**Attachment 1: Product information for AusPAR Pedea Emerge Health Pty Ltd PM-2015-04658-1-3 Final 10 November 2017. This Product Information was approved at the time this AusPAR was published.**

# DRAFT PRODUCT INFORMATION

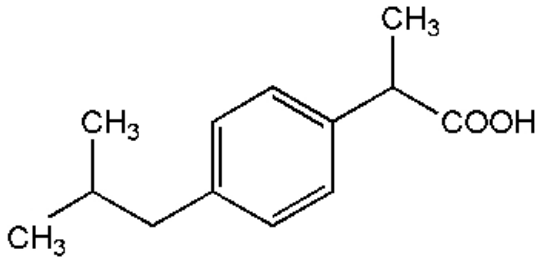
# PEDEA®

## NAME OF THE MEDICINE

Ibuprofen 5 mg/ml solution for intravenous infusion.

Ibuprofen is a white to almost white crystalline powder, insoluble in water, freely soluble in organic solvents (acetone, methanol and methylene chloride). It dissolves in alkali hydroxides and carbonates.

Its structural formula is:




Molecular formula: C13H18O2

Relative molecular mass: 206.3 g/mol

## DESCRIPTION

PEDEA 5 mg/ml solution for intravenous infusion is a colourless to slightly yellow solution. Each ml contains 5 mg of ibuprofen (CAS No. 15687-27-1). PEDEA 5 mg/ml, solution for intravenous infusion is dispensed in 2 ml colourless One-Point-Cut (OPC) type I glass ampoules and is supplied in packs of 4 x 2 ml ampoules.

Each ml of PEDEA also contains the following inactive ingredients: trometamol (3.78 mg), sodium hydroxide (0.14 mg), sodium chloride (7.3 mg), hydrochloric acid and water for injections. The headspace within the ampoules is filled with nitrogen.

## PHARMACOLOGY

### Pharmacodynamics

Ibuprofen is a non-steroidal anti-inflammatory drug (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 cyclooxygenase, 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.

### Pharmacokinetics

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.

## CLINICAL TRIALS

### Clinical development study

A multicenter double-blind randomised placebo-controlled study was undertaken to compare the prophylactic (N=55) versus the curative (N=66) use of PEDEA for inducing patent *ductus arteriosus* (PDA) closure. Upon confirmation of PDA patency, patients from the curative group received a course of 3 placebo injections in their first three days of life before receiving PEDEA treatment. The success rate was assessed by the percentage of patients with a closed PDA as evidenced by Echo-Doppler. Among 66 patients from the curative group, 25 patients received curative PEDEA treatment and in 12 of these patients (48%) this resulted in PDA closure. The success rate in the curative treatment group did not appear to be correlated to the gestational age (see table below).

**Table 1 – Success rate of Pedea curative treatment group, according to gestational age**

| | N, total | N', patients with closed PDA | Success rate (N'/N) |
|---|---|---|---|
| Overall | 25 | 12 | 48.0% |
| Gestational Age | | | |
| 24-25 | 3 | 1 | 33.3% |
| 25-26 | 8 | 5 | 62.5% |
| 26-27 | 7 | 1 | 14.3% |
| 27-28 | 7 | 5 | 71.4% |

Following curative PEDEA, 9 infants (36%) received a course of indomethacin due to

persistence of the PDA. However, only seven had a significant PDA as evidenced by Echo-Doppler. Six patients (24%) underwent surgical ligation. Among them 2 had failed to respond to indomethacin.

Safety was assessed by recording the occurrence of adverse events in both curative and prophylactic treatment groups (see table below).

**Table 2 – Adverse events recorded during a double-blind randomised placebo-controlled study comparing the prophylactic and curative uses of PEDEA for inducing *ductus* closure.**

| System Organ Class Preferred Term | Curative group N = 66 | | Prophylactic group N = 65 | | All N = 131 | |
|---|---|---|---|---|---|---|
| **Any Adverse event** | 31 | (47.0%) | 33 | (50.8%) | 64 | (48.9%) |
| **Respiratory, Thoracic and Mediastinal Disorders** | 9 | (13.6%) | 19 | (29.2%) | 28 | (21.4%) |
| **Hypoxia** | 6 | (9.1%) | 12 | (18.5%) | 18 | (13.7%) |
| **Pulmonary Hypertension and/or hypoxaemia** | 9 | (13.6%) | 15 | (23.1%) | 24 | (18.3%) |
| **Pulmonary Haemorrhage** | 2 | (3.0%) | 5 | (7.7%) | 7 | (5.3%) |
| **Other** | 5 | (7.6%) | 3 | (4.6%) | 8 | (6.1%) |
| **Nervous System Disorders** | 15 | (22.7%) | 10 | (15.4%) | 25 | (19.1%) |
| **Intraventricular Haemorrhage Neonatal** | 10 | (15.2%) | 4 | (6.2%) | 14 | (10.7%) |
| **Periventricular Leukomalacia** | 4 | (6.1%) | 3 | (4.6%) | 7 | (5.3%) |
| **Other** | 3 | (4.5%) | 3 | (4.6%) | 6 | (4.6%) |
| **Renal and Urinary Disorders** | 6 | (9.1%) | 10 | (15.4%) | 16 | (12.2%) |
| **Renal failure** | 2 | (3.0%) | 7 | (10.8%) | 9 | (6.9%) |
| **Anuria/Oliguria** | 2 | (3.0%) | 3 | (4.6%) | 5 | (3.8%) |
| **Oedema due to renal disease** | 2 | (3.0%) | 1 | (1.5%) | 3 | (2.3%) |
| **Other** | 2 | (3.0%) | 2 | (3.1%) | 4 | (3.1%) |
| **Infections and Infestations** | 7 | (10.6%) | 9 | (13.8%) | 16 | (12.2%) |
| **Gastrointestinal Disorders** | 6 | (9.1%) | 8 | (12.3%) | 14 | (10.7%) |
| **Intestinal perforation** | 1 | (1.5%) | 5 | (7.7%) | 6 | (4.6%) |
| **Necrotising Enterocolitis Neonatal** | 2 | (3.0%) | 5 | (7.7%) | 7 | (5.3%) |
| **Other** | 4 | (6.1%) | 2 | (3.1%) | 6 | (4.6%) |

The safety analysis showed a mild and transient effect of ibuprofen on renal function as well as a possible effect on the digestive tract (see 'ADVERSE EFFECTS'). The prophylactic group - in which PEDEA was injected within 6 hours of birth without prior confirmation of a PDA presence - displayed a total of 15 cases (23.1%) of pulmonary hypertension with refractory hypoxaemia, *versus* 9 cases (13.6%) in the curative group (p = 0.18). In 3 prophylactically treated patients, this occurred within an hour after the first dose of ibuprofen. This occurrence prompted premature study interruption and all further development on PEDEA prophylactic use for PDA closure, which is not a claimed indication.

### Retrospective study in Germany

A retrospective study was undertaken in the neonatology centre of the Charité-Virchow Hospital in Berlin (Germany), about the intravenous use of indomethacin, from 1998 to 2001 (N = 89) and of ibuprofen, from 2001 to 2003 (N = 93), for the treatment of PDA. In order to assess efficacy, the percentage of patients presenting a closed PDA after one treatment course was compared between both products (see Table 3).

**Table 3 – Number and percentage of patients presenting a closed PDA as evidenced by echography, after one treatment course with PEDEA or with indomethacin (monocentric retrospective study in Germany).**

| | PEDEA (N=93) | Indomethacin (N=89) | Fisher test |
|---|---|---|---|
| PDA closed N (%) | 53 (58.2%) | 68 (77.3%) | 0.007 |
| PDA open N (%) | 38 (41.8%) | 20 (22.7%) | |
| missing | 2 (2.1%) | 1 (2.2%) | |

It must be noted that a treatment course with PEDEA has duration of 3 days, as compared to 7 to 8 days with indomethacin. The extra days between the start of treatment and echographic assessment for indomethacin patients could have contributed to an increased rate of *ductus* closure. At the time of discharge, the efficacy of both treatments did not differ since the proportion of patients still displaying a PDA was the same for PEDEA and for indomethacin treated patients (18.3% and 18.0%, respectively).

## INDICATIONS

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

## CONTRAINDICATIONS

PEDEA should not be administered in the following instances:

- 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.

## PRECAUTIONS

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. In particular, severe hypoxaemia 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. Therefore, ibuprofen should not be used in infants with marked elevated bilirubin concentration.

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.

Chlorhexidine should not be used to disinfect the ampoule prior to opening as it is not compatible with the PEDEA solution (refer to 'DOSAGE AND ADMINISTRATION').

## INTERACTIONS WITH OTHER MEDICINES

The concomitant use of PEDEA with the following medical products is not recommended:

- **Diuretics** – ibuprofen may reduce the effect of diuretics; whilst the diuretic may increase the risk of nephrotoxicity of NSAIDs in dehydrated patients
- **Anticoagulants** – ibuprofen may increase the effect of anticoagulants and enhance the risk of bleeding
- **Nitric oxide** – as both medicinal products have an inhibitory effect on platelet function, their combination may in theory increase the risk of bleeding
- **Corticosteroids** – ibuprofen may increase the risk of gastrointestinal 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.

## ADVERSE EFFECTS

### Clinical development studies

A total of 273 patients have been treated with PEDEA for *ductus arteriosus* closure during sponsored clinical development studies during which PEDEA was injected at various doses either as a curative or as a prophylactic treatment for *ductus arteriosus* closure. In one of these studies, 66 patients were injected with saline to serve as control (see 'CLINICAL TRIALS'). The table below compiles the most frequent serious adverse events recorded after injection with placebo (N=66) or with PEDEA (N=273) during development studies.

**Table 4 – Most frequent serious adverse events (SAEs) recorded on Orphan Europe clinical development studies, during which 273 patients were injected with PEDEA and 66 patients with placebo (saline). N events: number of serious adverse events; %: percentage of events among total of events within a treatment group.**

| Serious Adverse Events | PEDEA, N events (%) | Placebo, N events (%) |
|---|---|---|
| Necrotising colitis | 17 (9.2%) | 0 (0.0%) |
| Intraventricular haemorrhage | 14 (7.6%) | 0 (0.0%) |
| Hypoxia | 12 (6.5%) | 6 (9.4%) |
| Pulmonary haemorrhage | 11 (6.0%) | 2 (3.1%) |
| Renal failure | 10 (5.4%) | 0 (0.0%) |

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| Serious Adverse Events | PEDEA, N events (%) | Placebo, N events (%) |
|---|---|---|
| Gastrointestinal/Intestinal perforation | 9 (4.9%) | 0 (0.0%) |
| Staphylococcal infection | 6 (3.3%) | 0 (0.0%) |
| Anaemia | 5 (2.7%) | 0 (0.0%) |
| Multi-organ failure | 5 (2.7%) | 0 (0.0%) |
| Staphylococcal sepsis | 4 (2.2%) | 0 (0.0%) |
| Bradycardia | 4 (2.2%) | 0 (0.0%) |
| Hypotension | 3 (1.6%) | 0 (0.0%) |
| Gastrointestinal haemorrhage | 3 (1.6%) | 0 (0.0%) |
| Candidiasis | 2 (1.1%) | 0 (0.0%) |
| Sepsis | 2 (1.1%) | 0 (0.0%) |
| Septic shock | 2 (1.1%) | 4 (6.3%) |
| Basal ganglia, cerebellar and cerebral haemorrhage | 2 (1.1%) | 1 (1.6%) |
| Periventricular leukomalacia | 2 (1.1%) | 4 (6.3%) |
| Hyperglycaemia | 2 (1.1%) | 0 (0.0%) |
| Pulmonary hypertension | 2 (1.1%) | 0 (0.0%) |
| Other SAEs | 67 (36.4%) | 47 (73.4%) |
| Total SAEs | 184 (100%) | 64 (100%) |

Necrotising enterocolitis and intraventricular haemorrhage were the two most frequent serious adverse reactions observed with PEDEA use in clinical studies. Hypoxia, pulmonary haemorrhage, renal failure and gastrointestinal/intestinal perforation were the next most commonly observed serious adverse events.

**Post-marketing experience**

Based on the number of PEDEA ampoules sold since granting of marketing authorisation in Europe (2004), it is estimated that a total of 92,156 patients have been treated with PEDEA.

The most frequent safety cases spontaneously reported between 2004 and 2014 are listed below, by System Organ Class in order of decreasing frequencies. Frequencies are defined as: rare (<100/100,000), or very rare (<10/100,000).

- Gastrointestinal disorders: *Rare:* intestinal perforation and necrotising colitis. *Very rare*: gastrointestinal haemorrhage and abdominal distension.
- Renal and urinary disorders: *Rare*: renal failure acute, oliguria, renal failure. *Very rare*: anuria.
- General disorders and administration site conditions: *Rare*: drug ineffective. *Very rare*: death, general physical health deterioration, generalised oedema, malaise, oedema, oedema peripheral, pneumatosis, death neonatal.
- Investigation: *Rare*: blood creatinine increased. *Very rare*: blood urea increased and urine output decreased.
- Nervous system disorders: *Rare*: intraventricular haemorrhage.
- Respiratory, thoracic and mediastinal disorders: *Very rare*: bronchopulmonary dysplasia, pulmonary arterial hypertension, pulmonary haemorrhage and pulmonary hypertension.
- Metabolism and nutrition disorders: *Very rare*: hyponatraemia and sodium retention.
- Cardiac disorders: *Very rare*: Arrhythmia, atrioventricular block second degree, bradycardia, cardiac failure, cyanosis central, persistent foetal circulation and tachycardia.

- Infections and infestations: *Very rare*: infection, neonatal infection, sepsis, sepsis neonatal, septic shock.
- Vascular disorders: *Very rare*: circulatory collapse, haemorrhage intracranial, hypertension, pallor, pulmonary hypertension, shock, and vasoconstriction.
- Injury, poisoning and procedural complications: *Very rare*: Inappropriate schedule of drug administration, incorrect dose administered, incorrect route of drug administration, prescribed overdose, underdose.
- Blood and Lymphatic system disorders: *Very rare*: thrombocytopenia and thrombocytopenia microangiopathy.
- Eye disorders: *Very rare*: retinopathy and retinopathy of prematurity.
- Surgical and medical procedures: *Very rare*: Laser therapy and off label use.
- Musculoskeletal and connective tissue disorders: *Very rare*: hypotonia and necrotising fasciitis.
- Pregnancy, puerperium and perinatal conditions: *Very rare*: bronchopulmonary dysplasia.
- Skin and subcutaneous tissue disorders: *Very rare*: rash macular and rash morbilliform.

Overall, during the 10-year period from 2004 and 2014, a total of 360 adverse events to PEDEA injected for *ductus* closure were spontaneously reported for an estimated exposure of around 92.000 patients. As for the clinical trial experience, necrotising enterocolitis and intraventricular haemorrhage were among the most frequently reported adverse events following PEDEA injection, and have each been reported in around 25 of 100.000 patients treated.

## DOSAGE AND ADMINISTRATION

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

A course of therapy is defined as three intravenous infusions of PEDEA given at 24-hour intervals. The first infusion should be given after the first 6 hours of life.

The ibuprofen dose is adjusted to the body weight as follows:

- 1$^{st}$ infusion: 10mg/kg,
- 2$^{nd}$ and 3$^{rd}$ infusions: 5mg/kg.

If anuria or manifest oliguria occurs after the first or second dose, the next dose should be withheld until urine output returns to normal levels. If the *ductus arteriosus* does not close 48 hours after the last infusion 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.

**Administration:**

For intravenous use only.

Chlorhexidine should not be used to disinfect the neck of the ampoule, as it is not compatible with the PEDEA solution. Therefore, for asepsis of the ampoule before use, ethanol 60% or

isopropyl alcohol 70% is recommended. When disinfecting the neck of the ampoule with an antiseptic, to avoid any interaction, the ampoule must be completely dry before opening.

PEDEA should be administered as a short infusion over 15 minutes, preferably undiluted. If necessary, the infusion 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. PEDEA is for single use in one patient only. Discard any residue.

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

Pedea solution must not be in contact with any acidic solution such as certain antibiotics or diuretics. Before and after administration of PEDEA, 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.

## OVERDOSAGE

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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

## PRESENTATION AND STORAGE CONDITIONS

PEDEA is dispensed as a 2 ml solution in a colourless, Type I glass ampoule. Each pack contains four ampoules.

### Storage Conditions

Store below 30 °C. Do not freeze.

## NAME AND ADDRESS OF THE SPONSOR

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## POISON SCHEDULE OF THE MEDICINE

Schedule 4

## DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

14 MARCH 2017

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