SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ibuprofen Gen Orph 5 mg/mL solution for injection/infusion.

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 2.95 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection/infusion.

Clear, colourless to slightly yellow solution.
The pH is between 7.5 and 8.5 and osmolality is between 280 and 320 mOsm/kg.

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 Ibuprofen Gen.Orph 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 Ibuprofen Gen.Orph 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.

Ibuprofen Gen.Orph should be administered as a short infusion over 15 minutes, preferably undiluted.

The total volume of solution injected should take into account the total daily fluid volume administered. For instructions on handling of the medicinal product before administration see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance 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, 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 Ibuprofen Gen.Orph 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, Ibuprofen Gen.Orph 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 Ibuprofen Gen.Orph 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. Ibuprofen Gen.Orph must therefore be used cautiously in the presence of an infection (see also section 4.3).

Ibuprofen Gen.Orph 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.

Renal tubular acidosis and hypokalaemia may occur following acute overdose and in patients taking ibuprofen products over long periods at high doses (typically greater than 4 weeks), including doses exceeding the recommended daily dose.

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).

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per 2 mL, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of Ibuprofen Gen.Orph 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 Fertility, 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 and clinical trials with ibuprofen. 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.

Tabulated list of adverse reactions

- Reported adverse reactions are listed in the table below according to MedDRA system organ class and frequency. 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), and not known (cannot be estimated from the available data).

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Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1. Tabulated list of adverse reactions

System organ class (SOC)	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very common	Thrombocytopenia, Neutropenia
Metabolism and nutrition disorders	Not known	Hypokalaemia**
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
	Not known	Gastric perforation
Skin and subcutaneous tissue disorders	Not known	Acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)
Renal and urinary disorders	Common	Oliguria, Fluid retention, Haematuria
	Uncommon	Acute renal failure
	Not known	Renal tubular acidosis**
Investigations	Very common	Blood creatinine increased, Blood sodium decreased
** see below* *** Renal tubular acidosis and hypokalaemia have been reported in the post-marketing setting typically following prolonged use of the ibuprofen component at higher than recommended doses.*		

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 ibuprofen 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 ibuprofen 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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Prolonged use at higher than recommended doses may result in severe hypokalaemia and renal tubular acidosis.Symptoms may include reduced level of consciousness and generalised weakness (see section 4.4 and section 4.8).

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 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 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 ibuprofen 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 ibuprofen 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 ibuprofen.

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.

Pharmacokinetic/pharmacodynamic 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 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

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Chlorhexidine must not be used to disinfect the neck of the ampoule as it is not compatible with the Ibuprofen Gen.Orph solution.

Ibuprofen Gen.Orph 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

3 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.

Ibuprofen Gen.Orph is supplied in packs of 4 × 2 mL ampoules.

6.6 Special precautions for disposal

As for all parenteral products, ampoules of Ibuprofen Gen.Orph 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.

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 Ibuprofen Gen.Orph 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 Ibuprofen Gen.Orph, 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Gen.Orph
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92213 Saint Cloud Cedex
France

8 MARKETING AUTHORISATION NUMBER(S)

PL 47541/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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