PROPOSED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

PEDEA (solution for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of the solution contains 5 mg ibuprofen.

Each 2 mL ampoule contains 10 mg ibuprofen.

Excipient(s) with known effect:

Sodium 7,5 mg/mL.

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to slightly yellow solution, free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PEDEA may be used for the 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 IV doses of PEDEA given at 24 hour intervals. The first injection should be given after the first 6 hours of life.

The PEDEA 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.

If the *ductus arteriosus* does not close within 48 hours after the last injection or if it reopens, a second course of 3 doses, as above, may be given.

If the condition in unchanged after the second course of therapy, surgery of the patent *ductus arteriosus* may be necessary.

Method of administration

For intravenous infusion 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

PEDEA is contraindicated in neonates with:

- hypersensitivity to ibuprofen or to any of the excipients listed in section 6.1
- 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, 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.

As the 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 in preterm infants.

If hypoxaemia occurs during or following PEDEA infusion, close attention should be paid to pulmonary artery pressure.

Since PEDEA 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, PEDEA should not

be used in infants with a markedly elevated bilirubin concentration.

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

As PEDEA may decrease the clearance of aminoglycosides, strict surveillance of their serum levels is recommended during co-administration with PEDEA (see section 4.5) since acute renal failure has recurred when aminoglycosides were given together with PEDEA. Acute renal failure often presents with oliguria and increased weight.

Careful monitoring of both renal and gastrointestinal function is recommended. When gastrointestinal bleeding or ulceration occurs in patients receiving PEDEA, treatment with PEDEA should be stopped (see section 4.3).

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported with the use of non-steroidal anti-inflammatory drugs (NSAIDSs) such as PEDEA (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 medicines such as PEDEA. PEDEA 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.

PEDEA may mask the usual signs and symptoms of infection. PEDEA must therefore be used cautiously in the presence of an infection (see section 4.3).

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

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.

PEDEA contains less than 1 mmol sodium (15 mg) per 2 mL that is to say essentially "sodium-free".

4.5 Interaction with other medicines and other forms of interaction

The potential adverse medicine reactions of particular concern with PEDEA, result from its high degree of binding to albumin in the plasma.

The effects of PEDEA on renal function may lead to reduced excretion of some medicines.

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

- *Diuretics and other antihypertensive medicines:*

  Diuretics can increase the risk of nephrotoxicity of PEDEA in dehydrated patients. The antihypertensive effects of some antihypertensive medicines including ACE inhibitors, beta blockers and diuretics may be reduced. There may also be an increased risk of hyperkalaemia with ACE inhibitors and potassium sparing diuretics.
- *Anticoagulants:*

  PEDEA may increase the effect of anticoagulants and enhance the risk of bleeding.
- *Corticosteroids:*

  PEDEA may increase the risk of gastrointestinal bleeding and ulceration.
- *Nitric oxide:*

  Since both PEDEA and nitric oxide inhibit platelet function, their combination may increase the risk of bleeding.
- *Other NSAIDs (including aspirin):*

The concomitant use of more than one NSAID should be avoided because of the increased risk of adverse effects.

- *Zidovudine:*

  There may be an increased risk of haemotoxicity during concomitant use of zidovudine and PEDEA; blood counts one to two weeks after starting use together are recommended.

- *Ritonavir:*

  Concomitant use may increase the plasma concentrations of PEDEA.

- *Aminoglycosides:*

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

4.6 Fertility, pregnancy and lactation

Not applicable. PEDEA is indicated for preterm infants.

4.7 Effects on ability to drive and use machines

Not applicable. PEDEA is indicated for preterm infants.

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.

Adverse reactions reported are listed below, by MEDRA system organ class and by CIOMS frequency categories. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000), very rare (< 1/10 000).

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

Cardiac disorders:

Frequency unknown:

Hypertension, cardiac failure

Respiratory, thoracic and mediastinal disorders:

Very common:

Bronchopulmonary dysplasia

Common:

Pulmonary haemorrhage

Uncommon:

Hypoxaemia *, pulmonary hypertension

Gastrointestinal disorders:

The most commonly observed adverse events are gastrointestinal in nature.

Common:

Necrotising enterocolitis, peptic ulcers, intestinal perforation or gastrointestinal bleeding, sometimes fatal.

Nausea, vomiting, diarrhoea, flatulence, constipation, dyspepsia, abdominal pain, melena, hematemesis, ulcerative stomatitis, exacerbation of colitis and Crohn's disease, gastritis

Frequency unknown:

Gastric perforation

Skin and subcutaneous tissue disorders:

Frequency unknown:

Bullous reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP)

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 trial where PEDEA was administered prophylactically during the first 6 hours of life, severe hypoxaemia 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 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

No case of overdose has been reported with intravenous ibuprofen such as PEDEA 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 1 000 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 overdosage of 469 mg/kg, a 16 month old child developed an apnoeic episode with seizures and a fatal aspiration pneumonia.

Prolonged use at higher than recommended doses or overdose may result in renal tubular acidosis and hypokalaemia.

The management of PEDEA overdose is supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 3.1 Antirheumatics (anti-inflammatory agents).

Pharmacotherapeutic group: Other cardiac preparations, ATC code: C01 EB16.

Ibuprofen inhibits the synthesis of prostaglandins. Since prostaglandins are involved in the persistence of the *ductus arteriosus* after birth, this inhibitory effect is thought to be the main mechanism of action of ibuprofen in this indication.

5.2 Pharmacokinetic properties

Distribution

Although a great variability is observed in the premature population, peak plasma concentrations of ibuprofen are measured around 35-40 mg/L after the initial loading dose of 10 mg/kg as well as after the last maintenance dose, regardless of the 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 mL/kg according to various studies). The central volume of distribution may depend on the status of the *ductus arteriosus* and decrease as the *ductus arteriosus* 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

The elimination rate is markedly lower than in older children and adults, with an elimination half-life estimated at approximately 30 hours (16-43 hours). The clearance of both ibuprofen 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol

Sodium chloride

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for injections

6.2 Incompatibilities

PEDEA must not be mixed with any other medicines except those mentioned in section 6.6.

PEDEA is incompatible with acidic solutions such as certain antibiotics and diuretics, and must not come in contact with any acidic solution. A rinse of the infusion line must be performed between each medicine administration (see section 6.6).

6.3 Shelf life

4 years.

To avoid any possible microbiological contamination, PEDEA should be used immediately after first opening.

6.4 Special precautions for storage

Store at or below 25 °C.

For storage conditions after first opening of PEDEA see section 6.3.

6.5 Nature and contents of container

Colourless, clear 2 mL Type I glass ampoule.

PEDEA is supplied in packs of 4 x 2 mL ampoules.

6.6 Special precautions for disposal and other handling

The 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.

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 for injection to adjust the injection volume.

The total volume of solution injected should take into account the total daily fluid volume administered. A maximum maintenance 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 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBERS

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