomethacin (38%) in the follow-up study.

Three cases of pulmonary hypertension with refractory hypoxaemia in neonates less than 28 weeks of gestational age, treated prophylactically with ibuprofen within six hours of birth, prompted the discontinuation of the IBU/PROPHYL/2000 trial. This led to the abandonment of any further investigation of prophylactic use. The events occurred at three different centres, and were described as severe refractory hypoxemia occurring just after the administration of the loading dose of ibuprofen in the first 6 h of life in infants less than 28 weeks gestation. The events were refractory to increased ventilator support and administration of exogenous surfactant, but responded rapidly to nitric oxide. In two of the cases, additional doses of ibuprofen were given without further problems. These events appear isolated and related to the prophylactic use of ibuprofen. The proposed PI contains a warning advising that Pedea should not be used prophylactically within 6 hours of birth without confirmation of PDA.

Risk management plan

TGA's Pharmacovigilance and Special Access Branch (PSAB) has accepted the EU-RMP for Pedea (ibuprofen) (version 2, 30 July 2011), with ASA version 0.2 (25 October 2016).

The sponsor proposes routine pharmacovigilance, with no planned or ongoing pharmacovigilance studies.[8] The only remaining outstanding recommendations from the RMP evaluator involve changes to the CMI.

Risk-benefit analysis

Delegate's considerations

This submission consisted only of a limited number of clinical studies, and did not include the published literature that was part of the European marketing submission.

- Quality: There are outstanding issues relating to the details of endotoxin removal from empty ampoules, and revisions to the labelling and quality aspects of the Product Information.
- Nonclinical: The evaluator had no objections to the registration of Pedea.
- Dose: The dose regimen is based on the results of a single published study. The 10/5/5 regimen represents a compromise between efficacy and safety in 27-29 week gestational age infants, but may not be optimal for lower gestational age infants. This dose regimen was used in almost all of the studies covered by the Cochrane review.
- Efficacy: Efficacy of ibuprofen was demonstrated in a small clinical study, supported by published systematic literature reviews. The main efficacy study consisted of only 25 infants. Efficacy data were available for 159 infants from other studies. The submitted studies enrolled only infants below 30 weeks gestation, and did not directly compare ibuprofen with indomethacin. Overall success rate of a single course of ibuprofen was 48% in the primary efficacy study. By comparison, information from a systematic literature review included in the Australian PI for Indomethacin IV Mylan

[8] Routine pharmacovigilance practices involve the following: (a) All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner; (b) Reporting to regulatory authorities; (c) Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling; (d) Submission of Periodic Safety Update Reports (PSURs); and (e) Meeting other local regulatory agency requirements.

appears to give a success rate around 68% following a single course of treatment, across all doses covered by the PI. Cochrane reviews concluded that ibuprofen and indomethacin were equally effective in achieving PDA closure.

- Safety: Safety of ibuprofen was demonstrated in clinical trials and post-marketing experience. Comparative safety with indomethacin was described, although no direct comparative study was performed. Ibuprofen appeared to have improved renal safety over indomethacin; incidence of bronchopulmonary dysplasia was similar between the two drugs. Ibuprofen did not lead to significant increases in bilirubin levels. New safety signals identified during over 10 years of use (with around 100,000 infants treated) as a marketed product in Europe included acute renal failure, pulmonary hypertension, and interaction with aminoglycosides. There were three cases of pulmonary hypertension with refractory hypoxaemia in neonates treated prophylactically with ibuprofen in clinical trials. These events appear isolated and related to the prophylactic use of ibuprofen. Long-term safety at two years was demonstrated, with ibuprofen and indomethacin showing similar incidence of cerebral palsy and hearing loss, and no difference in neurodevelopmental scores.
- Indication: The sponsor requests the following indication:

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

The clinical evaluator recommends the following indication:

> *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.*

In contrast, the approved indication for the comparator, indomethacin, is:

> *Indomethacin IV Mylan is indicated for the closure of patent ductus arteriosus in premature babies. Clear-cut clinical evidence of a haemodynamically significant patent ductus arteriosus should be present, such as respiratory distress, a continuous murmur, a hyperactive precordium, cardiomegaly and pulmonary plethora on chest x-ray. Indomethacin IV Mylan. should only be used in a hospital under supervision of a specialist neonatologist.*

The PI contains sufficient warning against the prophylactic use of ibuprofen, and it is considered that, given the context of use, the wording "haemodynamically significant" does not require further explanation in the indication. Although the submitted studies did not include infants older than 29 weeks gestation, there does not seem to be evidence for decreased efficacy or a worse safety profile in older neonates. ACMs advice is requested on this matter.

A suggested wording for the indication is as follows, with the statement "Pedea should only be used in a hospital under the supervision of a specialist neonatologist" being included in the Dosage and Administration section of the PI:

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

- Data Deficiencies: The submitted studies did not directly compare ibuprofen and indomethacin. The studies did not include infants 30 weeks gestation or older. The sponsor did not provide an integrated safety summary, and will be asked to provide this as part of their pre-ACM response.
- Conditions of Registration: The following are proposed as conditions of registration and the sponsor is invited to comment in the pre ACM response:

The implementation in Australia of the EU Risk management Plan for Pedea (ibuprofen) (version 2, 30 July 2011), with Australian Specific Annex version 0.2 (25 October 2016).

Summary of issues

The primary issues are as follows:

- The submitted studies were small and did not involve direct comparison with current treatments.
- The ibuprofen dose proposed is based on the results of a single published study.
- The submitted studies enrolled only neonates under 30 weeks gestational age.
- There is little long-term safety data.

Proposed action

The Delegate has no reason to say, at this time, that the application for Pedea should not be approved for registration.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

- Were there adequate numbers of patients in the efficacy studies?
- Is there sufficient support for the proposed dosage regimen?
- Do the data support the proposed age range of less than 34 weeks gestation?
- Is there adequate long-term safety information?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Questions for sponsor

The sponsor is requested to address the following issues in the pre ACM response:

- Please provide an integrated safety study from the clinical trial program, including treatment-emergent adverse events, serious adverse events, deaths, laboratory abnormalities and any adverse events of special interest.
- Please indicate the regulatory status of Pedea in Canada and New Zealand.

Response from sponsor

Question for sponsor 1

"Please provide an integrated safety study [summary] from the clinical trial program, including treatment-emergent adverse events, serious adverse events, deaths, laboratory abnormalities and any adverse events of special interest."

Sponsor response 1

Please refer to the attached document "Integrated Safety Summary of Clinical Development Studies with Pedea". This summary outlines the treatment emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, laboratory abnormalities and adverse events of special interest related to Pedea.

Question for sponsor 2

"Please indicate the regulatory status of Pedea in Canada and New Zealand."

Sponsor response 1

Pedea is not registered in the US, Canada or New Zealand. In the US, a similar product to Pedea is already registered: Neoprofen (ibuprofen lysine) injection for IV use. The Marketing Authorization Holder is Recordati Rare Diseases Inc. In Canada, Pedea has been supplied for several years as an unapproved product, under the Special Access Programme. In New Zealand, Pedea has been supplied through a similar program, as a Section 29 unapproved product.

Advisory Committee considerations

The Advisory Committee on Medicines (ACM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Pedea solution for injection containing 5 mg/mL of ibuprofen to have an overall positive benefit-risk profile for the indication:

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

In making this recommendation, the ACM:

- noted that ibuprofen works as well as indomethacin.

Proposed conditions of registration

ACM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- an additional statement in the PI:

> *Pedea should only be used in a hospital under the supervision of a specialist neonatologist*

Specific advice

ACM advised the following in response to the Delegate's specific questions on this submission:

- *1. Were there adequate numbers of patients in the efficacy studies?*

ACM advised that patient numbers were small but sufficient in the efficacy studies taking into consideration that recruitment is a problem with paediatric and neonatal studies. Although there were only a small number of studies, results from all the studies were very consistent.

- *2. Is there sufficient support for the proposed dosage regimen?*

ACM advised that there was sufficient support for the proposed dosage regimen taking into consideration the balance of efficacy and safety concerns.

- *3. Do the data support the proposed age range of less than 34 weeks gestation?*

ACM advised that the data provided did support the proposed age range with several studies which included a small number of babies of <34 weeks. The ACM noted that infants >30 weeks rarely have a problematic PDA.

- *4. Is there adequate long-term safety information?*

ACM advised that there was inadequate long term safety data; however, one poor quality study suggested ibuprofen is as safe as indomethacin, the standard treatment for PDA.

Short term outcomes predictive of neurodevelopmental problems (IVH, BPD, ROP) appear similar.

ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Pedea (ibuprofen 10 mg/2 mL solution for IV infusion 2 mL glass ampoule), indicated for:

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

Specific conditions of registration applying to these goods

- The Pedea EU-RMP, version 2, Data Lock Point 30 July 2011, with ASA version 0.2, dated 25 October 2016, and any subsequent revisions, as agreed with TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Pedea at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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