SCIENTIFIC DISCUSSION

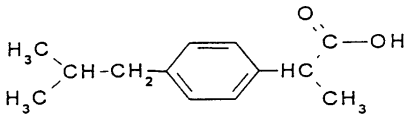
This module reflects the initial scientific discussion for the approval of Pedea. For information on changes after approval please refer to module 8.

1. Introduction

On 14 February 2001, the European Commission to Orphan Europe, France, granted orphan designation for ibuprofen for the treatment of patent ductus arteriosus.

Pedea solution for injection is an aqueous solution of ibuprofen intended for intravenous administration for the treatment of haemodynamically significant *patent ductus arteriosus* (PDA) in preterm neonates of gestational age less than 34 weeks. Maximum dose level is 10-mg/kg body weights. The solution for injection contains 10 mg ibuprofen in a 2 ml ampoule. Ibuprofen has been marketed as an analgesic and anti-inflammatory drug since the 1960's. The first published clinical use in PDA was described in a letter to the Lancet in 1995.

Ibuprofen is a non-selective inhibitor of cyclo-oxygenase, leading to reduce synthesis of prostaglandins. Ibuprofen is a racemic mixture of S (+) and R (-) enantiomers. *In vivo* and *in vitro* studies indicate that the S (+) isomer is responsible for the clinical activity. Ibuprofen is (+/-)-2-(p-isobutylphenyl) propionic acid ($C_{13}H_{18}O_2$) with a molecular weight of 206.3; and has the structure shown below.



In the normal foetus the ductus arteriosus (DA) connects the main pulmonary trunk to the descending aorta, in effect it acts as a 'short circuit' to divert blood from the relatively high-pressure pulmonary circulation of the non-aerated lungs. At term the ductus is about 10 mm in diameter, similar to the descending aorta. However, it differs from other vessels of the foetal circulation in that the media is composed mainly of a spiral layer of muscle fibre and the intima is thicker and develops mounds or cushions in the third trimester of pregnancy. Constriction of the musculature of the ductus is inhibited by local and circulating prostaglandins and by low oxygen tension of the blood.

At birth the lungs expand and arterial oxygen content rapidly rises, circulating prostaglandin levels fall: both these changes will tend to initiate ductal closure. In full-term infants closure begins at birth and is complete by about twelve hours. However, in premature infants circulating prostaglandin levels are higher than at term, and respiratory difficulties may lead to a state of hypoxia; both of which contribute to the failure of the ductus to close generating a 'left to right' anatomical shunt through the patent ductus. The consequence of this is relative underperfusion of the systemic circulation and overperfusion or the pulmonary circulation.

The pulmonary effects of PDA include an increase in pulmonary blood flow and pressure leading to pulmonary oedema and occasionally, pulmonary haemorrhage. Lung compliance is decreased and the risk of bronchopulmonary dysplasia is increased.
The effect of the cardiac shunt is to enlarge the left atrium and left ventricle. Despite an increase in left ventricle output, systemic perfusion is reduced. Reduced renal and gut blood flow impairs renal function and increases the incidence of intestinal ischaemia. PDA is linked to intra-cranial haemorrhage and ischaemia from cerebral steal and fluctuations in cerebral blood flow.

The frequency of PDA is inversely related to gestational age being higher in infants of lower gestational age. About 42% of infants under 1 kg at birth have a patent DA, falling to 21% for those

weighing 1-1.5 kg, and 7% for those 1.5-1.75 kg. The risk is increased by the presence of Respiratory Distress Syndrome.

Prostaglandins are synthesised from arachidonic acid by cyclooxygenase. Therefore, non-steroidal anti-inflammatory drugs (NSAIDs) that inhibit cyclooxygenase are likely to reduce prostaglandin levels and promote closure of the DA.

Animal data and the observation that in human congenital heart disease, the DA could be prevented from closing by infusion of prostaglandins led to the hypothesis that it could be pharmacologically closed by inhibition of prostaglandin synthesis. This was demonstrated and published in 1976 by groups working in San Diego and San Francisco using the NSAID indomethacin (NEJM, 1976).

Indomethacin has been shown to block the release of vasodilator prostaglandins at the site of the PDA. In a double-blind, randomised, placebo controlled study from 1983, Gersony et al. showed that in 460 pre-term newborns <1.75 kg, PDA closure at 48 hours occurred with indomethacin in 75-80% of cases, compared to 25-30% with placebo. Some 21% of patients needed a further dose of indomethacin.

In the early 1980's, Perlman et al., 1981, observed an increase in cerebrovascular resistance and hypercapnoea while the DA is patent, with reversal following closure. The haemodynamic disturbance caused by ductal opening and closure was thought to be a causative or a contributory factor to a feared complication of prematurity: subependymal and intraventricular haemorrhage (IVH). The opportunity to pharmacologically close the patent DA offered the hope of removing a source of haemodynamic instability and protecting against IVH.

The studies of Banstra et al., 1988, and Bada et al., 1989, involved well over 100 patients each and showed a beneficial effect of treatment with indomethacin.
The study by Ment et al., 1994, confirmed the hypothesis that prophylactic indomethacin has a protective effect against IVH. The investigators enrolled 431 neonates of 600 – 1250 g birth weight and found a statistically significant ($p = 0.03$) reduction; 12% of indomethacin and 18% of placebo treated infants developed IVH in the first five days of life.

However, the functional benefit of prophylactic indomethacin in terms of survival without neurological impairment has been disappointing. A recent large study (Schmidt et al., 2001) in 1202 infants with birth weight of 500 – 999 g found benefits in short-term outcomes: PDA was found in 24% of indomethacin and 50% of placebo treated infants; the corresponding rates of severe IVH were 9% and 13%. However, the rate of survival without neurological impairment at 18 months was 47% for indomethacin and 46% for placebo ($p = 0.61$).
A meta-analysis by Fowlie et al., 1996, showed that when used prophylactically within 24 hours of birth in pre-term infants <1750 g, indomethacin reduces the incidence of PDA by about 36% (95% CI of 26-47%). There was a trend for a reduction in mortality, but no improvement in neurological outcome at five years.

Thus, for many years there has been concern that indomethacin causes a reduction in cerebral blood flow and though this might have a protective effect against haemorrhage it might contribute to ischaemic injury and contribute to long-term cerebral damage. However, recent long-term follow up (Vohr et al., 2003) suggests that later neurological impairment is associated with the occurrence of IVH in the neonatal period rather than treatment with indomethacin.

Adverse events with indomethacin include a worsening renal function, bowel ischaemia, prolongation of bleeding time, and reduced cerebral blood flow and oxygenation.

Ibuprofen was developed as an alternative to indomethacin for PDA in the hope that it might be as effective in the pharmacological management of PDA with possibly a better safety profile due to a lesser effect on the systemic blood flow *(see clinical part)*.

Current treatments for PDA include also the correction of anaemia to maintain oxygen carrying capacity and the optimising of fluid balance.

Pedea is indicated for treatment of a haemodynamically significant patent *ductus arteriosus* in preterm newborn infants less than 34 weeks of gestational age. Treatment with Pedea should only be carried out in a neonatal intensive care unit under the supervision of an experienced neonatologist.

The applicant has submitted documentation covering non-clinical and clinical study reports based on studies carried out by the applicant and bibliographic references. The relevance of the data submitted which concern a product different from Pedea has been addressed satisfactorily. Where certain studies were lacking, justifications have been given (see also non-clinical and clinical aspects).

2. Chemical, pharmaceutical and biological aspects

Composition
Pedea is presented in the form of solution for injection containing 5 mg/ml of ibuprofen. Other ingredients are trometamol, sodium chloride, sodium hydroxide, hydrochloric acid 25% and water for injections.
The solution is filled into 2 ml Type I glass ampoules.

Active substance
The active substance ibuprofen complies with the Ph. Eur. A certificate of Suitability of the Monograph of the European Pharmacopoeia (CEP) is available for the manufacturer of the active substance.
Batch analytical data in two consecutives batches demonstrate conformance with the specifications.

A validated HPLC method is used to assess the content and purity of ibuprofen. Hence, the quality of ibuprofen can be properly controlled and assured using the proposed testing methods and specifications.

Stability of the active substance
No stability data are provided on the grounds that the CEP defines a re-test period for the substance when stored in fibre drums.

Other ingredients
With the exception of hydrochloric acid, all excipients comply with the requirements of relevant Ph. Eur. monographs. Hydrochloric Acid 25% is tested according to the current monograph of the Ph. Helv. Appropriate certificates of analysis are presented for each excipient, showing that the compendial requirements were met. All the excipients are commonly used in parenteral formulations.
None of the materials are stated to be of animal origin, therefore there is no TSE risk.
The solution is filled into 2 ml colourless OPC (One-Point-Cut) Type I glass ampoules with blue point. The ampoules meet the standard of quality of glass with hydrolytic resistance (Ph. Eur).

Product development and finished product
The aim of the development was an aqueous ibuprofen solution which is suitable for intravenous injection and which remains stable over a period of time as long as possible.
The basic idea was to make the composition as simple as possible and with well-known excipients. Due to the poor solubility of ibuprofen in water in the acidic pH-range, the solution was adjusted to achieve a good solubility using sodium hydroxide and hydrochloric acid 25%. The solubility was additionally improved by the addition of a small amount of trometamol. Finally, sodium chloride is added to adjust the tonicity of the solution and to avoid irritation.

The medicinal product is prepared under very clean conditions, including sterile filtration of the bulk solution and filling of the solution in previously sterilised ampoules; finally the ampoules are sterilised in a steam autoclave (121°C for 20 minutes). Based on the microbiological quality requirements of the ingredients and the demonstrated performance of the filling process and the final sterilisation, it can be

concluded that the manufacturing method is capable of producing a sterile and pyrogen free finished product.

Considering the simple nature of the formulation, the detailed account given for the manufacturing process, the finished product can be properly controlled using the proposed testing methods and specifications.

Product Specification
The product specifications include tests by validated methods for appearance, ibuprofen identification (HPLC, TLC) and assay (HPLC, 10.0 mg ± 5%, 9.50 mg to 10.50 mg), purity (HPLC), clarity and opalescent, visible and invisible particle, coloration, density, pH, extractable volume, osmolality, sterility and endotoxins.
Degradation products are controlled and their limits are justified by reference to stability studies and toxicology studies.
The tests and limits of the specifications for the finished product are appropriate to control the quality of the finished product for their intended purpose.
Batch analysis data on three batches confirm satisfactory uniformity of the product at release.

Stability of the Product
The shelf life specification is the same as the release specification.
The stability testing on ibuprofen ampoules has been carried out on three production scale batches, these batches have been stored under the following different conditions; in the pack as intended for marketing: refrigerator for 12 months (2-6°C, no humidity controls), 25°C/60% RH and 31°C/70% RH for 60 months (48 month results are available) and, 41°C/drying cabinet for 9 months instead of the recommended 40°C/75% RH. Finally, batches were also stored at 21°C/50% RH for 36 months.
Even though, these conditions are not standard, in view of the well-known stability characteristics of this established substance, they may be accepted.

Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

3. Toxico-pharmacological aspects

GLP
Four volumes of data have been submitted the great majority of which is bibliographic. The two studies sponsored by the applicant specifically in support of this procedure: an acute i.v. Toxicity study in the weaned and adult rat; and a local tolerance study; were both conducted in accordance with GLP.

Pharmacology

Primary pharmacodynamics

In vitro and *in vivo* studies

The applicant reviewed the main relevant published pharmacological studies conducted in animals in the proposed indication of PDA. The results of the studies were considered as valid and acceptable. In addition, there was no justification to support the primary pharmacological activity of ibuprofen in

preclinical *in vivo* or *ex vivo* animal models of PDA since the potential of ibuprofen to close the DA had already been shown at the time when the development of Pedea was started.

The ductus arteriosus (DA) has an intrinsic tone and patency is an active state that is maintained by prostaglandins, mainly PGE2 which is the most potent DA relaxing agent known (Coceani et al., 1994, Smith et al., 1994). Although it is ~1000 times less potent than PGE2, the DA also relaxes in response to high concentrations of PGI_2 and there is functional evidence to suggest a dilator role for PGI2. Although native prostaglandins are all agonists at other types of prostaglandin receptors, albeit at least an order of magnitude less potent, PGI2 is not effecting relaxation via the PGE2 receptor. The presence of PGI2 receptors in the DA has been demonstrated and, as in other blood vessels, PGI2 is the main arachidonic acid product in the DA; approximately 10 times as much PGI2 as PGE2 is synthesised (Coceani et al., 1980). It appears therefore that PGI2 also plays a physiological role in the maintenance of the patency of the DA.

Studies in genetically engineered cyclooxygenase-deficient mice suggest that patency can be maintained in the foetus by maternally synthesised prostaglandins (Loftin et al., 2001).
Further, administration of various NSAIDs in late pregnancy is known to cause premature closure of the DA in many species, including humans (Van den Veyver et al., 1993). Studies in pregnant rats have demonstrated dose-related constriction of the DA as a general property of acidic NSAIDs, with indomethacin and ibuprofen being amongst the most potent (Momma et al., 1983, Momma et al., 1984, Momma et al., 1990). Comparing clinical doses, ibuprofen was more potent than indomethacin, although the effect of indomethacin was more prolonged, possibly because its plasma half-life in the rat is longer than that of ibuprofen (Adams et al., 1969).

Coceani et al., 1979, first studied the Pharmacology specific to the proposed indication in animals. Although indomethacin did not induce closure of the DA in pre-term rat foetuses, there appear to be species differences (Momma et al., 1983, Sharpe et al., 1974). In lambs, the prostaglandin mechanism responsible for maintenance of DA patency becomes functional earlier in gestation; ibuprofen has been shown to contract foetal lamb DA *in vitro* over the last trimester of gestation and constriction of foetal DA by ibuprofen was reported to be stronger in tissue from pre-term than in that from full-term foetuses (Coceani et al., 1979, Friedman et al., 1976, Heyman et al., 1976). Ibuprofen was shown to close the DA in lambs (Coceani et al., 1979) and not to affect basal CBF, cerebral metabolic rate, intestinal or renal hemodynamics in animal models, in contrast to indomethacin.
As NSAIDs given during human pregnancy cause premature closure of the DA, the mechanism appears to be functional in the human pre-term infant (Malcolm et al., 1993).

The PGE2 receptor exists as four distinct subtypes denoted EP 1 to EP 4 (Coleman et al., 1994). The receptor subtypes functioning in the DA have been investigated in a number of animal species but it is not clear whether inter-species differences exist (Segi et al., 1998).
A study in foetal rabbit tissue suggests that dilation of the DA is mediated via the EP 4 receptor; the inability of indomethacin to effect closure of the DA in EP 4 deficient mice is supports this, but as these mice survive in utero an alternative mechanism must also exist, possibly involving other subtypes (or perhaps the PGI2 receptor) (Nguyen et al. 1997, Segi et al., 1998). Agonists for EP I and EP 3 receptors also contract foetal rabbit DA *in vitro* but foetal piglet DA has been shown to express EP receptors 2, 3 and 4 in equivalent density, but no EP 1 receptor (Bhattacharya et al., 1999, Smith et al., 1995).
In the newborn piglet the density of the EP 2 receptors is maintained but there is a complete loss of the EP3 and EP 4 receptors resulting in a reduction of total PGE2 binding capacity, which must contribute to the reduced responsiveness of the DA to prostaglandins after birth even if other factors are also involved. It also suggests that in the newborn piglet dilation of the DA by prostaglandins is mediated via the EP 2 receptor (Bhattacharya et al., 1999).

After birth the closure of the DA occurs in two steps; the first step is a functional closure, caused by constriction of the medial muscle layer and usually occurs in the first few hours after birth, this is then followed by anatomical closure involving infolding of the epithelium and disruption of the subintimal layers, which is usually completed by the second week of life. The process of closure of the DA after

birth is similar in all mammalian species, although there are differences in closure rate and morphology (Clyman et al., 1983, Clyman et al., 1999, Hörnblad et al., 1967).

During the first step, the DA becomes less responsive to oxygen and PGE2; the changes that affect this must include the down-regulation of EP receptors. Ischaemia of the medial muscle (resulting from reduced blood flow) appears to be the stimulus for the second step (Bhattacharya et al., 1999, Clyman et al., 1983, Clyman et al., 1999).

The mechanism underlying the closure of the DA at birth is complex and is probably not yet completely elucidated (Coceani et al., 1980). The sudden increase in blood oxygen tension produced by the first breath and the drop in circulating prostaglandin levels that occurs after parturition have long been considered to be implicated (Hammerman et al., 2001).

Maintenance of the ischaemic state is required for completion of anatomical remodelling and the longer the DA remains constricted the less it is able to respond to the dilation stimulus of prostaglandins. Therefore, when the DA remains patent in the newborn, constriction by any means followed by maintenance of the ischaemic state should allow anatomical remodelling.

It has recently been shown that, despite the fact that in the newborn COX 2 and not COX 1 is expressed in the DA, it is circulating prostaglandin produced systemically by COX I and not local prostaglandin synthesised by COX 2 that maintains the patency of the DA (Guerguerian et al., 1998). Indomethacin has been shown to close the DA in the newborn piglet and as a selective COX 1 inhibitor (but not a selective COX 2 inhibitor) was also shown to effect closure, it appears that constriction of the DA is purely prostaglandin-mediated and the vasoconstrictive properties of indomethacin are making no contribution. Therefore, although there has been no actual demonstration in newborn animals that ibuprofen will constrict the DA, it can also be expected to be effective. The extended plasma half-life in the human neonate will also contribute to the maintenance of constriction that is required for anatomical remodelling to take place.

Secondary pharmacodynamics

The effects resulting from inhibition of prostaglandin synthesis after administration of NSAIDs have been well characterised and the applicant has provided a review of the effects of ibuprofen on different organs and systems and clarified its effects on cerebral and renal blood flow and its action on the pulmonary circulation

The biological activities of the prostanoids (the autocoids generated via the cyclooxygenase pathway) are extremely diverse. They produce their effects by acting on specific receptors and the specific biological activity results from local generation of the specific prostanoids and the tissue distribution of the various types of receptors (Coleman et al., 1994). Inhibition of prostaglandin synthesis may therefore interfere with these processes and result in unwanted side effects.

The adverse effects resulting from inhibition of prostaglandin synthesis after oral administration of NSAIDs are well known. The most common, the occurrence of gastro-intestinal bleeding, is
usually a consequence of long-term administration; the incidence in humans is much lower for ibuprofen than for any other NSAID (Langman et al., 1994, Henry et al., 1996, Henry et al., 1999). Potential for renal toxicity is inherent in all NSAIDs as a result of inhibition of the synthesis of PGE2 and PGI2 which are involved in the maintenance of renal blood dynamics, but usually toxicity only occurs when renal perfusion is impaired (Whelton et al., 1991). The risk for adverse effects in children aged ~8 months has been shown to be low after oral administration of ibuprofen (Lesko et al., 1995).

Although ibuprofen inhibits thromboxane (TxA2) biosynthesis and causes a dose-related inhibition of *ex vivo* aggregation of rat platelets after oral administration, it has little anti-coagulative activity (Evans et al., 1991, Rainsford et al., 1999). Its anti-thrombotic effect *in vivo* is weak, after i.p. administration in rabbits it was about 450 times less effective than Indomethacin (DiPasquale et al., 1997, Royer et al., 1985). It is also a weak inhibitor of platelet aggregation in man.

Prostaglandins are involved in the physiological regulation of vascular tone, usually exerting a vasodilatory effect. However, in adult animals the effects of intravenous administration of ibuprofen on blood-flow are limited. Administered intravenously to adult baboons, ibuprofen 50 mg/kg (either as four bolus doses of 12.5 mg/kg at 6 hourly intervals or as a continuous infusion over 24 hours) produced only mild or insignificant changes in haemodynamic parameters (mean arterial pressure, central venous pressure and heart rate) (Rao et al., 1994).
In adult mongrel dogs, however, ibuprofen 10 mg/kg i.v, increased aortic blood pressure by 20% and caused a slight, although significant reduction of the renal blood flow (Feigen et al., 1981). The reference drug indomethacin, 2.5 mg/kg, produced a similar effect on aortic and renal flow but, whereas this dose of ibuprofen had no significant effect on mesenteric blood flow, indomethacin rapidly reduced mesenteric blood flow by 50%. Both drugs similarly attenuated the responses to arachidonic acid (i.e. inhibited prostaglandin synthesis) at the doses used, but, unlike the effects on renal vascular resistance, the ability of indomethacin to elicit mesenteric vasoconstriction was shown to be independent of its inhibition of prostaglandin synthesis.

In the premature human newborn, in the presence of a PDA, there is a redistribution of systemic blood flow, which can lead to impaired perfusion of some organ systems, with the gastrointestinal tract, kidneys and brain being especially vulnerable (Hammerman et al., 2001). The effects of intravenous ibuprofen on regional blood flow to these organs have been investigated in newborn animals.

Ibuprofen, 0.02 and 0.2 mg/kg i.v. produced a dose-related increase in renal vascular resistance (RVR) with consequent decrease in renal blood flow (RBF) and glomerular filtration rate (GFR) in newborn rabbits (Chamaa et al., 2000). Urinary volume, unaffected at the lowest dose, was decreased at 0.2 mg/kg. A ten-fold increase in dose to 2.0 mg/kg had little further effect.
The investigators concluded that the renal effects of ibuprofen in the newborn rabbit are at least as great as those of indomethacin, but no reference group was included in this study and the data for indomethacin, quoted from an earlier study, are for a single dose, 2.0 mg/kg only.
Although the values for changes in RVR, RBF, GFR and urinary volume are comparable with those at the same dose of ibuprofen, there is no data for lower doses of indomethacin and consequently no information on the dose at which maximal response is achieved.

In a study in newborn piglets the doses of ibuprofen and indomethacin effective in closure of PDA in the human premature infant were compared directly (Speziale et al., 1999). A much higher dose of ibuprofen (20 mg/kg i.v.) than in the previous study increased vascular resistance in the renal cortex and medulla (by 40 and 50 % respectively) at 90 and 120 minutes after administration. After a dose of indomethacin of 0.3 mg/kg, (much lower than that quoted in the previous study) RVR increased to a greater extent (66 and 70 % respectively) at 40 minutes after injection and the blood flow was significantly decreased. Consequently, the potential for ibuprofen to affect renal blood flow appears to be no greater than that of indomethacin.
In the same study, ibuprofen showed no effect on gastrointestinal blood-flow in the newborn piglet, whereas indomethacin rapidly almost doubled vascular resistance in duodenum/jejunum, ileum and colon (Speziale et al., 1999).

Ibuprofen was shown in the newborn piglet not to affect cerebral vascular resistance or have any significant effects on total or regional cerebral blood flow either at a dose comparable to that used clinically for closure of the DA (20 mg/kg i.v.) or at a higher dose (30 mg/kg) at which prostaglandin synthesis was markedly decreased (Pellicer et al., 1999, Speziale et al., 1999). In contrast, indomethacin exerted a significant vasoconstrictive effect in the brain even at a dose of 3 mg/kg that did not affect cerebral prostaglandin synthesis with vascular resistance being doubled at maximal response to 0.3 mg/kg, the dose used for closure of the DA (Chemtob et al., 1991). Consequently, unlike indomethacin, ibuprofen would not be expected to exacerbate the effects of PDA on cerebral blood flow.

Although prostanoids do not play a critical role in the regulation of basal CBF in the newborn, they do however playa role in setting the blood pressure limits within which autoregulation of cerebral blood flow can be maintained in the newborn (Chemtob et al., 1990, Chemtob et al., 1991). In newborn piglets, although global and regional blood flow was maintained at a constant proportion of mean

blood flow over a blood pressure range of 50-90 mm Hg in the control group, it varied markedly outside these limits. However, in a group treated with ibuprofen (30 mg/kg i.v.) the blood pressure range over which cerebral blood flow did not vary significantly was extended to 37-117 mm Hg. In addition, at the lowest blood pressure investigated (30 mm Hg), the decrease in cerebral blood flow was significantly less in the ibuprofen-treated group than in the control group (30% compared to 75%, $p<0.001$). Consequently, ibuprofen not only has no deleterious effect on cerebral blood flow even in the newborn, but where blood flow is reduced it may assist in its maintenance.

Indomethacin has been reported to inhibit physiological carbon dioxide-induced cerebral vasodilation during normoxic hypocarbia (Pellicer et al., 1999). Prostaglandins do not appear to be involved in the mechanism and ibuprofen (30 mg/kg i.v.) had no effect in newborn piglets under these conditions.
Under artificial ventilation, frequently a necessity in premature human infants, cardiac output is decreased (Malcolm et al., 1993). When cardiac output falls the decrease in blood flow is not distributed equally amongst the different vascular beds; blood flow to the brain is maintained with that to the kidney and gut being compromised. In artificially ventilated, newborn piglets, cardiac output decreased with increasing airways pressure. Blood flow to colon, ileum and kidney decreased with increasing pressure but cerebral flow was maintained. As prostaglandin levels were unaffected they do not appear to be involved in the underlying mechanism and intravenous, administration of ibuprofen, 40 mg/kg, did not influence the effects of artificially ventilation on regional blood flow; in contrast indomethacin, 0.3 mg/kg, further reduced blood flow to the ileum and brain.

In the lung the low vascular tone of both arterial and vascular vessels characteristic of the adult pulmonary circulation is maintained by basal production of vasodilatory prostaglandins, mainly PGI2 and the adult pulmonary circulation shows little or no response to physiological or pharmacological stimulation (Abman et al., 1989).

The sudden and dramatic decrease in PVR that occurs at birth is essential for normal transition from foetal to neonatal circulation, with the pulmonary circulation being required to dilate to accommodate an eight- to ten-fold increase in blood flow. Several physiological stimuli contribute to the fall in PVR, amongst them, rhythmic distension of the lung and increased oxygen tension as well as the haemodynamic stress resulting from constriction of the DA. The final mediator of stress-induced vasodilation is nitric oxide (NO), which appears to play a greater part in the regulation of PVR in the perinatal pulmonary circulation than PGI2 and it has been shown that PGI2 exert its effects mainly via release of NO (Storme et al., 1999).
It is not therefore surprising that in the term neonatal lamb, although pulmonary vasodilation induced by rhythmic distension without oxygenation was inhibited in the presence of a NSAID, there was no effect on oxygen-induced pulmonary vasodilation which is mediated by direct activation of nitric oxide synthase (NOS) by oxygen (Velvis et al., 1991, Zenge et al., 2001). In the full term neonatal lamb, although dose related pulmonary vasoconstriction was observed after acute administration of indomethacin the response was no longer present after repeated dosing, suggesting that the neonatal lung adapts to chronic inhibition of prostaglandin synthesis by the development of NO-based mechanisms and prostaglandins are not essential for maintenance of pulmonary vascular tone (Lock et al., 1980).

If the oxygen stimulated mechanism for activation of NO synthesis has not yet developed in a very premature baby inhibition of rhythmic distension-induced vasodilation by administration of an NSAID very soon after birth could allow a myogenic response and therefore pulmonary vasoconstriction. If the DA and/or foramen ovale is still patent (as in the cases in the clinical trial) an increase in PVR would re-establish the foetal pattern of circulation, reducing pulmonary blood flow, decreasing oxygenation, which in its turn causes metabolic acidosis and hypoxia. As the vasodilatory response to hypoxia is prostaglandin mediated this will also be suppressed (Leeman et al., 1999).

Free radicals have been implicated in the development of injury to the immature retina. Asphyxia increases the levels of both free radicals and prostaglandins and using newborn piglets, a species with retinal characteristics similar to those of the human, ibuprofen has been used to demonstrate that the cyclooxygenase pathway is probably the source of free radicals after asphyxia. Administration of a cyclooxygenase inhibitor may therefore protect the retina in the premature newborn when blood flow

is compromised. Indomethacin may not afford the same overall advantage as it has been shown to impair retinal haemodynamics in the newborn piglet by a mechanism unrelated to inhibition of prostaglandin synthesis whereas ibuprofen enhances retinal and choroidal blood flow autoregulation in newborn piglets (Chemtob et al., 1991, Parys-Van Ginderdeuren et al., 1992).
Further, ibuprofen appears to exert a cytoprotective effect on the intestinal mucosa (Grosfeld et al., 1983). In an experimental model of bowel ischemia in rats, animals treated with ibuprofen had significantly lower incidence of intestinal necrosis (Grosfeld et al., 1983). It is suggested that the protective effect of ibuprofen results from inhibition of synthesis of thromboxane, which is a vasoconstrictor.

Like all the carboxylic acid NSAIDS, ibuprofen binds to serum albumin at the same site as bilirubin (Cooper-Peel et al., 1996). In an *in vitro* study using infant blood serum ibuprofen, at a concentration close to that seen in clinical use for closure of the DA (750 µmol/l, i.e. 154.7 µg/ml), increased the free bilirubin fraction fourfold at a bilirubin to albumin molar ratio (B:A) of 1:2. No absolute values for free bilirubin concentration are quoted in the publication and it is not clear whether the free bilirubin concentration reaches a level at which a premature infant would be at risk for bilirubin encephalopathy. A later study (Ma et al., 2002) using a different method with albumin solutions at varying concentrations, reports that significant displacement does not occur until the B:A ratio reaches 2:1 (no effect at 1.5:1) and at an ibuprofen concentration of 285 µg/ml (no effect at 200 µg/ml compared to a clinical level of 180 µg/ml).

Some NSAIDs appear to modulate signal transduction pathways involved in immune cell maturation and apoptosis and consequently have anti-inflammatory and anti-proliferative effects independent of cyclooxygenase and prostaglandin synthesis inhibition (Tegeder et al., 2001). These effects vary between the individual drugs. The properties which ibuprofen does not share with indomethacin are inhibition of the transcription factor NF-KB, interference with the MAP kinase cascade at two points, stimulation of a shock factor release and expression of a nuclear receptor. The *in vitro* IC50 concentrations required are at least 100-fold those effective in inhibition of COX enzymes. These properties are unlikely to be relevant in short-term administration.

Safety pharmacology

After many years of use, the risks for adverse effects on major physiological systems after oral administration of ibuprofen are well characterised and are always related to the primary effect of inhibition of prostaglandin synthesis. The effects of intravenously administered ibuprofen on physiological systems, which may be compromised in the presence of a PDA, have been investigated in newborn animals *(see secondary pharmacodynamics)*. Conventional safety pharmacology studies would add nothing to the information already available for ibuprofen.

Pharmacokinetics

Pharmacokinetics and ADME characteristics were studied in rats, rabbits and dogs (Adams et al., 1969, Adams et al., 1970, Mills et al., 1973). Adams et al., 1969, detailed pharmacokinetics of ibuprofen after a single dose, pharmacokinetics of ibuprofen after repeated administration and distribution in the different tissues of rats, rabbits and dogs. Mills et al., 1973, studied the metabolism and excretion of ibuprofen in rats, baboons and dogs.
As the pattern of effects reported in these species is similar, the results of the studies can be considered as valid and acceptable. In addition, it was considered unethical and unnecessary to undertake extensive animal studies to obtain information on what was already known for humans.

Ibuprofen has a short plasma half-life in both animals and adult humans. It is cleared by oxidative metabolism and is mainly excreted in urine as conjugates of its metabolites. All metabolites found in man are present in the animal species used for toxicity studies and all are pharmacologically inactive. Ibuprofen is a racemic compound; its activity resides in the S-isomer, the R-isomer is inactive. Like many propionic acid derivatives, it undergoes metabolic inversion. This is uni-directional in all species examined, including man, with the inactive R-isomer being converted to the active S form.

In the human premature neonate, the plasma half-life of ibuprofen after i.v. administration is 30hrs compared with 2hrs after oral administration in the adult, a value which is achieved in infants by about 6 months of age (Aranda et al., 1997, Kelley et al., 1992). Although immature renal function may contribute to the slow elimination, it is likely that limited capacity for metabolism is the main cause of the prolonged plasma half-life. Ibuprofen is metabolised by oxidation and carboxylation of the isobutyl side chain followed by conjugation of the metabolites. The activity of the cytochrome P450 complex and NADPH cytochrome c reductase are very much lower in the newborn than in adults and glucuronidation capacity is greatly reduced (Warner et al., 1986). Presumably the deficit is even greater in the premature neonate. It has also been reported that whilst clearance and volume of distribution in infants (6-18 months) are similar to adults, plasma concentrations of the R-isomer after administration of the racemate are considerably higher than those of the S-isomer (Rey et al., 1994). This suggests that stereo inversion capacity may also be reduced in infants. This is not unlikely as the mechanism of stereo-inversion involves formation of the R-ibuprofen-CoA complex and the activity of the enzymes required may also be deficient in the human neonate. It is possible that this could both enhance efficacy by providing a prolonged release of the pharmacologically active S-isomer and also limit potential toxicity.

Drug interactions

Most clinically significant drug interactions result from the ability of NSAIDs to inhibit cyclooxygenase, thereby reducing prostaglandin biosynthesis. Some NSAID drug interactions result from the fact that NSAIDs are highly bound to plasma proteins and thus may compete with other drugs for binding sites. Data referring to interactions studies conducted in animals with ibuprofen are very sparse. However, this point is further addressed in the clinical part and taking into account the specificity of the target population, the applicant considers that animal findings would not better contribute to the knowledge of potential interactions of ibuprofen with concomitant drugs commonly used in neonates suffering from PDA.

Toxicology

Single dose toxicity and Repeat dose toxicity

Single dose toxicity studies were performed in mice, rats and dogs in 1969 (Adams et al., 1969), but taking into consideration the new route of administration and the target population, the applicant conducted an acute toxicity study with Pedea in the weaned and the adult rats by the intravenous route.

The same authors (Adams et al., 1969) studied repeated dose toxicity – long-term during 26 weeks in rats and dogs. It was considered that the published data available in rats and in dogs together with the results of the acute toxicity give sufficient information to assess toxicity of ibuprofen.
In addition, as in the local tolerance study no evidence of organ related toxicity was seen at necropsy after 5 daily injections, the applicant considered that additional repeat-dose studies were not deemed necessary.

Although the intravenous route has undertaken no repeated dose studies, such studies could add nothing to the information already available for ibuprofen. Either the dose would be sufficiently high to be lethal or, because ibuprofen is secreted into the stomach, there would be evidence of gastrointestinal irritation as seen after administration by other parenteral routes. Possibly, renal toxicity might be evident after repeated i. v. administration, but this is an established hazard. No evidence of organ related toxicity was seen at necropsy after five daily injections of the maximum therapeutic dose. The actual risks arising from prolonged inhibition of prostaglandin synthesis as a result of the prolonged retention of ibuprofen in the premature neonate can only be assessed in the clinic.

In the acute toxicity study undertaken in weaned and adult rats, the symptoms observed, after intravenous administration (i.e. CNS depression) were consistent with those seen after oral administration, but at higher doses were sufficiently extensive to cause death. All deaths were rapid and there was a clear demarcation between lethal and non-lethal doses. The cause of death was CNS

depression; as ibuprofen readily penetrates the brain it is not surprising that the acute intravenous toxicity of the formulation was not significantly different in weanling and adult rats. Although it is not practical to ascertain whether there is a clear difference in sensitivity in premature animals, the potential hazard has been established.

The maximum non-lethal dose administered was 265 mg/kg (Davies et al., 1993). The blood volume of a rat has been reported to be 5-7% of the body weight, taking a mid value of 6%, and a haematocrit of 46 (ibid), total plasma volume would be 32.4 ml/kg, therefore the 'instantaneous' plasma concentration on administration of this dose would be 8.2 mg/ml, (i.e. 8200mg/l). Making a comparable calculation for a human neonate, plasma volume 41.5 ml/kg, injection of the maximal dose of 20mg/kg would give an instantaneous concentration of 0.5mg/ml (500mg/l) (Aranda et al., 1997, Low et al., 1963).

In the premature human neonate binding to plasma albumin is lower than in the adult and similar to that in the rat (95%); levels of free drug will therefore be comparable and about one-sixteenth of the maximal value which could have been achieved in the rat after a dose at which transient CNS depression was observed. At the plasma concentrations of 180mg/l reported effective in therapeutic use the safety factor is ~45 (Aranda et al., 1997, Van Overmeire et al., 1999).

Genotoxicity *in vitro* and *in vivo*

Mutagenic potential was investigated in Europe, India and in the USA. Oldham and al., 1986, tested ibuprofen for mutagenic activity in the Ames test using five strains of S. typhimurium and activation by liver microsomes from three different species. No mutagenic activity was observed.

Ibuprofen, like three other NSAIDs, also gave negative results in a multi gene assay using B. subtilis, which showed a positive effect for clofibrate (Van Overmeire et al., 1999). In 1997, an Indian team (Philipose et al., 1997) confirmed lack of mutagenic potential in an Ames test. In the same paper these authors concluded that ibuprofen was "weakly mutagenic" in an *in vivo* sister chromatid exchange (SCE) study using bone marrow cells (Philipose et al., 1997). This conclusion was based on a very slight dose-related trend to increase in SCE/cell which was significantly different from control ($p<0.01$) at the mid and high dose levels, although the value did not reach double the control level even at the high dose (Philipose et al., 1997). However, where such a three-point monotonic response occurs without inducing doubling of the SCE incidence, the highest dose increase is required to be at the significance level of $p<0.001$ for the response to be considered positive (Tucker et al., 1993). The results reported in this study do not fulfil this criterion.

No evidence for an effect on SCE has been found in clinical use. There was no increase in the incidence of SCE after clinical use of NSAIDs in two studies that included ibuprofen (Kullich et al., 1986, Ozkul et al., 1996). Although the number of patients was not high in either study there has also been a negative report from a study with NSAIDs in which ibuprofen was not included, by investigators who have been able to pick up a positive response in patients on anti-convulsive therapy using the same methods in a similar size population (Sardas et al., 1991, Sardas et al., 1994).

Carcinogenicity

Carcinogenicity studies were performed in the EU in the 1960s in mice and rats (Adams et al., 1970). Although the carcinogenicity study carried out during the original development of ibuprofen cannot be considered adequate by current standards, no positive response was evident. Although prostaglandins are involved in cell proliferation, neoplasia and the immune response, there has been no indication from the carcinogenicity studies carried out to current standards with newer NSAIDs that inhibition of prostaglandin synthesis *per se* has any carcinogenic potential.

Frequent use of NSAIDs has in fact been reported to be beneficial in the treatment of colorectal cancer and although no negative correlations with other types of malignancy were found in this large epidemiological study, it is noteworthy that no positive correlations emerged (Rosenberg et al., 1991). NSAIDs inhibit tumorigenesis in the lung induced in animals by the N-nitrosamine L8 NNK (4-

(methylnitrosamino]-1-(3-pyridyl]-1-butanone) found in tobacco smoke. The mechanism appears to be related to inhibition of prostaglandin synthesis rather than direct inhibition of NNK- LID induced lipid peroxidation or oxidative DNA damage. It has also been suggested that inhibition of prostaglandin synthesis may suppress tumour incidence by enhancing apoptosis in carcinogen-initiated rat colon cells (Nicholson et al., 1998).

NSAIDs have also been reported to be cytotoxic in vitro to a wide range of tumour types, including breast and renal cancer cells, whilst being less toxic to normal non-malignant cell lines.

During evaluation of a clinical trial application a query was made regarding the potential mutagenicity of metabolites other than those normally found in the adult, which might be present in the premature neonate (Brocks et al., 1999). The molecular structure of ibuprofen is relatively simple; it possesses no group such as an ester or an amide that could be readily hydrolysed and it is eliminated by oxidative metabolism and conjugation. No hydroxylation of the phenyl ring or of the propionic acid group has ever been detected. The capacity of the neonate to carry out the metabolic processes is likely to be reduced, resulting in a prolonged plasma half-life, but it seems very unlikely that the premature neonate would have the capacity to metabolise ibuprofen by routes not seen in the adult. Before the mutagenic potential of abnormal metabolites could be investigated their existence and structure would have to be established.

Considering the above data already available and the extensive use of ibuprofen in other indications for many years, it was considered that the study of the genotoxic and carcinogenic potential of ibuprofen is sufficiently documented in the literature.

Reproductive and developmental studies

Reproduction studies with ibuprofen were performed in rats and rabbits (Adams et al., 1969).
Considering that Pedea will be exclusively administered to premature neonates, the target population is not at risk regarding pregnancy. It is therefore sufficiently justified not to extensively assess possible embryotoxic and/or perinatal toxicities of ibuprofen in such a population.
However, the following supportive data were retrieved from the literature regarding 'Fertility and General Reproductive performance':
Ibuprofen, 20 mg/kg/day administered in the diet to male and female rats for 60 days prior to mating had no adverse effect on fertility or reproductive function. When administered from day 1 of gestation to caesarean section on day 20 there may have been some early total litter losses at a dose of 180-mg/kg/day i.g. (NOEL 60 mg/kg/day).
In the rabbit, the ratio of implants to corpora lutea was reduced in comparison to controls at a dose of 60 mg/kg/day orally given over days 1 - 29 of gestation (NOEL 20 mg/kg/day). This effect is seen with many Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) as prostaglandins are involved in implantation.

External, visceral and skeletal malformations and skeletal variations were comparable to controls in litters from rats given ibuprofen over days 1-20 of gestation at dose levels up to 180 mg/kg/day, a dose at which growth rate was reduced (NOEL 60 mg/kg/day, intestinal lesions present from 20 mg/kg/day).
Malformations showed no relationship to dose in rabbits given ibuprofen at dose levels up to 60-mg/kg/day i.g. Post-implantation loss and foetal weight and viability were comparable to controls. Weight gain was reduced from 20 mg/kg/day and gastric lesions were present from 7.5 mg/kg/day.
In rats given ibuprofen at doses up to 20 mg/kg/day from day 1of gestation to parturition, litter size, viability indices at birth and weaning and weight at weaning were comparable in treated and control animals. The original studies (Adams et al., 1969) do not record any observations of an effect on parturition.

Local tolerance

The applicant to assess the effects of daily intravenous administration of Pedea for 5 days has performed a local tolerance study in rabbits. The intravenous, intra-arterial and perivenous routes were

investigated. This study showed that the formulation is well tolerated; local effects were related to the injection rather than the solutions (either preparation or vehicle) administered. There was no difference between the test article and the two control groups (vehicle and saline) in terms of local tolerance. Although the difference did not reach significance, the anti-inflammatory effect of ibuprofen was apparent at the injection site after i.v. administration, with the mechanical trauma of the injection (haematoma and erythema) being observed after the first administration of saline or vehicle but not until after the fifth injection of the formulation. There was no evidence of organ related toxicity at necropsy after 5 daily injections.

Other toxicity studies

Excipients and impurities

The formulation contains trometamol (2-amino-2-hydroxymethyl-1,3-propanediol, also referred to as TRIS or THAM, 7.56 mg/2 ml, a concentration of 0.03 M. The quantity administered in a single dose will be 7.56 mg/kg and the maximum total dose of trometamol will be 15.12 mg/kg.
On injection, it distributes to the extracellular space and is rapidly excreted via the kidney in its protonated form by glomerular filtration. Trace amounts are metabolised by oxidation in hepatocytes(<1 %). Accumulation occurs only when repeated high doses are administered at short intervals. It is therefore to be expected that the small quantity of trometamol present in the formulation (pH 7.4) will be excreted very rapidly. In the acute toxicity studies made for this indication the vehicle for the concentrated ibuprofen solution was the same as the formulation to be marketed and at the maximum administrable volume, 10 ml/kg, the vehicle was indistinguishable from the saline control. The volume administered was five times the therapeutic dose.

In a study investigating toxicity in animals, reported in 1961, the intravenous LD50 for 0.3 M trometamol in mice was 16.5 mmols/kg (55 ml of this solution) (Roberts et al., 1961). Convulsions were observed immediately before death. Neutralising the solution with HCl (pH 7.4) decreased the LD50 value to 12.9 mmole/kg (29 ml of this solution), i.e. approximately 150 times the quantity in the proposed therapeutic dose. There were no observable effects in mice or rabbits given bolus injections of 50 ml/day of a 0.155 M solution (i.e. about half the LD50) for 10 days, whether alkaline or acidified, about 75 times the proposed therapeutic dose, given at three times the concentration of this formulation.

The toleration of quantities much higher than the LD50 when given slowly confirms that trometamol is very rapidly excreted and the greater quantity tolerated when buffered to a physiological pH is in conformity with its being excreted faster in the ionised state (it is ~80% dissociated at pH 7.4).

The effects of trometamol on PVR and blood flow at varying oxygen tensions have been investigated in neonatal calves (Rudolph et al., 1966). When ventilated with pure oxygen, infusion of trometamol buffer decreased pulmonary vascular resistance in proportion to the increase in blood pH achieved, with a corresponding increase in pulmonary blood flow and, although PVR was increased by hypoxia at acid pH, decreasing the oxygen concentration of the inspired air had minimal effect on PVR at blood pH ~7 3. The direct effect of trometamol infusion on the pulmonary vasculature would therefore be opposite to that required to cause the observed cases of hypoxaemia (see clinical safety).

Un-ionised trometamol can slowly penetrates erythrocytes (Ben-Isaac et al., 1972). The increase in intracellular pH increases the affinity of haemoglobin for oxygen (Bohr effect) and, after infusion of the quantity of alkaline trometamol used in the treatment of acidaemia, contributes to arterial hypoxia. Trometamol buffered to pH 7.4 does not enter erythrocytes and again the adverse events in the clinical trial cannot be attributed to this effect.

Trometamol also acts as an osmotic diuretic, which further promotes the excretion of not only bicarbonate but also other weak organic acid anions such as salicylate and therefore ibuprofen. It seems unlikely that the dose being administered with this formulation will decreases the plasma half-life of ibuprofen to any significant extent. The hypoglycaemia reported after infusion of doses in excess of 500mg/kg (4mmol/kg) of alkaline trometamol also results from increased insulin release at

an alkaline intracellular pH and cannot occur after the infusion of small quantities of buffered trometamol.

Impurities

Process and degradation impurities consist of substances related to ibuprofen. Two of these (2-[4-butylphenyl] propionic acid and 4-isobutylacetophenone) are present in all ibuprofen preparations and are within the limits prescribed in the Ph. Eur. The databases RTECS, HSDB, TSCA, OHMT ABS, CHRIS, IRIS, CHEMBANK and DOSE have been searched and no reports of toxicity relating to these compounds or to the four compounds specific to this preparation have been found.

Ecotoxicity/environmental risk assessment

Art. 8 of Directive 2001/83/EC, as amended, requires the applicant to indicate any potential risks exhibited by the medicinal product for the environment and to perform an evaluation, if applicable, of the precautionary and safety measures to be taken during the storage of the product, the environmental release following use in patients as well as the disposal of unused or waste products.

Pedea is intended for the treatment of PDA in premature neonates. The maximum prevalence of this cardiac disorder in the EU was estimated to 2.13 per 10,000 persons by the COMP during the Orphan Designation procedure. If one considers that the overall PDA prevalence without any considerations of the gestational age is 31%, the total number of neonates in the EU presenting a PDA would be theoretically 80,000 in 2000. Therefore, if one considers that the maximum dosage for 2 full courses of treatment (i.e. 3 injections x 2) is 40 mg/kg/patient [(10 + 5 + 5) x 2] and that the maximum body weight of a neonate is 3 kg, the quantity of the medicinal product to be consumed per year in the EU would not represent more than 9.6 kg of ibuprofen (40.10^{-6} x 80,000 x 3).

The applicant therefore considers that it is not relevant to assess the environmental risk of ibuprofen and related compounds' release in the water compartment. Indeed this quantity, which is obviously overestimated, is very negligible compared to the large quantity of ibuprofen used in other non-orphan indications. Given the low extent of use of ibuprofen in the present claimed indication and the absence of any genotoxic potential, it is very unlikely that Pedea may represent a risk for the environment following its prescribed usage in the target population or further to its accidental release and dispersion into the environment.

Discussion on the non-clinical aspects

The applicant has conducted two novel studies to support the current application: an acute toxicity study in the weaned and adult rat; and a local tolerance study in the rabbit. These were conducted to support the safety evaluation of i.v. ibuprofen for the current indication. The remainder of the non-clinical part of the application is bibliographic.

The cited literature varies by age: Research published between 1960 and 1989 (n=34) may be lacking methodologically in comparison with those published since 1990 (n=65). However, confidence in the data from these older studies comes from the unity of results with more recent studies, and in the light of the vast clinical experience with ibuprofen. There are sufficient data available on ibuprofen to support pre-clinical safety, with relevant clinical data taking precedence. Thus there would be little to gain from the conduct of further pre-clinical studies. Further, in relation to the indication sought, the product is to be administered in life-threatening situations by highly specialised practitioners.

The published literature fulfils the level of detail necessary to substantiate the non-clinical pharmacodynamics, pharmacokinetics, and toxicology of ibuprofen for the proposed clinical indication of intravenous use in premature human neonates to close a PDA. The published literature is extensive and much of it has been in the public domain for at least twenty years. It is considered that the normal dossier requirements are satisfied and the application can be considered a full 'mixed' application in accordance with art. 8 (3) and Annex I part II.7 of Directive 2001/83/EC, as amended.

Pharmacodynamics
The pharmacodynamic profile of ibuprofen has been extensively characterised (Coceani et al., 1980, Coceani et al., 1994, Smith et al., 1994, Loftin et al., 2001, Van der Veyver et al., 1993, Momma et al., 1983, Momma et al., 1984, Momma et al., 1990, Adams et al., 1969, Sharpe et al., 1974, Coceani et al., 1979, Friedman et al., 1976, Heyman et al., 1976, Malcolm et al., 1993, Coleman et al., 1994, Segi et al., 1998, Nguyen et al., 1997, Bhattacharya et al., 1999, Smith et al., 1995, Clyman et al., 1983, Clyman et al., 1999, Hörnblad et al., 1967, Hammerman et al., 2001) but there are no useful animal models of the postnatal patent DA. However, there is little doubt that DA patency is maintained by systemic prostaglandins, and that, although a drop in circulating prostaglandin levels is not normally the primary defining event of DA closure, the administration of inhibitors of prostaglandin synthesis (in this case ibuprofen) trigger the required constriction of the ductus musculature, thus effecting closure. This principle has been adequately demonstrated clinically, and further preclinical pharmacology studies are not required for the proposed indication.

The applicant discusses secondary pharmacodynamic effects of NSAIDs extensively. There are good non-clinical data available to support the use of ibuprofen in favour of the reference drug indomethacin, which is known to cause adverse events unrelated to inhibition of prostaglandin synthesis in the proposed patient population *(see also clinical part)*.

Pharmacokinetics
The known PK profile of ibuprofen, along with the superiority of clinical PK data on neonates negates the requirement to conduct further investigations in animals (Aranda et al., 199, Kelley et al., 1992, Warner et al., 1986, Rey et al., 1994).

Toxicology
The toxicology programme is very limited but in view of the extensive preclinical and clinical data already available relating to the biological properties of ibuprofen this is considered acceptable.

The acute i.v. study in the weaned and adult rat does not add to our knowledge of ibuprofen toxicity. However, the applicant to generate a crude but acceptable calculation of a safety factor uses it.
In the acute toxicity study, symptoms consistent with CNS depression were observed. This was considered to be the cause of death at high doses since almost all deaths occurred rapidly.
Based on the maximum non-lethal dose of 265mg/kg and reasonable assumptions of blood volume in rats and human neonates, the applicant has calculated a safety margin of ~45x compared with the effective clinical dose.

I.v. repeat-dose toxicity studies are not available, however, it is accepted that conduct of such studies would add little to the current knowledge base (Davies et al., 1993, Aranda et al., 1997, Low et al., 1963, Van Overmeire et al., 1999, Oldham et al., 1986).
There are no concerns with regards to mutagenicity / carcinogenicity for the current indication (Oldham et al., 1986, Shoba et al., 1985, Philipose et al., 1997, Tucker et al., 1993, Kullich et al., 1986, Ozkulet al., 1996, Sardas et al., 1991, Sardas et al., 1994, Rosenberg et al., 1991, Nicholson et al., 1998, Brocks et al., 1999, Brinkman et al., 1960).

The applicant has provided a rationale for the safety of small amounts of trometamol present in the formulation (Brinkman et al., 1960, Nahas et al., 1963, Nahas et al., 1998, Rudolph et al., 1966, Ben-Isaac et al., 1972).

The local tolerance study conducted for this application demonstrated mechanical damage in treated and control animals, and that ibuprofen has an initial, beneficial, effect due to its anti-inflammatory properties.

In consideration of the proposed indication and patient population, and in light of clinical data gathered from over 1000 preterm newborns, the toxicity profile of ibuprofen is acceptable for the current indication. All preclinical data considered relevant to clinical safety have been included in the Summary of Product Characteristics (SPC) for Pedea. With the exception of an acute toxicity study, no further studies have been carried out in juvenile animals with Pedea.

4. Clinical aspects

GCP

The clinical studies conducted by the applicant were of good scientific quality, and appear well conducted and reported. Studies from the literature have, with occasional exceptions, been published in peer-reviewed journals; the standard ranges from excellent to acceptable. No evident problems arise from GCP issues.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption – Bioavailability

Study report 9-33/93 describes a healthy volunteer trial in twelve adult male and female subjects carried out in 1993 using an intravenous formulation of ibuprofen. Each subject received a single dose of 400 mg in 50 ml water for injection infused over 15 minutes; blood samples were taken at intervals over the ensuing eight hours: the resultant pharmacokinetic variables are shown in the table below.

Group mean (SD) pharmacokinetic indices for intravenous ibuprofen

$AUC_{0\rightarrow\infty}$ (μg.min/ml)	C_{max} (μg/ml)	MRT (min)	CL (ml/min)	Vt (L)	Vss (L)	$T_{1/2}$ (min)
8.89 (1.6)	66.07 (8.99	137.83 (21.34)	53.06 (9.58)	8.22 (1.50)	7.21 (1.12)	108.35 (14.12)

Much of the published efficacy data on closure of PDA were generated using an intramuscular preparation of ibuprofen lysine (Imbun®) administered intravenously. In order to establish the comparability of that preparation and Pedea the applicant has conducted a bioavailability study of the two preparations.

Study IBU/00/BIOEQ/FR compared the pharmacokinetics of ibuprofen in eighteen healthy adult male volunteers who received single intravenous doses of 5 mg/kg infused over 15 minutes in an open label, two-way crossover design.

Group mean (SD) pharmacokinetic parameters for R- ibuprofen

	C_{max} (μg/ml)	$AUC_{0\rightarrow\infty}$ (μg.min/ml)	$T_{1/2}$ (min)
Ibuprofen (Pedea)	28.4 (3.7)	46.7 (7.9)	3.04 (0.94)
Reference (Imbun)	27.3 (2.8)	44.4 (5.15)	3.27 (1.52)
90% CI	0.98-1.10	0.98-1.11	

Group mean (SD) pharmacokinetic parameters for S- ibuprofen

	C_{max} (μg/ml)	$AUC_{0\rightarrow\infty}$ (μg.min/ml)	$T_{1/2}$ (min)
Ibuprofen (Pedea)	26.5 (3.2)	63.1 (11.6)	2.4 (0.3)
Reference (Imbun)	25.7 (2.8)	60.2 10.3	2.3 (0.3)
90% CI	0.98-1.08	1.01-1.08	

Distribution

In Study IBU/PROPHYL/2000 undertaken by the applicant, V (taken to mean volume of distribution) is listed as having a group mean of 238 (s.d. 125) ml. The publication by Aranda et al., 1997, gives a mean (s.d.) of 62.1 (3.9) ml/kg; and that by Van Overmeire et al. 1999, 0.35 (0.15) L/kg. For reference the volume of distribution in human adults cited in the literature is frequently ten litres and above depending on the study and the enantiomer.
Studies of distribution in human body fluids, e.g. synovial, skin blister, CSF, have been carried out (Brocks et al., 1999); as they are not directly relevant to the application they are not further discussed here.
Ibuprofen is highly (~99%) protein bound in adults, but did Aranda et al bind only 95% in the study.

Elimination

Ibuprofen is extensively metabolised in the liver to pharmacologically inactive metabolites. It is mainly oxidized followed by acyl-glucuronidation. Two major metabolites account for 35% and 26% of drug related material recovered in urine. The principle agents of metabolism are cytochrome P450 isoenzymes CYP2C9 and CYP2C8 (Brocks et al., 1999).
Ibuprofen has two optical isomers the R form is pharmacodynamically inactive or little active. *In vivo* the R from is metabolised to the S form with about 60% completeness. The opposite conversion is thought not to occur.
Ibuprofen is mainly excreted in the urine (about 80%) as unchanged (1%) or acyl-glucuronidated ibuprofen (10-13%), but mostly in the form of its metabolites: hydroxy ibuprofen 25%, carboxy ibuprofen 45% Biliary elimination of ibuprofen and its metabolites is a minor pathway (< 2%).

Dose proportionality and time dependencies

There is good evidence of dose proportionality and linearity in adult volunteers and patients at doses commonly used in therapeutic practice. However, there is no experimental evidence that this is also the case in neonates. The frequent blood sampling necessary to formally define dose proportionality and time dependency makes it unfeasible in premature infants.

Target population

Study IBU025329-PK was a clinical and pharmacokinetic evaluation of the effect of ibuprofen on closure of the DA in premature infants of 28 weeks gestation or less. An initial injection of 10 mg ibuprofen was given within six hours of birth, two subsequent 5 mg injections were given at 24 and 48 hours; blood samples were also taken at those times. Infants who had ultrasonic evidence of PDA received a subsequent 'curative' treatment according to the same schedule. Population pharmacokinetic methods and modelling were used to derive pharmacokinetic parameters.

Sixty-two infants were studied, 33 male and 29 female, their mean gestational age was 26.6 weeks and weight at Day 3 was 0.82 kg. Only 10 infants received 'curative' treatment and PK data are not available for all of them. Although not a formal estimate of Cmax the data could be considered as a reasonable approximation.

Mean (s.d.) ibuprofen concentration following three doses of ibuprofen treatment of PDA. Time (t) is hours post administration of the first dose.

S-ibuprofen (µg/ml)			R-ibuprofen (µg/ml)		
t=0	t=72	t=96	t=0	t=72	t=96
34.9 (14.6)	34.4 (13.5)	17.9 (12.2)	7.5 (8.6)	0.3 (0.2)	0.3 (0.2)

Special populations

Impaired renal/hepatic function
A review by D. Brocks and F. Jamali (The Pharmacokinetics of ibuprofen in humans and animals, Published Taylor and Francis, 1999) indicates that the plasma concentrations of the s-enantiomer were raised in the presence of renal impairment. The authors note a similar finding in patients with hepatic cirrhosis. Quantitative data are not given.

Gender
There is reasonable evidence that there is not a gender difference in adults with respect to the pharmacokinetics of ibuprofen. There are no data in neonates; however, although pharmacokinetics in neonates may be different from adults there is no reason to suspect a gender difference.

Pharmacodynamics

Mechanism of action

A published review by Van Overmeire et al., 2000, provides a good overview of the mechanism of action of ibuprofen. The applicant has not carried out any studies of the pharmacodynamics of ibuprofen.

In the normal foetus the DA connects the main pulmonary trunk to the descending aorta. It differs from other vessels of the foetal circulation in that the media is composed mainly of a spiral layer of muscle fibre and the intima is thicker and develops mounds or cushions in the third trimester of pregnancy; functionally it could be regarded as a sphincter.

Constriction of the musculature of the ductus is inhibited by local and circulating prostaglandins and by low oxygen tension of the blood. At birth the lungs expand and arterial oxygen content rapidly rises, circulating prostaglandin levels fall: these changes will tend to initiate ductal closure. However in premature infants circulating prostaglandin levels are higher than at term, and respiratory difficulties may lead to a state of hypoxia; both of which contribute to the failure of the ductus to close leading to abnormal haemodynamics. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce prostaglandin levels and promote closure of the DA. The incidence of PDA is inversely proportional to the gestational age and birth weight of the infant. For full term babies it is about 1:2000; for very low birth weight babies it is about 35%, and for those with respiratory distress syndrome it is about 45-50%.

Primary pharmacology

Varvarigou et al., 1996, published the first study of prophylactic ibuprofen in the prevention of PDA. They investigated the effect of a single dose of ibuprofen lysine 10 mg/kg followed by 5 mg/kg at 24 and 28 hours (n = 12) or single dose of ibuprofen lysine 10 mg/kg (n = 11) or a single dose of saline. The three-dose schedule was chosen on the basis of the recommendations of fever reduction and the one dose to assess the minimum effective dose. The multiple dose-regimen gave a sustained reduction in PGE2 levels and its metabolite 6-keto-PGF1α followed the same pattern.

Mean (s.d.) prostaglandin E_2 levels (pg/ml) following single and repeat doses of ibuprofen

	Pre dose	24 hours	48 hours	72 hours
PGE_2 following single dose	1871 (696)	1171 (1903)	383 (265)	3232 (2420)
PGE_2 following three doses	1867 (641)	717 (349)	622 (168)	810 (304)

Although the Varvarigou study lacks untreated control data to indicate changes in prostaglandins with time the differences between the short and long treatments strongly indicate a treatment effect. There were benefits for the three dose regimen in terms of duct closure, less requirement for ventilatory support and shorter hospital stay compared to the single dose and saline treatments: the effects of the latter two appeared very similar. The paper effectively set the state of the art for ibuprofen intervention

in terms of dose and was copied by subsequent investigators. The applicant subsequently carried out a small study trying to further investigate the optimal dose-regimen (see clinical efficacy).

Secondary pharmacology

Cerebral blood flow
Mosca et al., 1997, compared the efficacy and effects on cerebral blood volume, blood flow and oxygenation of 0.2 mg/kg of indomethacin (n = 8) or 10 mg/kg ibuprofen (n = 8) in infants of less than 31 weeks gestation with confirmed PDA. Both treatments were given as single doses infused over one minute. Cerebral blood volume was measured by near infrared spectroscopy. For indomethacin, mean (s.d.) blood volume was 2.4 (0.4) ml/100 g before treatment and 1.9 (0.3) ml/100 g after treatment; the equivalent figures for ibuprofen were 2.7 (0.3) ml/100 g and 3.1 ml/100 g the difference is not statistically significant, however a significant difference (p = 0.02) was seen in cerebral blood flow which was reduced by 62 (318) μL/100 g following indomethacin and increased by 207 (200) μL/100 g one hour after administration of indomethacin and ibuprofen respectively.

Mosca et al., 1999, demonstrated in a non-comparative open study that ibuprofen 10 mg/kg infused over one minute did not alter cerebral vasoreactivity to a transient increase in arterial CO_2 tension. The clinical significance of this finding is unknown.

Naulaers et al., 2002, studied changes in cerebral blood volume associated with administration of 10 mg/kg of ibuprofen or the same volume of normal saline (placebo). For both interventions there was a mean change (95% C.I.) in cerebral blood volume of 0.3 (0 – 0.06) ml/100 g.

Patel et al., 1995, compared the efficacy and effects on cerebral blood flow of 0.1 mg/kg of indomethacin (n = 15) or 10-mg/kg ibuprofen (n = 6) or 5-mg/kg ibuprofen in infants of less than 28 weeks gestation with confirmed PDA. Change in cerebral volume (CBV) was measured by near infrared spectroscopy. For ibuprofen (both doses) the median change in CBV was 0 ml/100 g (25^{th} to 75^{th} centiles = 0.1 to –0.1 ml/100 g). For indomethacin the median change was -0.4 ml/100 g (-0.3 to –0.5).

Patel et al., 2000, in a double blind trial, compared the efficacy and effects on cerebral blood flow of 0.20 – 0.25 mg/kg of indomethacin three doses 12 hourly (n = 15); or 10/5/5 mg/kg ibuprofen three doses 24 hourly (n=18) in premature infants with confirmed PDA. Change in cerebral blood flow, measured by near infra-red spectroscopy, following the first dose was the primary comparator For indomethacin the mean (s.d.) CBF was 13.6 (4.1) ml/100 g/min before and 8.3 (3.1) ml/100 g/min after treatment. For ibuprofen CBF was 13.3 (3.2) ml/100 g/min before and 14.9 (4.7) ml/100 g/min after treatment.

Romagnoli at al., 2000, conducted a non-comparative open study of the effects of administration of 10 mg/kg ibuprofen (Arfen®) infused as a single dose over 30 minutes on cerebral blood flow in infants of gestational age thirty weeks or less. Thirteen had echocardiographic evidence of PDA and four did not. Blood flow was measured by doplar ultrasonography. The authors conclude that there were favourable haemodynamic changes in the PDA group but not in those without PDA.

Renal blood flow
The Romagnoli at al. study cited above also studied renal blood flow by means of doplar ultrasonography; and the authors' conclusions also apply to renal blood flow.

Pezzati et al., 1999, conducted an open study comparing the effects of 0.2 mg/kg indomethacin (n = 8) and 10 mg/kg ibuprofen (n = 9) infused over 15 minutes on renal blood flow (measured by ultrasonography) in infants of 33 weeks gestational age or less with PDA. There were statistically significant reductions in renal blood flow following indomethacin but not ibuprofen.

Mesenteric blood flow
Mesenteric blood flow was also measured in the Pezzati et al. paper cited above and found to be reduced following indomethacin but not ibuprofen.

Clinical Events/complications
Events of clinical significance related to prematurity and/or PDA and blood flow in specified organs are as follows:
- cerebral blood flow = IVH
- renal blood flow = renal failure, oliguria, fluid overload
- mesenteric blood flow = necrotising enterocolitis, intestinal perforation.

Patel et al., 2000, refers to one indomethacin treated patient who developed necrotising enterocolitis. Otherwise there is no mention in the studies of the clinical events listed, suggesting they did not occur or if they did they are not reported.

Relationship between plasma concentration and effect

The applicant has not formally addressed this topic. However, given the very large intra-individual variability for the pharmacokinetics of ibuprofen it is difficult to see how meaningful information could be provided. No equivalent data have been found in the much wider published literature on indomethacin.

Interaction studies

The applicant has not carried out any specific interaction studies, relying only on the clinical trial data, where concomitant medication is common. Neonatal intensive care is a complex situation with high morbidity and mortality where drug interactions may not be obvious.

Clinical experience shows that, almost inevitably, neonates with PDA will receive multiple co-medications as well as ibuprofen. No evidence of an interaction emerges, but such is the morbidity of the population the possibility cannot be excluded with certainty.
Based on published data, as a NSAID, ibuprofen may interact with the following medicinal products:
- diuretics: ibuprofen may reduce the effect of diuretics; diuretics can increase the risk of nephrotoxicity of NSAIDs in dehydrated patients.
- anticoagulants: ibuprofen may increase the effect of anticoagulants and enhance the risk of bleeding.
- corticosteroids: ibuprofen may increase the risk of gastrointestinal bleeding.
- nitric oxide: since both medicinal products inhibit platelet function, their combination may in theory increase the risk of bleeding.
- other NSAIDs: the concomitant use of more than one NSAID should be avoided because of the increased risk of adverse reactions.

Adequate information has been included in section 4.5 of the SPC.

Genetic differences in PD response

As discussed above it is possible that some of the inter-individual variability in blood levels may be due to polymorphism of CYP isoenzymes.

Discussion on Clinical Pharmacology

Pharmacokinetics
The pharmacokinetics of Pedea was first studied in healthy volunteers (Pharmakin 1993 and Bioequivalence study 2000). In addition, during the dose range study performed on the product (Moriette et al., 2003) and as part of the trial on Pedea comparing prophylactic versus curative ibuprofen (Cephac pharmacokinetic report 2003), pharmacokinetics parameters were determined. Finally, two publications support the pharmacokinetics of ibuprofen administered intravenously (Aranda et al., 1997, and Van Overmeire et al., 2001).

Ibuprofen is a propionic acid derivative with two isomers; most anti-inflammatory activity is attributed to the S-isomer. Pedea is the racemic form and in common with other ibuprofen preparations there is uni-directional conversion of the R- to the S-enantiomer.
It is metabolised in the liver by oxidation and subsequent aryl glucoronidation to inactive metabolites. Hydroxylated metabolites have also been identified. Metabolism involves cytochrome P450 CYP2C9 and CYP2C8.
CYP2C activity is low until one week after birth and then rises to a third of the adult level within a month, irrespective of gestational age. Glucuronidation is also reduced in the newborn. Other factors in pre-term neonates that influence kinetics include reduced renal function, concomitant therapy, and albumin and bilirubin concentrations.
About 80% is excreted in the urine, 1% as unchanged and the rest as metabolites. Biliary excretion is <2%.

The applicant's bioequivalence study in healthy volunteers has provided sufficient data to evaluate the pharmacokinetic parameters of both formulations discussed in the literature: the i.m. ibuprofen lysinate formulation administered intravenously and the Pedea formulation. Data showed that there was no statistical difference between pharmacokinetics of ibuprofen as a free base and ibuprofen lysinate administered intravenously.

After a loading dose of 10 mg/kg, peak concentrations in the three studies in premature newborns were similar at 35-40 μg/ml. Residual concentrations were about 10-15 μg/ml 24 hours after the last dose of 5 mg/kg in two studies. Concentrations tended to be higher in those with a lower gestational age. The peak plasma concentrations measured in premature infants were similar to those obtained from infants and children after oral ibuprofen. In contrast, slower elimination caused a longer half-life in the premature, being about 30 hours compared to 1.5-2 hours in infants more than three months of age. Clearance increases with gestational age from 24-28 weeks.

With reference to study IBU025329-PK, the figures for blood levels at 72 hours are based on only 4 infants in whom curative treatment was given and for whom blood drug level data are available.
What is evident from the data is the very considerable inter-individual variation in blood levels. Similar high variability is also evident from published studies. Aranda et al. found a five-fold difference between the lowest and highest individual elimination rate constant and Van Overmeire et al. found elimination rates ranging from 1.5 to 26.1 mg/kg/h. Both authors comment that the pharmacokinetics of ibuprofen were not evidently related to infants' birth weight or gestational age and speculate that the very high inter-individual variability may be due to genetic polymorphism particularly of CYP2C and/or differences in protein binding.

The volume of distribution was about 200 ml/kg. Protein binding in cord blood was about 95% compared to 99% in adult plasma. In common with other non-steroidal anti-inflammatory drugs, such as indomethacin, ibuprofen is bound to albumin and might displace bilirubin.
An *in vitro* study calculated that at 155 μg/ml, high by therapeutic standards, ibuprofen could displace bilirubin to increase the free fraction of bilirubin by about four-fold, Cooper-Peel et al., 1996. This might increase the risk of bilirubin encephalopathy in sick premature infants. However, Ma et al., 2002, suggested that significant bilirubin displacement is unlikely at therapeutic concentrations until an ibuprofen concentration in the region of 285 μg/ml *(see clinical safety)*.

Pharmacodynamics
The applicant has not carried out any studies of the pharmacodynamics of ibuprofen. However, the pharmacodynamic action of ibuprofen in closure of PDA is reasonably well understood from the published literature. There is considerably less understanding of the direct and indirect (through duct closure) effects on organ blood flow.

The applicant has reviewed pertinent publications addressing this topic either in animals or in human newborn infants. The applicant focused on the effects of ibuprofen on cerebral haemodynamics and on mesenteric and renal blood flow. Further, the applicant has provided sufficient justifications why additional pharmacodynamics studies were not deemed necessary.

As NSAIDs reduced foetal urine output and hence amniotic fluid volume, these drugs, which are prostaglandin synthetase inhibitors, were used to treat polyhydramnios. The observation that –among others - indomethacin may also lead to a premature closure of the foetal ductus in utero prompted its development to the treatment of PDA of preterm newborns.

In a multicentre trial involving babies under 1,750 g birthweight (Gersony et al., 1983) who had developed a symptomatic PDA, indomethacin closed the PDA within 48 hours in nearly 80% of infants, whereas spontaneous closure occurred in less than 30% of controls. Further on, many other studies have demonstrated similar results.

In an early administration trial of the drug, neonatologists showed that the primary pharmacodynamic effects of ibuprofen on the DA were supported by its direct effect on prostaglandins (Varvarigou et al., 1996).

Ibuprofen inhibits cyclooxygenase. In pre-term infants it significantly reduces the concentration of both PGE_2 and prostacyclin, as measured by its 6-keto metabolite. As indomethacin is thought to act by the same mechanism, no further primary mechanism of action studies were performed.

The applicant presented a review of five randomised double-blind studies, which measured cerebral haemodynamics in pre-term newborns.

As for indomethacin, the pharmacodynamics effects of ibuprofen on the cerebral hemodynamics of preterm newborns presenting with PDA were investigated (Patel et al., 1995, and Patel et al., 2000). Both studies were comparative to indomethacin and they used the same formulation of ibuprofen as the one referred to in the present application, i.e. Pedea. The first exploratory study was only published as a letter to the editor and the second one was published several years after its completion. Both confirmed the favourable effect of ibuprofen on cerebral hemodynamics as observed in animals, and confirmed their own previous findings on indomethacin.

In a similar study carried out with ibuprofen lysinate, results were in line (Mosca et al., 1997). A more recent pharmacodynamics study confirmed the absence of cerebral effects of ibuprofen on cerebral hemodynamics (Mosca et al., 1999).

More recently, results as part of a large comparative and prophylactic trial showed similar pharmacodynamic results on cerebral hemodynamics. Ibuprofen, at the proposed therapeutic dose, was no different from placebo in terms of cerebral blood flow and oxygenation, Naulaers et al., 2002.
Finally, a Doppler study performed on peripheral organs usually affected by indomethacin, i.e. on the main arteries of the gut and of the kidney, confirmed the favourable pharmacodynamics profile on peripheral circulation of ibuprofen as compared to indomethacin (Pezzati et al., 1999). In infants with a gestational age less than 33 weeks, ibuprofen lysine 10 mg/kg, n=9, did not decrease mesenteric and renal blood flow, whereas indomethacin 0.2 mg/kg, n=8, did, Pezzati et al., 1999.

It is thought, from an open label study by Romagnoli et al., 2000, that ibuprofen did not have a detrimental effect on cerebral blood flow when the PDA is closed, but that there is a rapid improvement in renal and cerebral blood flow secondary to the effect of the drug in closing the ductus and stopping the left to right shunt. In a prophylactic study carried out with ibuprofen lysinate, Romagnoli confirmed that any hemodynamics modification of cerebral or renal blood flow were related to ibuprofen's primary effect on the PDA.

Clinical efficacy

The applicant has conducted a dose-range study (Moriette et al., 2003) in order to determine whether the empirical dose regimen was effectively associated with the best efficacy/safety ratio. In addition, the applicant has performed another study with Pedea comparing curative versus prophylactic ibuprofen administration (Rozé et al., 2003).
In addition, 15 publications support the efficacy of ibuprofen to close a PDA.

Dose response study

IBU/99/Dose range

Description of the study:
The trial was conducted in 2000-2001 at Hôpital Cochin, Paris, in a non-placebo controlled design. The primary objective of this study was to determine the lowest effective dose of Pedea required to obtain a PDA closure rate of 80% in preterm neonates of 27-29 weeks of gestational age and in 50% of neonates with 24-26 weeks of gestational age.
For inclusion patients had to be within the specified gestational ages and to have echocardiographic evidence of PDA and to be at least 72 hours and no more than 120 hours old. Ductal closure was assessed by echocardiography and had to occur within 72 hours of treatment initiation. Patients were treated with ibuprofen infused over 15 minutes every 24 hours according to the following regimens:

- 5 – 2.5 – 2.5 mg/kg;
- 10 – 5 – 5 mg/kg;
- 15 – 7.5 – 7.5 mg/kg;
- 20 – 10 – 10 mg/kg.

The trial employed a continual re-evaluation (Baysian) design. Cohorts of three patients were assigned to each dose and following review of the outcome the dose/response relationship was re-evaluated, and the dose closest to giving an 80% probability is chosen as the dose for the next cohort. This process is repeated until 20 patients have been recruited.

Outcome:
Two different sub-analyses were undertaken; one in infants aged 27-29 weeks of gestational age (n=21) and one in infants aged 24-26 weeks of gestational age (n=22).

21 infants aged 27-29 weeks of gestational age were recruited, one of whom died. They received three doses of Pedea ibuprofen, which were 5-2.5-2.5 mg, n=2; 10-5-5 mg, n=8; 15-7.5-7.5 mg, n=11; and no patients were allocated to the highest proposed dose of 20-10-10 mg. The PDA closure rates in the three treated groups were 0/1 (the other infant in this group, who received Pedea, died), 6/8 and 10/11. In the four patients whose PDA did not close, one infant at the 5 mg/kg dose closed with three days of the last infusion, and one at the 15 mg/kg dose closed within five days. Two required surgical closure, both at the 10 mg/kg dose, after one was given a repeat dose of ibuprofen and one indomethacin, without success.
The median ibuprofen concentration at 72 hours was 17 µg/ml in both the closure and non-closure group and success did not correlate with the ibuprofen plasma concentration.
From these small numbers the applicant chose the dose 10-5-5 mg as the minimally effective dose.

Demographic data and outcome of the dose ranging study in infants 27-29 weeks of gestational age:

Initial dose (mg/kg)	5 (n=2)	10 (n=8)	15 (n=11)
Median gestational age (weeks)	27	28	28
Birth weight (range in kg)	0.77 – 1.23	0.67 – 1.18	0.79 – 1.58
Success/failure	0/1	6/2	10/1

Outcome data in infants 24-26 weeks of gestational age:

Initial dose group (mg/kg)	5	10	15	20
No. treated	7	7	6	2
Duct closed	1/7	2/6	2/6	1/1
Oliguria		6/7		
Enteropathy		1/7		
Death	1		1	

Main study

IBU/PROPHYL/2000

This study was a double-blind placebo controlled trial conducted in eleven centres in France from March 2001 to March 2002.

Outcomes/endpoints:
The primary aim was to compare the proportion of patients requiring surgical ligation of PDA after prophylactic versus after curative administration of intravenous ibuprofen.
The main pre-specified analysis was a comparison of prophylactic treatment with ibuprofen as compared to placebo.
The second pre-specified analysis was a comparison of curative treatment with ibuprofen as compared to placebo.
The proportion of patients experiencing specified complications of PDA/prematurity (e.g. intraventricular haemorrhage) was a secondary efficacy/safety comparison.

Study participants:
Patients were to be premature neonates with a gestational age of less than 28 weeks; and to be less than six hours old at the time of randomisation. Patients with other major illness not related to prematurity (e.g. infection) were excluded, as were patients where the mother had used potentially nephrotoxic medication in the three days prior to delivery.

Randomisation and treatments:
Eligible patients were randomised (1:1) to; prophylactic ibuprofen 10 mg/kg as a loading dose with two subsequent intravenous infusions of 5 mg/kg at 24 hour intervals, or to placebo (an equivalent volume on 0.9% saline given at equivalent times). Both treatments were initiated on Day 1 of the study.

The need for surgical ligation was based on [persistence of] PDA with the criteria described below and at least one of the following; need for mechanical ventilation or CPAP; impossibility of enteral feeding as defined by an increase of less than 12 ml/day for three days.

Echocardiographic evaluation:
The need for a curative (open) treatment with ibuprofen was determined by echocardiographic evidence of a haemodynamically significant PDA with at least two of the following criteria being present; left atrial/aortic root ratio > 1.48; retrograde or absent flow in the anterior cerebral artery or the descending thoracic aorta; pulsatile flow in the ductus arteriosus; diastolic flow in the pulmonary artery of > 20 cm/s. Echocardiographic evaluations of the ductus arteriosus were performed on days 3, 7, 14, 21, at discharge from the centre and at any other time considered clinically necessary.

Sample size:
The patient sample size estimate was based on a historically controlled study showing a surgical ligation rate of 21% with the prophylactic method and 41% with the 'curative' method. The minimum sample size to give 80% power of detecting a difference with $\alpha = 0.05$ was 83 patients; however the target number was set at 110 because of the expected mortality rate of 25%.

Recruitment:
Late in 2001 there were three reports, in infants who had received prophylactic treatment, of hypoxaemic pulmonary hypertension following the loading dose of ibuprofen administered within the first six hours of life in very premature infants? This led to the halting of the study when approximately 60% of the intended number of patients had been recruited.

RESULTS

Due to the fact that the study was halted prematurely, the main pre-specified analysis was the comparison of 66 patients treated prophylactically with placebo compared with 65 patients who received prophylactic ibuprofen.
The second analysis was of 25 patients initially assigned to placebo but then requiring curative treatment with ibuprofen at a later stage in line with the echocardiography requirements discussed above.

Primary analysis

The main demographic characteristics of the enrolled study population are shown in the table below. There were minor but non-significant differences in some variables such as home/hospital delivery but in general the treatment populations were well matched.

Baseline characteristics of the study populations

	Placebo n = 66	Prophylaxis n = 65	
Proportion male (%)	47	54	NS
Median gestational age (weeks)	26	26	NS
Birth weight (range in kg)	0.43 – 1.18	0.3 – 1.30	NS
Mechanical ventilation (%)	94	88	NS
Surfactant treatment (%)	83	83	NS

47 of the 66 patients who were treated prophylactically with ibuprofen and 47 of the 65 patients, who received placebo, reached 36 weeks of gestational age. In those children who reached 36 weeks of gestational age, 5/47 in the placebo group and 0/47 in the prophylaxis group required surgery.

The tables below give the outcome in terms of the primary variable, requirement for surgery, and also in terms of the clinical complications of prematurity.

Pharmacological and surgical interventions to close PDA

	Randomised	
	Placebo = 66	Ibuprofen = 65
PDA identified at least once during study	36	18
No further Rx	41	63
Rescue ibuprofen	12	2
Rescue indomethacin	7	0
Need surgery	6	0
Needing surgery/alive at 36 weeks PCA*	5/47	0/47

* post-conceptual age

Proportion (%) of patients experiencing complications

	Placebo n = 66	Ibuprofen n = 65
Hypoxia and/or pulmonary hypertension	13.6	23.1
Pulmonary haemorrhage	3	7.7
Grade II-IV Intraventricular haemorrhage	22.7	10.8
Periventricular leukomalacia	6.1	4.6
Renal failure	3	10.8
Anuria/oliguria	3	4.6
Intestinal perforation	1.5	7.7
Necrotising enterocolitis	4.5	16.9
Death	28.8	27.7

Secondary analysis

In total there were 25 preterm infants who required curative treatment with ibuprofen, mean gestational age 26 weeks, range 24-27; mean birth weight 850 gm, range 630-1180. They were treated with Pedea (ibuprofen) in three doses of 10-5-5 mg, each dose at 24-hour intervals given by slow intravenous infusion. At recruitment they all had a visible PDA on echocardiogram with at least two of the four criteria discussed above.

PDA closure occurred in 12 (48%); back up indomethacin was given to 9 (36%); and surgical ligation carried out in 6 (24%).
Six of the infants died (24%), Five had an intraventricular haemorrhage grade III-IV (20%); one had periventricular leukomalacia (4%); and ten had bronchopulmonary dysplasia of the 19 who were alive at 36 weeks post conceptual age. At least one renal side effect occurred in 6 (24%): urine output <1 ml/kg in one; use of diuretic in three; sodium <130 mmol/l in two (see clinical safety).

Supportive studies

The outcome of supportive studies is shown in the tables below. The only direct (within study) comparison of prophylactic and therapeutic 'rescue' ibuprofen is in the publication by Dani et al., 2000, which demonstrated a highly significant ($p = 0.001$) reduction in PDA on the third day of life with prophylactic use but no benefit in terms of the complications of prematurity/PDA. The patients had a mean gestational age of 29 weeks.

Comparison of prophylactic and rescue ibuprofen

Study	Format	Prophylactic	Rescue	Comment
Dani	Prospective open parallel group	3/40 had PDA at day 3	21/40 had PDA at day 3	There was no benefit in terms of complications.

Data for ductus closure rates from papers, which carried out a head to head comparison of ibuprofen and indomethacin, are shown in the table below. It is evident that although there is considerable variability between studies overall there is similarity within studies.

Comparison of ibuprofen and indomethacin figures (no. of ductus closures/total patients (%))

Study	Format	WGA	Indomethacin	Ibuprofen	Comment
Akisu, 2001*	Prospective parallel group	<35	8/11 (73)	10/12 (83)	Administration was enteral
Lago, 2002	Prospective open parallel group	23-34	56/81 (69)	69/94 (73)	Nephrotoxicity was less with ibuprofen
Mosca, 1997	Prospective open parallel group	25-31	6/8 (75)	5/8 (63)	See pharmacodynamics above
Patel, 1995	Prospective open parallel group	23-28**	[8]/15 (57)	[10]/18 (57)	Numbers back calculated from %
Patel, 2000	Double blind prospective parallel group	23-35	14/15 (93)	14/18 (78)	Numbers back calculated from %
Plavka	Published as abstract only	mean 27	17/20 (85)	18/21 (86)	
Pezzati, 1999	Prospective open parallel group	26 - 32	8/8 (100)	9/9 (100)	See pharmacodynamics above
Van Overmeire '97	Prospective open parallel group	<33	15/20 (75)	16/20 (80)	Urinary output was better with ibuprofen
Van Overmeire '00	Prospective open parallel group	23-34	49/74 (66)	52/74 (70)	Nephrotoxicity was less with ibuprofen
Total		NA	181/252 (71.8%)	203/274 (74.1%)	

* Data from Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev. 2003;(2):CD003481. ** weeks of post-conceptual age. WGA = weeks of gestational age.

Analysis performed across trials (meta-analysis)

The applicant has conducted a meta-analysis of controlled trials of PDA where indomethacin was randomised against ibuprofen in pre-term infants less than 37 weeks gestational age. The infants were less than 28 days postnatal age and presented with an open PDA. For inclusion, studies had to include short-term efficacy measured by echocardiography and rate of surgical ligation.

Six randomised comparative studies versus indomethacin were included in the meta-analysis; the two by Van Overmeire, 1997, 2000 and those by Lago et al., 2002, Patel et al., 2000, Pezzati et al., 1999, and Mosca et al., 1997. Of these studies, 5 compared indomethacin with ibuprofen-lysine and one compared indomethacin with Pedea. In each study the same dosing regimen of ibuprofen was used: 10mg/kg followed 24 hours later with 5mg/kg followed 24 hours later with another dose of 5mg/kg. All indomethacin studies used a loading dose of 0.2 mg/kg with subsequent doses of 0.1-0.25 mg/kg given 12-24 hourly.
The PDA closure rate was 75% (168/223) in the ibuprofen group and 73% (150/206) in the indomethacin group. The Odds Ratio was 1.14 (95% CI 0.73 –1.77). The surgical ligation rate was 11.7% (26/223) in the ibuprofen group and 11.7% (24/206) in the indomethacin group. The corresponding Odds Ratio was 1.00 (95% CI 0.55 – 1.81). Mortality at 30 days was also evaluated although it was only reported in 3 of the 6 studies. 30-day mortality was 10.1% (19/188) in the ibuprofen group and 9.1% (16/175) in the indomethacin group, ratio 1.11, CI 0.55-2.24.
The surgical ligation rate was 26/223 (11.7%) for ibuprofen and 24/206 for indomethacin (11.7%), relative risk 1.00, CI 0.55-1.81.
Reopening of the duct occurred in 5 cases for ibuprofen and 2 cases for indomethacin.
Similar response rates were obtained where curative and prophylactic ibuprofen was compared.

On the basis of the analysis it can be concluded that ibuprofen and indomethacin are equivalent with regard to ductal closure, requirement for surgical ligation, perinatal mortality.

Discussion on clinical efficacy

Ibuprofen was developed as an alternative to indomethacin for PDA in the hope that it might be as effective with a better safety profile. The applicant has made good efforts in the generation of 'own data'. Three clinical trials have been conducted one addressing bioequivalence with the ibuprofen formulation usually used in the published literature. A second trial re-evaluated, and confirmed, the clinical dose regimen. Finally, a sizable trial of prophylactic versus as needed administration of ibuprofen was carried out in premature neonates with PDA. Pharmacokinetic data were also generated in the two clinical studies.

In addition, bibliographic data are submitted to support the choice of dose of ibuprofen and the use of a new formulation and route of administration for a new therapeutic indication, which is based on the well characterised mechanism of action of ibuprofen, i.e. inhibition of prostaglandin synthesis.

The published literature, together with the applicant's own generated data, is sufficient to fulfil the dossier requirements. In the light of an independent review of the literature on the use of ibuprofen for the closure of PDA, it is considered that the applicant's citation of the literature is accurate and complete. The published studies are often small, however, they do serve to provide a reasonable understanding of the effects of ibuprofen on blood-flow in various organs, and its clinical safety and efficacy.

It is considered that the normal dossier requirements are fully satisfied in accordance with Directive 2001/83/EC, as amended.

Study IBU/PROPHYL/2000 has been well conducted, analysed, and presented. Technically, however, it is a failed study in that it was stopped for safety reasons well before reaching its planned recruitment.
Indomethacin is an established treatment for pre-term neonatal patent PDA and placebo-controlled trials are therefore no longer ethically possible. The lack of echocardiographic assessment at baseline might have been to avoid the ethical difficulties of not administering a known effective treatment as early as possible in a very high-risk population and was 'necessary' given the planned trial design. However, it raises two problems. It must be assumed that the proportion and severity of PDA was equivalent in the two treatment groups. This is likely in view of their similar gestational age but it is unsatisfactory to have to make an estimate about such an important variable.

The results of the primary analysis from Study IBU/PROPHYL/2000 suggest that prophylaxis is of some benefit in avoiding surgery. However, this did not confer a mortality benefit and appears to have resulted in more complications at least some of which may be treatment related. Prophylactic use of Pedea in the first 3 days of life (starting within 6 hours of birth) in preterm newborn infants less than 28 weeks of gestational age was associated with increased incidence of renal failure and pulmonary adverse events including hypoxia, pulmonary hypertension, pulmonary haemorrhage, as compared to curative use (see clinical safety). Pedea should therefore not be used prophylactically, which has been adequately addressed in the Summary of Product Characteristics.

Neonatologists first investigated intravenous ibuprofen for the treatment and prevention of PDA in 1993. Subsequently only an intramuscular formulation of ibuprofen-lysine was available and this has been used in more recent trials administered intravenously. The applicant has chosen not to perform a comparative trial versus indomethacin but instead has chosen to perform a meta-analysis of existing studies.
Clearly a large prospective study comparing the efficacy and safety of Pedea to indomethacin would provide the highest standard of evidence to make a decision on the risk/benefit of Pedea in this indication. However, it is accepted that given the low prevalence of PDA it would take a long time to recruit sufficient infants to be able to show that Pedea was non-inferior to indomethacin.
The bioequivalence of Pedea (intravenous ibuprofen) to Imbun (ibuprofen-lysine IM formulation administered intravenously) for both R- and S-enantiomers in healthy volunteers has been shown and it therefore seems appropriate to include studies using the ibuprofen-lysine formulation in the meta-analysis. The meta-analysis can be considered to provide sufficient evidence of efficacy and safety of ibuprofen.

Given the pharmacokinetic results showing bioequivalence between Pedea and Imbun it is reasonable to assume these results relate to the efficacy of Pedea even though only one of the studies used the Pedea formulation. These data are not however sufficient to provide robust evidence of equivalence or non-inferiority between Pedea and indomethacin. This is because the confidence intervals for the odds ratio on the 3 endpoints listed are quite wide. However, given the rarity of PDA, these data do not provide any evidence that the efficacy of this formulation is any different to indomethacin.

The applicant's dose ranging study is limited and inadequate when taken on its own. However, when combined with the more impressive published data, the dose ranging study is consistent with the earlier studies and supports the choice of dose. This is the original regimen of 10-5-5 mg/kg described in the first study, by Varvarigou et al, 1996. The dosing interval is consistent with the pharmacokinetics of ibuprofen in premature infants.
The dose ranging study showed that the efficacy of the initial dose of 10 mg/kg and 15 mg/kg is similar. The sequential design of this study is acceptable for a dose ranging study but it is questioned how a study of sample size only 20 could provide robust evidence of the dose response relationship of Pedea. From this study it remains possible that the efficacy of an initial dose of 15mg/kg is superior to an initial dose of 10mg/kg. The applicant states that renal adverse effects are slightly higher at the 15mg/kg level and therefore the 10mg/kg dose is optimal. It is not clear from the data available which dose has the superior risk/benefit. The trade-off between potential increase in efficacy for the higher dose and associated renal toxicity would have to be investigated in a larger group of neonates to provide a clear evidence to decide which is the best dose. However, it is accepted that it would be difficult to conduct such a study.

Therefore, in the light of the information available from the dose-ranging study and the meta-analysis, it is considered that evidence has been provided to demonstrate that the efficacy of an initial dose of 10mg/kg of Pedea. The limited pharmacokinetic data support the hypothesis that a higher dose would not be more effective in that successful closure did not correlate with plasma ibuprofen concentration. The failures cannot be attributed to an inadequate plasma concentration of ibuprofen.

A course of therapy is defined as three intravenous doses of Pedea given at 24-hour intervals. The ibuprofen dose is adjusted to the body weight as follows:
- 1st injection: 10 mg/kg,
- 2nd and 3rd injections: 5 mg/kg.
Before administration of Pedea an adequate echocardiographic examination should be performed in order to detect a haemodynamically significant PDA. 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 be given. If the condition is unchanged after the second course of therapy, surgery of the patent DA may then be necessary.

However, based on the results from the dose-response study of Pedea in 40 preterm newborn infants, it is considered that sufficient information on efficacy in infants of 24-26 weeks of gestational age has not yet been provided.
The *ductus arteriosus* closure rate associated to the 10-5-5 mg/kg dose regimen was 75% (6/8) in neonates of 27-29 weeks' gestation and 33% (2/6) in neonates of 24-26 weeks' gestation.
A warning has therefore been introduced in Section 4.3 of the Summary of Product Characteristics, stating that in preterm newborn infants less than 27 weeks of gestational age, the closure rate of the *ductus arteriosus* was shown to be low at the recommended dose regimen.
The applicant has committed to conduct a clinical study in preterm newborn infants less than 28 weeks of gestational age with a haemodynamically significant PAD in order to evaluate the safety and efficacy of Pedea. Progress reports will be submitted to CHMP for review in line with predefined timeframes.

Clinical safety

The clinical safety documentation comprises the applicant's own data (in healthy adult volunteers and in the target population) and supportive data published in the literature.

Patient exposure

Two pharmacokinetic trials involved a total of 30 adult volunteers.
In the target population, data are available on 674 infants all <35 weeks gestational age treated for PDA with the ibuprofen-lysine formulation and in 312 infants who received the Pedea formulation.
Of the 312 who received the Pedea formulation: 82 infants of 23-28 weeks gestational age were treated curatively with Pedea in trials; 65 infants of 24-27 weeks gestational age were treated prophylactically with Pedea in trials; 111 infants were treated curatively and 54 treated prophylactically with Pedea on a named patient basis where the data were collected retrospectively.
Overall, the clinical safety documentation relates to 986 infants with PDA. Nearly all patients received the 10-5-5-mg/kg-dose regimen.

Adverse events

Because of the nature of prematurity, nearly all reported adverse events are serious.
Furthermore, it is virtually impossible to distinguish between drug induced and disease induced events. The applicant provided a review of clinical safety issues by organ, which is discussed below.

Serious adverse events/deaths/other significant events

Deaths:
The death rates for ibuprofen lysine, where it was reported, usually at one month were 37/320 (12%) for ibuprofen used curatively and 95/533 (18%) for ibuprofen used prophylactically. The

corresponding figures for indomethacin were 16-175 (9%) and 58/409 (14%) for control indomethacin or ibuprofen.
The published mortality rates range from 5 – 15% for rescue ibuprofen and from 0 – 28% for prophylactic ibuprofen; the range for indomethacin (prophylactic or rescue) was 3 - 29%. The death rate in the applicant's main clinical study was 28%.

Cerebrovascular events:
The incidence of grade III-IV intraventricular haemorrhage was 20/334 (6%) for ibuprofen used curatively and 31/420 (7%) for ibuprofen used prophylactically.
The corresponding figures for indomethacin were 13/178 (7%) when used curatively and 40/407 (10%) for indomethacin or curative ibuprofen used as control.
The event rate for grade III – IV intraventricular haemorrhage range from 0 – 11 % for ibuprofen (prophylactic or rescue) and from 0 – 23% for indomethacin (prophylactic or rescue). The rate in the applicant's main clinical study was 11% (prophylactic use).
Similarly, the range in the applicant's efficacy study for periventricular leukomalacia 9%, is within the published range (any treatment) of 3 – 11%.

The table below shows the rates for "all intraventricular haemorrhage" and "grade III and IV intraventricular haemorrhage" observed in trial IBU/PROPHYL/2000.

IVH Grade	Curative	Prophylactic
0	36 (54.4%)	40 (61.5%)
I	4 (6.1%)	4 (6.2%)
II	11 (16.7%)	14 (21.5%)
III	10 (15.2%)	7 (10.8%)
IV	5 (7.6%)	0

Gastrointestinal events:
Overall, the rates of necrotising enterocolitis and bowel perforation were 16/356 (4%) for ibuprofen and 12/198 (6%) for indomethacin used curatively.
The table below shows the rate of necrotising enterocolitis separately for all studies and all treatments. It should be noticed that the rate in the applicant's main study was 17% (prophylactic use), which is higher than might be expected. The published rates of necrotising enterocolitis range from 5% to 11%. Unfortunately, the only other study with a comparably high rate (Gonzales, 2000) is published only as an abstract and makes no comment on the issue. It is unclear whether bowel perforation is considered as a separate event from necrotising enterocolitis. The applicant's rate 8% is also high since the published rates range from 0 – 5%.

Rates of necrotising enterocolitis by treatment

Investigator	Gestational age	Curative ibuprofen	Curative indomethacin	Prophylactic ibuprofen
Van Overmeire, 1997	< 33	1/20 5%	1/20 5%	
Pezzati, 1999	<33	0/9 0%	0/8 0%	
Patel, 2000	< 36	0/18 0%	1/15 7%	
Van Overmeire, 2000	< 33	4/74 5%	8/74 11%	
Venkata, 2000	< 29	1/9 11%		
Lago, 2002	< 35	2/94 2%	2/81 2%	
Moriette, 2003	27-30	0/21 0%		
Gouyon, 2003	< 37	8/111 7%		4/54 7%
Varvarigou, 1996	< 33			0/12 0%
De Carolis, 2000	< 31			0/23 0%
Dani, 2000	< 34			0/40 0%
Gonzales, 2000	<1250g			5/54 9%
Van Overmeire, 2002	< 30			6/172 3%
Applicant	< 28			**11/65 17%**

Renal dysfunction:
Many of the studies examining renal function were conducted to investigate the potential pharmacodynamic advantage and not the renal safety of ibuprofen. They are quite small and are discussed in the pharmacodynamics section.
Two reasonably sized studies Van Overmeire et al., 2000 and Lago et al., 2002, did compare the nephrotoxicity of the two compounds. In the publication by Van Overmeire, oliguria was observed in 7% of patients treated with ibuprofen and in 1% of those treated with indomethacin. The authors of both papers comment on the pharmacodynamic advantage for ibuprofen.

Renal dysfunction by treatment

Investigator	Ibuprofen (Change in creatinine with treatment)	Indomethacin (Change in creatinine with treatment)	Ibuprofen (oliguria)	Indomethacin (oliguria)
Lago	0	+ 7 (µmol/l)	1/94	12/81
Van Overmeire	NA	NA	5/74	14/74

Results from four comparative trials with indomethacin suggested that indomethacin tended to reduce urine output and elevate serum creatinine for up to seven days. In three prophylactic trials there was no difference between the two treatments.
In the study by Rozé et al. of 60 neonates per group, ibuprofen was associated with a significant small decrease in urine output, decrease in urine sodium and increase in creatinine. In the large trial by Bray et al. of an open cohort of pre-term newborns treated prophylactically, 8 cases out of 111 had ibuprofen discontinued because of transient renal impairment. The applicant has plotted the incidence of oliguria, defined as urine output ≤1 ml/kg, for nine trials and suggests that for curative treatment the incidence was 19/343 (6%) for ibuprofen and 40/198 (20%) for indomethacin.
In total, oliguria or renal failure was reported in 13 of 199 patients and 30 of 199 patients had a measured urine output of less than one mg/kg/hour.

Haematological adverse events:
The published studies do not indicate any distinction between indomethacin and ibuprofen with regard to bleeding events or marrow suppression. In the prophylactic study conducted by the applicant, neutropenia (< 1500/mm^3) recorded during the first three days of life was found to be significantly more frequent for ibuprofen than for placebo ($p < 0.005$).

Respiratory adverse events:
As indicated in the efficacy section during the course of the prophylactic trial of Pedea, three independent cases of refractory hypoxaemia with pulmonary hypertension were reported. These were acute episodes occurring within one hour of the first infusion while patients were in a stable respiratory condition ($FiO_2 < 40\%$). Echocardiography showed severely decreased pulmonary blood flow. Hypoxaemia was reversed in a few minutes by inhaled nitric oxide therapy. The events have been published (Lancet 2002).
In total, 13.6 % of placebo treated patients and 23.1% of ibuprofen treated patients had pulmonary hypertension or pulmonary haemorrhage.

In the study by Van Overmeire et al. there was a non-significant disadvantage for ibuprofen compared to indomethacin with regard to bronchopulmonary dysplasia: 53% and 39% of patients respectively. This disadvantage was not observed in the study by Lago et al. study.

The incidence of bronchopulmonary dysplasia, defined as oxygen dependence either at 28 days or at 36 weeks of post conceptional age, appears higher after ibuprofen than after indomethacin based on published data. When used curatively, the incidence was 83/178 (47%) for ibuprofen and 51/159 (32%) for indomethacin.
In a clinical curative trial involving 175 preterm newborn infants less than 35 weeks of gestational age, the incidence of bronchopulmonary dysplasia at 36 weeks post-conceptional age was 13/81 (16%) for indomethacin versus 23/94 (24%) for ibuprofen.

Potential toxicity of trometamol:
Trometamol Tris Hydroxymethyl Amino-Methane (THAM) is a biologically inert amino alcohol, which buffers carbon dioxide and acids *in vitro* and *in vivo*. It is considered as an alternative to sodium bicarbonate as a method of correcting acidosis. It is well tolerated at concentrations of 3 – 5 mmol/kg but has been shown at 8.8 mmol/kg to cause hypoglycaemia, respiratory depression, hypotension and nausea. It is also an irritant to veins and tissue but this may be more related to the pH at which it is administered rather than intrinsic toxicity.

Pedea solution contains 0.03 mmol/ml of trometamol, used to solubilize the ibuprofen.
In one study, Gupta et al., 1967, where it was given as a 0.3 M solution at a dose of 1 ml/kg, it was not associated with an increase in arterial oxygen tension. In a second study, the same group found that oxygen tension increased in 7 cases was unchanged in 10 and fell in one case (Van Vliet and Gupta, 1973.) A third study by Baum and Robertson, 1975, found that a hypertonic solution of 0.58 M over 30 s caused an initial fall in arterial PO_2 in 5/6 infants with respiratory distress syndrome. Other adverse events associated with THAM were attributable to the infusion of a hyperosmolar solution.

Intravenous administration of trometamol in the treatment of acidaemia produces an increase in arterial pH. After administration of high doses (20 gm; ~300 mg/kg) a decrease in minute volume has been observed. Although this leads to alveolar hypoventilation and consequently arterial hypoxaemia, the primary event is depression of the respiratory centre by the alkaline arterial pH.

However, the normal buffering capacity of blood is not affected until the concentration of trometamol reaches >50 mmol/l, which is vastly in excess of the concentration that could be achieved in therapeutic use of Ibuprofen i.v. It is therefore unlikely that the instances of hypoxia observed in the clinical trials relate to the trometamol in the formulation, particularly as decreased pulmonary blood flow and not respiratory depression was apparently the cause of the adverse events.

Intravenous administration of trometamol has been used clinically for the treatment of metabolic acidosis for many years (Brinkman et al., 1960, Nahas et al., 1963) and is administered intravenously as a 0.3M solution, which is isomolar with plasma and ten times more concentrated than the Ibuprofen i.v. formulation (Nahas et al., 1963, Nahas et al., 1998). It has also been used in the treatment of infant respiratory distress syndrome and taking account of the lower glomerular filtration rate in neonates it is recommended that the dose is reduced to 5 -7 mmol/kg/day, more than 80 times the dose (0.06 mmol/kg) which will be administered with this formulation.

The content of trometamol is 0.06 mmol/ampoule and with a full treatment a 1.5 kg infant would receive 0.24 mmol. The literature contains reports of organ necrosis in neonates following administration via the umbilical vessels at doses of 3.6 to 108 mmol and in adults at 45 mmol following intravenous administration. The applicant points out that these concentrations are 15 times those in Pedea.

Laboratory findings:
Other than the raw data from studies IBU/PROPHYL/2000 and IBU/99/DOSRANGE the applicant does not present any information on laboratory findings. However, this omission is acceptable, the unwanted effects of ibuprofen are well known and are adequately addressed in the SPC.

The incidence of thrombocytopenia was low and not increased for those treated with ibuprofen compared to indomethacin. Neutropenia, $<1500/mm^3$, was significantly more common during the first three days of life with ibuprofen that placebo when preterm newborns were treated prophylactically. This may be a true finding, as a transient white count fall was associated with ibuprofen in 8 out of 55,785 children aged 6 months to 12 years in a trial using paracetamol as control, Lesko et al., 1995.The applicant has not investigated the potential for the bleeding time to increase when ibuprofen is combined with nitric oxide therapy.

Discontinuation due to adverse events
The applicant indicates that in 12 of 174 infants treatment was stopped due to adverse events. This includes 4 of 66 in the placebo treated arm of IBU/PROPHYL/2000. In ten cases the narrative suggests a rapid global deterioration in clinical condition and a decision not to further treat a dying infant.

Safety in special populations
No data I special populations are presented. However given the intended use this is considered acceptable.

Immunological events
There is no evidence that ibuprofen has effects on the immune system, other than perhaps occasionally and indirectly through marrow suppression.

Overdose
No case of overdose has been reported with intravenous ibuprofen in preterm newborn infants.
However, overdose has been described in infants and children administered oral ibuprofen: CNS depression, seizures, gastrointestinal disturbances, bradycardia, hypotension, apnoea, abnormal renal function, haematuria have been observed.
Massive overdose (up to more than 1000 mg/kg) has been reported to induce coma, metabolic acidosis, and transient renal failure. All patients recovered with conventional treatment. Only one recorded death has been published: after an overdose of 469 mg/kg, a 16-month old child developed an apnoeic episode with seizures and fatal aspiration pneumonia.
The management of ibuprofen overdose is primarily supportive.
Adequate information has been included in section 4.9 of the SPC.

Safety related to drug-drug interactions and other interactions
The applicant has not carried out any specific interaction studies, relying only on the clinical trial data, where concomitant medication is common. Neonatal intensive care is a complex situation with high morbidity and mortality where drug interactions may not be obvious. Adequate information has been included in section 4.5 of the SPC *(see clinical pharmacology).*

Post-marketing experience
Since Pedea was made available on a named-patient basis, 737 boxes of 4 ampoules were provided in 2001 and 1,696 boxes in 2002. The product has been used in the following European countries: Austria, Finland, France, Germany, Italy, Norway, Poland, Spain, Sweden, Switzerland and the United Kingdom. Two serious adverse events were reported during this 2-year period. One was progressive hypoxaemia following the third infusion of ibuprofen on Day 6 of an infant, gestational age 26 weeks. There was progressive recovery with nitric oxide and high frequency ventilation and minor echocardiographic signs of pulmonary hypertension 24 hours later. The second infant had a pulmonary haemorrhage and cardiac dysfunction after two doses on the second day of life and recovered with high frequency ventilation.

In addition, following the occurrence of three cases of reversible refractory hypoxaemia after prophylactic therapy in the clinical trial, a retrospective survey was undertaken by the applicant to add data about the safety of ibuprofen administration in preterm infants.
This included 165 preterm infants, approximately half below 27 weeks of gestational age. No cases of Pedea associated hypoxaemia were reported, although, as may be expected from their prematurity, major complications were common. In the late treatment group the incidence of complications appeared similar in the 62 infants treated with ibuprofen and the 65 treated with indomethacin. Unlike indomethacin, ibuprofen was not associated with water retention and hyponatraemia, or an increase in serum creatinine.

Discussion on clinical safety

Ibuprofen was developed as an alternative to indomethacin for PDA in the hope that it might be as effective with a better safety profile. The applicant has made good efforts in the generation of 'own data'. Three clinical trials have been conducted.
In addition, bibliographic data are submitted to support the choice of dose of ibuprofen and the use of a new formulation and route of administration for a new therapeutic indication, which is based on the well characterised mechanism of action of ibuprofen.

The published literature, together with the applicant's own generated data, is sufficient to fulfil the dossier requirements. In the light of an independent review of the literature on the use of ibuprofen for the closure of PDA, it is considered that the applicant's citation of the literature is accurate and complete. The published studies are often small, however, they do serve to provide a reasonable understanding of the effects of ibuprofen on blood-flow in various organs, and its clinical safety and efficacy.

It is considered that the normal dossier requirements are satisfied in accordance with Directive 2001/83/EC, as amended.

Evaluation of the safety of ibuprofen in the treatment of PDA, and particularly the safety relative to indomethacin is difficult due to the high background rate of mortality and morbidity in the treatment population and due to the small database. Moreover, the nature of the data, much of it in the form of published literature where safety information is not usually emphasised, adds to the difficulty.
Pedea is very likely to be associated with all the unwanted effects known from adult patients. Unfortunately, it is impossible to say whether there will be additional problems due to the fragility of the treatment population in this indication.

Indomethacin has an established positive benefit/risk for PDA when compared to placebo. The safety profile of ibuprofen seems to compare favourably with indomethacin and therefore appears acceptable for PDA, although the cause of adverse events in preterm neonates is complex.
It is possible that ibuprofen may be less detrimental to cerebral blood flow when compared to indomethacin. It is also possible that occasional cases of acute hypoxia shortly after infusion might be more common with ibuprofen than with indomethacin.
However, there appears to be sufficient data available from animal studies to support the hypothesis that the adverse events in the clinical trial relate to the extreme prematurity of the babies and administration in the first hours after birth.

In the absence of a direct head-to-head comparative trial versus indomethacin, the applicant has provided data supporting the efficacy of ibuprofen in PDA closure.
From the extensive clinical trials meta-analysis it emerges that the rate of closure of PDA achieved with ibuprofen is similar to that expected with equivalent use of indomethacin. Both compounds results in considerably lower rates of PDA at whatever time point the assessment is made. However, this does not seem to confer a benefit with respect to overall survival or the frequency of intraventricular haemorrhage, necrotising enterocolitis, bronchopulmonary dysplasia and renal impairment. It seems probable that the database is too small to show anything other than a major difference in any of those clinical events.

Indomethacin has been used for almost three decades in the prophylaxis and treatment of PDA. The applicant considers that ibuprofen has similar efficacy and a better safety profile than indomethacin; the latter through less disturbance in systemic blood flow and reduction in some common clinical complications of prematurity.

However, the quality of the publications supporting the contention that ibuprofen is safer than indomethacin is not impressive. It is acknowledged that there are ethical and technical reasons, which make it very difficult to conduct clinical trials in premature neonates. However, only four papers involved a direct comparison and only one was double blind. Despite these limitations the literature is consistent in showing that there are differences in haemodynamics following intervention with

ibuprofen and indomethacin, the former causing less disturbance. If the clinical complications of prematurity, intraventricular haemorrhage, mesenteric ischaemia etc. relate in part to NSAID intervention as distinct from closure of PDA, then ibuprofen could offer a safety advantage related possibly to a lesser impact on systemic haemodynamics.

Of some concern are the three cases of hypoxaemia in the prophylactic trial in patients who were stable before Pedea was injected. As this had not been reported with ibuprofen lysine, there is the possibility that an excipient may have contributed. The main reassurance from the published data with THAM (Tris buffer, or trometamol) infusions in neonates is that hypoxaemia was uncommon with infusions of 0.3 mmol/ml, equivalent to 100 ampoules/kg of Pedea. This appears to be a reassuring safety margin for the excipient trometamol in Pedea where it is used as a solubilising agent. The cases of hypoxaemia may have been detected by more careful monitoring than in earlier trials. One explanation might be that in some neonates endogenous prostanoids are important in maintaining pulmonary vascular patency.

The phenomenon of pulmonary hypertension has not been reported in trials with ibuprofen lysine used to cure PDA, although there are three cases reported with indomethacin. It is possible Pedea has a product specific side effect, although the applicant appears to have excluded the possibility of precipitation/embolisation.
Some infants may be dependent on prostanoids to maintain normal patency of the pulmonary circulation, a deficiency of which can be compensated for with nitric oxide. This raises the possibility that nitric oxide might contribute to the unwanted patency of PDA.
In the bibliographic review respiratory outcome appears similar for ibuprofen and indomethacin. In contrast, the prophylactic trial with Pedea showed a trend for an increase in the use of inhaled nitric oxide and high frequency ventilation.

With regards to the reported adverse events for ibuprofen in the clinical trials, the extreme prematurity of preterm newborns, and the variability involved with such a fragile population and the possibility of a role for underlying conditions, means that it is difficult to ascertain whether haemodynamic consequences may or may not be treatment-related. All adverse events in this population are viewed as serious, but this must be considered in the context of the clinical condition, and the specialist situations and knowledge attached to clinical treatment administration.

Before administration of Pedea an adequate echocardiographic examination should be performed in order to detect a haemodynamically significant PDA and to exclude pulmonary hypertension and ductal-dependent congenital heart disease. Pedea is contraindicated in congenital heart disease in which patency of the DA is necessary for satisfactory pulmonary or systemic blood flow (e.g. pulmonary atresia, severe tetralogy of Fallot, severe coarctation of the aorta).

The results of the primary analysis from Study IBU/PROPHYL/2000 suggest that prophylaxis is of some benefit in avoiding surgery. However, this did not confer a mortality benefit and appears to have resulted in more complications at least some of which may be treatment related. Prophylactic use of Pedea in the first 3 days of life (starting within 6 hours of birth) in preterm newborn infants less than 28 weeks of gestational age was associated with increased incidence of renal failure and pulmonary adverse events including hypoxia, pulmonary hypertension and pulmonary haemorrhage, as compared to curative use. In particular, severe hypoxemia with pulmonary hypertension was reported in 3 infants within one hour of the first infusion and was reversed within 30 min after start of inhaled nitric oxide therapy.
Pedea should therefore not be used prophylactically, which has been adequately addressed in the Summary of Product Characteristics. Further, Pedea is also contraindicated in infants with significant impairment of renal function.

Since ibuprofen was shown *in vitro* to displace bilirubin from its binding site to albumin, the risk of bilirubin encephalopathy in premature newborn infants may be increased. Therefore, ibuprofen should not be used in infants with marked unconjugated hyperbilirubinaemia.

As a non-steroidal anti-inflammatory drug (NSAID), ibuprofen may mask the usual signs and symptoms of infection. Pedea must therefore be used cautiously in the presence of an infection.

As ibuprofen may inhibit platelet aggregation, premature neonates should be monitored for signs of bleeding. Consequently, Pedea is contraindicated in infants with active bleeding, especially intracranial or gastrointestinal haemorrhage and in infants with thrombocytopenia or coagulation defects. Careful monitoring of both renal and gastrointestinal function is recommended.
Adequate information has been included in sections 4.3 and 4.4 of the SPC.

Sufficient information on the safety and efficacy of Pedea in the younger cohort of patients (<27 weeks of gestational age) has not yet been provided. A warning has therefore been introduced in Section 4.3 of the Summary of Product Characteristics, stating that in preterm newborn infants less than 27 weeks of gestational age, the closure rate of the *ductus arteriosus* was shown to be low at the recommended dose regimen.
The applicant has therefore committed to conduct a clinical study in preterm newborn infants less than 28 weeks of gestational age with a haemodynamically significant PAD in order to evaluate the safety and efficacy of Pedea. Progress reports will be submitted to CHMP for review in line with predefined timeframes.

Furthermore, the applicant has committed to initiate a Post-Marketing Surveillance Programme designed to record neurological/ sensorial and pulmonary outcomes at 18 months of corrected age in a group of preterm infants treated with Pedea in the neonatal period.

5. Overall conclusions and benefit/risk assessment

Quality
The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology
The pharmacodynamic profile of ibuprofen has been extensively characterised. The known pharmacokinetic profile of ibuprofen, along with the superiority of clinical pharmacokinetic data in neonates negates the requirement to conduct further investigations in animals.
In consideration of the proposed indication and patient population, and in the light of clinical data gathered from over 1000 preterm newborns, the toxicity profile of ibuprofen is acceptable for the current indication. All non-clinical data considered relevant to clinical safety have been included in the Summary of Product Characteristics (SPC) for Pedea.

Efficacy
Ibuprofen is a non-selective inhibitor of cyclo-oxygenase, leading to reduce synthesis of prostaglandins. Since prostaglandins are involved in the persistence of the *ductus arteriosus* after birth, this effect is believed to be the main mechanism of action of ibuprofen in this indication.
In a dose-response study of Pedea in 40 preterm newborn infants, the *ductus arteriosus* closure rate associated to the 10-5-5 mg/kg dose regimen was 75% (6/8) in neonates of 27-29 weeks' gestation and 33% (2/6) in neonates of 24-26 weeks' gestation.
The applicant's studies and the meta-analysis of the published clinical studies suggest that ibuprofen is efficacious in this condition. This is in keeping with the known pharmacology of cyclooxygenase inhibition and its effect on PDA. It is likely that the dose chosen for ibuprofen is appropriate, although the results from the small numbers recruited into the applicant's dose ranging study add little to the published literature. However, a warning has therefore been introduced in the SPC, stating that in preterm newborn infants less than 27 weeks of gestational age, the closure rate of the *ductus arteriosus* was shown to be low at the recommended dose regimen.

Safety

Data are currently available on approximately 1,000 preterm newborn from both literature with ibuprofen and clinical trials with Pedea.

Indomethacin has an established positive benefit/risk for PDA when compared to placebo. The safety profile of ibuprofen seems to compare favourably with indomethacin due to a lesser effect on the systemic blood flow. However, causality of adverse events in preterm neonates are difficult to assess since they may be related to the haemodynamic consequences of the PDA as well as to the direct effects of ibuprofen.

Before administration of Pedea an adequate echocardiographic examination should be performed in order to detect a haemodynamically significant PDA and to exclude pulmonary hypertension and ductal-dependent congenital heart disease. Pedea is contraindicated in congenital heart disease in which patency of the DA is necessary for satisfactory pulmonary or systemic blood flow.

Since prophylactic use in the first 3 days of life (starting within 6 hours of birth) in preterm newborn infants less than 28 weeks of gestational age was associated with increased pulmonary and renal adverse events, Pedea should not be used prophylactically. Further, Pedea is also contraindicated in infants with significant impairment of renal function.

As ibuprofen may inhibit platelet aggregation, premature neonates should be monitored for signs of bleeding. Consequently, Pedea is contraindicated in infants with active bleeding, especially intracranial or gastrointestinal haemorrhage and in infants with thrombocytopenia or coagulation defects. Careful monitoring of both renal and gastrointestinal function is recommended.

Benefit/risk assessment

Following the review of the submitted documentation, and the final SPC and letter of undertaking, the CPMP agreed that efficacy has been shown that is clinically relevant and the safety profile of Pedea is in line with the results described in the literature, which allow a conclusion on an acceptable benefit/risk for the treatment of a haemodynamically significant PDA in preterm newborn infants less than 34 weeks of gestational age. However, in preterm newborn infants less than 27 weeks of gestational age, the closure rate of the *ductus arteriosus* was shown to be low at the recommended dose regimen.

The applicant has therefore committed to conduct a clinical study in preterm newborn infants less than 28 weeks of gestational age with a haemodynamically significant PDA in order to further evaluate the safety and efficacy of Pedea.

Since prophylactic use in preterm newborn infants less than 28 weeks of gestational age was associated with an increased frequency of adverse events, the risk/benefit may be considered adverse if ibuprofen is used prophylactically.

Furthermore, the applicant has committed to initiate a Post-Marketing Surveillance Programme designed to record neurological/ sensorial and pulmonary outcomes at 18 months of corrected age in a group of preterm infants treated with Pedea in the neonatal period.

Recommendation

”Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk ratio of Pedea in the treatment of a haemodynamically significant PDA in preterm newborn infants less than 34 weeks of gestational age was favourable and therefore recommended the granting of the marketing authorisation.”

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- Appendices: Study Information
- Appendices: Patient Data Listings
- Appendices: Patient Data Listings (continued)
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