PEDEA® SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pedea 5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 5 mg ibuprofen.
Each 2 ml ampoule contains 10 mg ibuprofen.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

For intravenous use only. Treatment with Pedea should only be carried out in a neonatal intensive care unit under the supervision of an experienced neonatologist.
A course of therapy is defined as three intravenous 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.

If the *ductus arteriosus* does not close 48 hours after the last injection or if it re-opens, a second course of 3 doses, as above, may be given.
If the condition is unchanged after the second course of therapy, surgery of the patent *ductus arteriosus* may then be necessary.

Method of administration:
Pedea should be administered as a short infusion over 15 minutes, preferably undiluted. If necessary, the injection volume may be adjusted with either sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection. Any unused portion of the solution should be discarded.
The total volume of solution injected should take into account the total daily fluid volume administered.

If anuria or manifest oliguria occurs after the first or second dose, the next dose should be withheld until urine output returns to normal levels.

4.3 Contraindications

Pedea is contraindicated in neonates with:
- life-threatening infection;

- active bleeding, especially intracranial or gastrointestinal haemorrhage;
- thrombocytopenia or coagulation defects;
- significant impairment of renal function;
- congenital heart disease in which patency of the *ductus arteriosus* is necessary for satisfactory pulmonary or systemic blood flow (e.g. pulmonary atresia, severe tetralogy of Fallot, severe coarctation of the aorta);
- known or suspected necrotising enterocolitis;
- hypersensitivity to ibuprofen or to any of the excipients.

4.4 Special warnings and special precautions for use

Before administration of Pedea an adequate echocardiographic examination should be performed in order to detect a haemodynamically significant patent *ductus arteriosus* and to exclude pulmonary hypertension and ductal-dependent congenital heart disease.

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 (see sections 4.8 and 5.1). 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.

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 (see section 5.2). 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.

Pedea should be administered carefully to avoid extravasation and potential resultant irritation to tissues.

As ibuprofen may inhibit platelet aggregation, premature neonates should be monitored for signs of bleeding.

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

Careful monitoring of both renal and gastrointestinal function is recommended.

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 (see section 5.1).

4.5 Interaction with other medicinal products and other forms of interaction

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.
- aminoglycosides: since ibuprofen may decrease the clearance of aminoglycosides, their co-administration may increase the risk of nephrotoxicity and ototoxicity (see section 4.4).

4.6 Pregnancy and lactation

Not relevant

4.7 Effects on ability to drive and use machines

Not relevant

4.8 Undesirable effects

Data are currently available on approximately 1,000 preterm newborn from both the literature concerning ibuprofen and clinical trials with Pedea. Causality of adverse events reported in the preterm newborn is difficult to assess since they may be related to the haemodynamic consequences of the patent *ductus arteriosus* as well as to direct effects of ibuprofen.

Reported adverse events are listed below, by system organ class and by frequency. Frequencies are defined as: very common (> 1/10), common (>1/100, <1/10) and uncommon (>1/1,000, <1/100).

Blood and lymphatic system disorders	*Very common*: Thrombocytopenia, Neutropenia
Nervous system disorders	*Common*: Intraventricular haemorrhage, Periventricular leukomalacia
Respiratory, thoracic and mediastinal disorders	*Very common:* Bronchopulmonary dysplasia *Common*: Pulmonary haemorrhage *Uncommon:* Hypoxemia
Gastrointestinal disorders	*Common*: Necrotizing enterocolitis, Intestinal perforation *Uncommon*: Gastrointestinal haemorrhage
Renal and urinary disorders	*Common*: Oliguria, Fluid retention, Haematuria Uncommon: Acute renal failure
Investigations	*Very Common:* Blood creatinine increased, Blood sodium decreased

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.

In a clinical trial where Pedea was administered prophylactically during the first 6 hours of life, severe hypoxemia with pulmonary hypertension was reported in 3 newborn infants less than 28 weeks of gestational age. This occurred within one hour of the first infusion and was reversed within 30 minutes after the inhalation of nitric oxide.

4.9 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 a fatal aspiration pneumonia.

The management of ibuprofen overdose is primarily supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other cardiac preparations, ATC code: C01 EB16

Ibuprofen is a NSAID that possesses anti-inflammatory, analgesic and antipyretic activity. 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 a non selective inhibitor of cyclo-oxygenase, leading to reduced 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.

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. Conversely, a lower incidence of neonatal grade III-IV intraventricular haemorrhage and of surgical ligation was associated with prophylactic use of Pedea.

5.2 Pharmacokinetic properties

Although a great variability is observed in the premature population, peak plasma concentrations are measured around 35-40 mg/l after the initial loading dose of 10 mg/kg as well as after the last maintenance dose, whatever gestational and postnatal age. Residual concentrations are around 10-15 mg/l 24 hours after the last dose of 5 mg/kg.
Plasma concentrations of the S-enantiomer are much higher than those of the R-enantiomer, which reflects a rapid chiral inversion of the R- to the S-form in a proportion similar to adults (about 60%).

The apparent volume of distribution is on average 200 ml/kg (62 to 350 according to various studies). The central volume of distribution may depend on the status of the ductus and decrease as the ductus closes.

Elimination rate is markedly lower than in older children and adults, with an elimination half-life estimated at approximately 30 hours (16–43). The clearance of both enantiomers increases with gestational age, at least in the range of 24 to 28 weeks.

In vitro studies suggest that, similarly to other NSAIDs, ibuprofen is highly bound to plasma albumin, although this seems to be significantly lower (95 %) compared with adult plasma (99 %). Ibuprofen competes with bilirubin for albumin binding in newborn infant serum and, as a consequence, the free fraction of bilirubin may be increased at high ibuprofen concentrations.

In preterm newborns ibuprofen significantly reduced plasma concentrations of prostaglandins and their metabolites, particularly PGE2 and 6-keto-PGF-1-alpha. Low levels were sustained up to 72 hours in neonates who received 3 doses of ibuprofen, whereas subsequent re-increases were observed at 72 hours after only 1 dose of ibuprofen.

5.3 Preclinical safety data

There are no preclinical data considered relevant to clinical safety beyond data included in other sections of this Summary of Product Characteristics. With the exception of an acute toxicity study, no further studies have been carried out in juvenile animals with Pedea.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol,
sodium chloride,
sodium hydroxide (for pH adjustment),
hydrochloric acid 25% (for pH adjustment),
water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Pedea solution must not be in contact with any acidic solution such as certain antibiotics or diuretics. A rinse of the infusion line must be performed between each product administration (see section 6.6).

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Colourless type 1 glass ampoule.
Pedea is supplied in packs of 4 x 2 ml ampoules.

6.6 Instructions for use and handling

As for all parenteral products, ampoules of Pedea should be visually inspected for particulate matter and the integrity of the container prior to use. Ampoules are intended for single use only, any unused portions must be discarded.

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

The required volume to be given to the infant should be determined according to body weight, and should be injected intravenously as a short infusion over 15 minutes, preferably undiluted.

Use only sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution to adjust injection volume.
The total volume of solution injected to preterm infants should take into account the total daily fluid volume administered. A maximal volume of 80 ml/kg/day on the first day of life should usually be respected; this should be progressively increased in the following 1-2 weeks (about 20 ml/kg birthweight/day) up to a maximal volume of 180 ml/kg birthweight/day.

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

After first opening of an ampoule, any unused portions must be discarded.

From a microbiological point of view, the product should be used immediately.

7. MARKETING AUTHORISATION HOLDER

Orphan Europe SARL
Immeuble “Le Wilson”
70 avenue du Général de Gaulle
F-92800 Puteaux - France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/284/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 July 2004

10. DATE OF REVISION OF THE TEXT