

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen Gen.Orph 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.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

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.

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 NSAIDs (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 ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1\ 000$, $< 1/100$), rare ($\geq 1/10\ 000$, $< 1/1\ 000$), very rare ($< 1/10\ 000$), and not known (cannot be estimated from the available data).

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

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)
Renal and urinary disorders	Common	Oliguria, Fluid retention, Haematuria
	Uncommon	Acute renal failure
Investigations	Very common	Blood creatinine increased, Blood sodium decreased
* <i>see below</i>		

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-conceptual 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 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 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

2 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 and other handling

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 in PVC-free bag 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 in PVC-free bag.

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
185 Bureaux de la Colline
92213 Saint Cloud Cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1791/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.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

Haupt Pharma
1 rue Comte de Sinard
26250 Livron-sur-Drôme
France

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ibuprofen Gen.Orph 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, 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 SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach 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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gen.Orph
185 Bureaux de la Colline
92213 Saint Cloud Cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1791/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

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

Ibuprofen Gen.Orph 5 mg/mL solution for injection
Ibuprofen
IV use

2. METHOD OF ADMINISTRATION

See leaflet

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg / 2 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Ibuprofen Gen.Orph 5 mg/mL solution for injection

Ibuprofen

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ibuprofen Gen.Orph is and what it is used for
2. What you need to know before you take Ibuprofen Gen.Orph
3. How to take Ibuprofen Gen.Orph
4. Possible side effects
5. How to store Ibuprofen Gen.Orph
6. Contents of the pack and other information

1. What Ibuprofen Gen.Orph 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.

Ibuprofen Gen.Orph, when given to your baby, can help to close the *ductus arteriosus*.

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

2. What you need to know before you take Ibuprofen Gen.Orph

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

Do not use Ibuprofen Gen.Orph

- if your baby is allergic (hypersensitive) to ibuprofen or any of the other ingredients of Ibuprofen Gen.Orph;
- 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).

Warnings and precautions

- Before treatment with Ibuprofen Gen.Orph, your baby's heart will be examined to confirm that the *ductus arteriosus* is open.
- Ibuprofen Gen.Orph 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 Ibuprofen Gen.Orph only after careful consideration of your baby's condition.
- Ibuprofen Gen.Orph 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.
- Ibuprofen Gen.Orph 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.
- Ibuprofen Gen.Orph may be less effective in very premature babies less than 27 weeks of gestational age.
- Serious skin reactions have been reported in association with Ibuprofen Gen.Orph treatment. You should stop taking Ibuprofen Gen.Orph 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.

Other medicines and Ibuprofen Gen.Orph

Tell your doctor or pharmacist if your baby is taking, has recently taken or might take any other medicine.

Certain medicines, if given together with Ibuprofen Gen.Orph, 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 other NSAIDs: the concomitant use of more than one NSAID should be avoided because of the increased risk of adverse reactions.
- 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.

Ibuprofen Gen.Orph contains sodium

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

3. How to take Ibuprofen Gen.Orph

Ibuprofen Gen.Orph 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 Ibuprofen Gen.Orph 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.

If you have any further questions on the use of this medicine, ask your baby's doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine 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 possible side effects are listed below.

Very common (may affect more than 1 in 10 people)

- 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 (may affect up to 1 in 10 people)

- 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 (may affect up to 1 in 100 people)

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

Not known (frequency cannot be estimated from the available data)

- 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 Ibuprofen Gen.Orph if you develop these symptoms and seek medical attention immediately. See also section 2.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ibuprofen Gen.Orph

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the 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, Ibuprofen Gen.Orph should be administered immediately.

Do not use this medicine if you notice visible signs of deterioration of the solution.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ibuprofen Gen.Orph 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 (for pH adjustment) and water for injections. See section 2. Ibuprofen Gen.Orph contains sodium.

What Ibuprofen Gen.Orph looks like and contents of the pack

Ibuprofen Gen.Orph 5 mg/mL solution for injection is a clear, colourless to slightly yellow solution. Ibuprofen Gen.Orph 5 mg/mL solution for injection is supplied in cartons of four 2 mL ampoules.

Marketing Authorisation Holder

Gen.Orph
185 Bureaux de la Colline
92213 Saint Cloud Cedex
France

Manufacturer

Haupt Pharma
1 rue Comte de Sinard
26250 Livron-sur-Drôme
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

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The following information is intended for healthcare professionals only:

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.

Posology and method of administration (see also section 3)

For intravenous use only. Treatment with Ibuprofen Gen.Orph 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 Ibuprofen Gen.Orph 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

Ibuprofen Gen.Orph 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 in PVC-free bag. 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 Ibuprofen Gen.Orph 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 Ibuprofen Gen.Orph 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 PVC-free bag.

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 Ibuprofen Gen.Orph 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 in PVC-free bag.