ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Pedea 5 mg/ml solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of the solution contains 5 mg ibuprofen.
Each ampoule of 2 ml contains 10 mg ibuprofen.

Excipients: each ml contains 7.5 mg of sodium.

For a full list of 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

Treatment with Pedea should only be carried out in a neonatal intensive care unit under the supervision of an experienced neonatologist.

Posology
A course of therapy is defined as three intravenous injections of Pedea given at 24-hour intervals. The first injection should be given after the first 6 hours of life.
The ibuprofen dose is adjusted to the body weight as follows:
- 1st injection: 10 mg/kg,
- 2nd and 3rd injections: 5 mg/kg.

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

Method of administration
For intravenous use only.
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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients;
- 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;

4.4 Special warnings and 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 at any gestational age (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. If hypoxaemia occurs during or following Pedea infusion, close attention should be paid to pulmonary pressure.

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 elevated bilirubin concentration.

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 (see also section 4.3).

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.

Severe skin reactions

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported rarely in association with the use of NSAIDSs (see section 4.8). Patients appear to be at highest risk of these reactions early in the course of therapy, the onset of the reaction occurring in the majority of cases within the first month of treatment. Acute generalised exanthematous pustulosis (AGEP) has been reported in relation to ibuprofen-containing products. Ibuprofen should be discontinued, at the first appearance of signs and symptoms of severe skin reactions, such as skin rash, mucosal lesions, or any other sign of hypersensitivity.

In preterm newborn infants less than 27 weeks of gestational age, the closure rate of the *ductus arteriosus* (33 to 50%) was shown to be low at the recommended dose regimen (see section 5.1).

This medicinal product contains less than 1 mmol sodium (15 mg) per 2 ml, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of Pedea with the following medicinal products is not recommended:
- 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 reactions 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

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 *Unknown:* Gastric perforation
Renal and urinary disorders	*Common*: Oliguria, Fluid retention, Haematuria Uncommon: Acute renal failure
Investigations	*Very Common:* Blood creatinine increased, Blood sodium decreased
Skin and subcutaneous tissue disorders	*Not known:* Acute generalised exanthematous pustulosis (AGEP)

* *see below*

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. There have also been post-marketing reports of pulmonary hypertension where Pedea was administered to premature neonates in the therapeutic setting.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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

Distribution
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.

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.

Elimination
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.

PK-PD relationship
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.
To avoid any possible microbiological contamination, the product should be used immediately after first opening.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other 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.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
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

Date of first authorisation: 29 July 2004
Date of renewal: 29 July 2009

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web site of the European medicines Agency (EMEA) http://www.emea.europa.eu

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Recordati Rare Diseases
Immeuble “Le Wilson”
70, avenue du Général de Gaulle
F- 92800 Puteaux,
France

or

Recordati Rare Diseases
Eco River Parc
30, rue des Peupliers
F-92000 Nanterre
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON TEXT

1. NAME OF THE MEDICINAL PRODUCT

Pedea 5 mg/ml solution for injection
Ibuprofen

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Excipients: trometamol, sodium chloride, sodium hydroxide, hydrochloric acid 25%, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
4 x 2 ml ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use as short infusion
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

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

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After first opening of an ampoule any unused portions must be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Recordati Rare Diseases
Immeuble “Le Wilson”
70 avenue du Général de Gaulle
F- 92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/284/001

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

GLASS AMPOULE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Pedea 5 mg/ml solution for injection
Ibuprofen
IV use

2. METHOD OF ADMINISTRATION

See leaflet

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg / 2 ml

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Pedea 5mg/ml solution for injection
Ibuprofen

Read all of this leaflet carefully before this medicine is administered to your baby.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for your baby. Do not pass it on to others. It may harm them, even if their symptoms are the same as your baby's.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or your pharmacist.

In this leaflet:

1. WHAT PEDEA IS AND WHAT IT IS USED FOR

While a baby is inside its mother's womb it does not need to use its lungs. An unborn baby has a blood vessel called the *ductus arteriosus* near the heart which allows the baby's blood to bypass the lungs and circulate to the rest of the body.
When the baby is born and starts using its lungs the *ductus arteriosus* normally closes. However, in some cases this does not happen. The medical term for this condition is 'patent *ductus arteriosus'*, i.e. an open *ductus arteriosus*. This can cause heart problems in your baby. This condition is much more frequent in premature newborn than in full-term newborn infants.
Pedea, when given to your baby, can help to close the *ductus arteriosus*.

The active substance in Pedea is ibuprofen. Pedea closes the *ductus arteriosus* by inhibiting the production of prostaglandin, a naturally occurring chemical in the body which keeps the *ductus arteriosus* open.

2. BEFORE PEDEA IS ADMINISTERED TO YOUR BABY

Pedea will only be given to your baby in a special neonatal intensive care unit by qualified health care professionals.

Do not use Pedea
- if your baby is allergic (hypersensitive) to ibuprofen or any of the other ingredients of Pedea;
- if your baby has a life-threatening infection which has not been treated;
- if your baby is bleeding, especially if the bleeding is inside the skull or in the intestines;
- if your baby has a decrease of blood cells called platelets (thrombocytopenia) or other problems with their blood clotting;
- if your baby has kidney problems;
- if your baby has other problems with their heart which require the *ductus arteriosus* to remain open so that adequate circulation of the blood is maintained;
- if your baby has or is suspected to have certain problems with their intestines (a condition called necrotising enterocolitis);

Take special care with Pedea
- Before treatment with Pedea, your baby's heart will be examined to confirm that the *ductus arteriosus* is open.
- Pedea should not be given in the first 6 hours of life.
- If your baby is suspected of having liver disease, signs and symptoms of which include yellowing of the skin and eyes.
- If your baby is already suffering from an infection that is being treated, the doctor will treat your baby with Pedea only after careful consideration of your baby's condition.
- Pedea should be carefully administered to your baby by the healthcare professional, to avoid damage to the skin and surrounding tissues.
- Ibuprofen may reduce the ability of your baby's blood to clot. Your baby should therefore be watched for signs of prolonged bleeding.
- Your baby may develop some bleeding from the intestines and the kidneys. To detect this, your baby's stools and urine may be tested to determine if there is any blood present in them.
- Pedea may reduce the amount of urine your baby passes. If this is significant, your baby's treatment may be stopped until the volume of urine returns to normal.
- Pedea may be less effective in very premature babies less than 27 weeks of gestational age.
- Serious skin reactions have been reported in association with Pedea treatment. You should stop taking Pedea and seek medical attention immediately, if you develop any skin rash, lesions of the mucous membranes, blisters or other signs of allergy since this can be the first signs of a very serious skin reaction. See section 4.

Using other medicines
Please tell your doctor or pharmacist if your baby is taking or has recently taken any other medicines, including medicines obtained without a prescription.

Certain medicines, if given together with Pedea, may cause side effects. These are detailed below:

- your baby may have problems passing urine and may have been prescribed diuretics. Ibuprofen may reduce the effect of these medicines.

- your baby may be given anticoagulants (medicine preventing blood clotting). Ibuprofen may increase the anti-clotting effect of this product.

- your baby may be given nitric oxide to improve blood oxygenation. Ibuprofen may increase the risk of bleeding.

- your baby may be given corticosteroids to prevent inflammation. Ibuprofen may increase the risk of bleeding in the stomach and intestines.

- your baby may be given aminosides (one family of antibiotics) to treat infection. Ibuprofen may increase blood concentrations and thus increase the risk of toxicity on kidney and ear

Important information about some of the ingredients of Pedea
This medicinal product contains less than 1 mmol sodium (15 mg) per 2 ml, i.e. essentially 'sodium-free'.

3. HOW PEDEA IS USED

Pedea will only be given to your baby in a special neonatal intensive care unit by qualified healthcare professional.

A course of therapy is defined as three intravenous injections of Pedea given at 24 hour intervals. The dose to be administered will be calculated from the weight of your baby. It is 10 mg/kg for the first administration and 5 mg/kg for the second and the third administrations.

This calculated amount will be given by infusion in a vein over a period of 15 minutes.
If after this first course of treatment, the *ductus arteriosus* is not closed or re-opens, your baby's doctor may decide to give a second course of treatment.

If after the second course of treatment, the *ductus arteriosus* is still not closed, a surgery may then be proposed.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Pedea can cause side effects, although not everybody gets them. However, it is difficult to distinguish them from frequent complications occurring in premature babies and complications due to the disease.

The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Very common:
- Decrease in the number of platelets in the blood (thrombocytopenia),
- Decrease in white blood cells called neutrophils (neutropenia),
- Increase in creatinine level in the blood,
- Decrease in sodium level in the blood,
- Breathing problems (bronchopulmonary dysplasia),

Common:
- Bleeding inside the skull (intraventricular haemorrhage) and brain injury (periventricular leukomalacia),
- Bleeding in the lung,
- Perforation of the intestine and injury of intestinal tissue (necrotizing enterocolitis),
- Reduced volume of urine passed, blood in the urine, fluid retention

Uncommon:
- Acute failure of the kidney's functions
- Bleeding in the intestine
- Below normal oxygen content in the arterial blood (hypoxemia)

Not known:
- Perforation of the stomach
- A red, scaly widespread rash with bumps under the skin and blisters mainly localized on the skin folds, trunk, and upper extremities accompanied by fever at the initiation of treatment (acute generalised exanthematous pustulosis). Stop using Pedea if you develop these symptoms and seek medical attention immediately. See also section 2.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your baby's doctor or your pharmacist.

5. HOW TO STORE PEDEA

Keep out of reach and sight of children.

Do not use Pedea after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

After opening, Pedea should be administered immediately.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Pedea contains

- The active substance is ibuprofen. Each ml contains 5 mg ibuprofen. Each 2 ml ampoule contains 10 mg ibuprofen.
- The other ingredients are trometamol, sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid 25% (for pH adjustment) and water for injections.

What Pedea looks like and contents of the pack
Pedea 5mg/ml solution for injection is a clear, colourless to slightly yellow solution.
Pedea 5mg/ml solution for injection is supplied in cartons of four 2 ml ampoules.

Marketing Authorisation Holder
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Manufacturer

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This leaflet was last approved in

Detailed information on this medicine is available on the European medicines Agency website: http://emea.europa.eu

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The following information is intended for medical or healthcare professionals only:

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.

Posology and method of administration (see also section 3)

For intravenous use only. Treatment with Pedea can 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 PDA may then be necessary.
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.

Method of administration:
Pedea should be administered as a short infusion over 15 minutes, preferably undiluted. To facilitate the administration an infusion pump may be used.
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 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.

Incompatibilities

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.

This medicinal product must not be mixed with other medicinal products except sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution.

In order to avoid any substantial variation of pH due to the presence of acidic medicinal products that could remain in the infusion line, the latter must be rinsed before and after administration of Pedea with 1.5 to 2 ml of either sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution.