NOXAP.® Handled with extreme care.

NOXAP® 800 ppm & 200 ppm (medicinal gas)
Nitric Oxide Selective Pulmonary Vasodilator

NOXAP® 800 ppm & 200ppm

NOXAP® is a medicinal gas with nitric oxide as the active ingredient and is for hospital use. Inhaled nitric oxide is a selective pulmonary vasodilator.

NOXAP® 800 ppm

Key characteristics

NOXAP® is available in two cylinder sizes

10 litres (2 m3) & 20 litres (4 m3) and in the following dosages: 800 ppm & 200 ppm mol/mol

Key benefits

Application

Allows safe and precise delivery of nitric oxide, using conventional and high frequency ventilators, from as low as 5 ppm at 1 l/min to 20 ppm at 25 l/min

Characteristic

The cylinder contains 800 ppm of nitric oxide, almost twice the amount of nitric oxide than similar sized cylinders otherwise available.

Safe for the patient and hospital staff

- Reduces the risk of a rebound effect in the patient.
- Fewer cylinder replacements, which in turn minimise the number of connections of the pressure regulator to the cylinder.
- Reduces need for constant cylinder manipulation, helping to keep intensive care units clean and free of traffic.

Economy

- Streamlines internal hospital logistics.
- Economy of scale; more quantity of nitric oxide in the same sized cylinder.

NOXAP® 200 ppm

Key characteristics

NOXAP® is available in two cylinder sizes

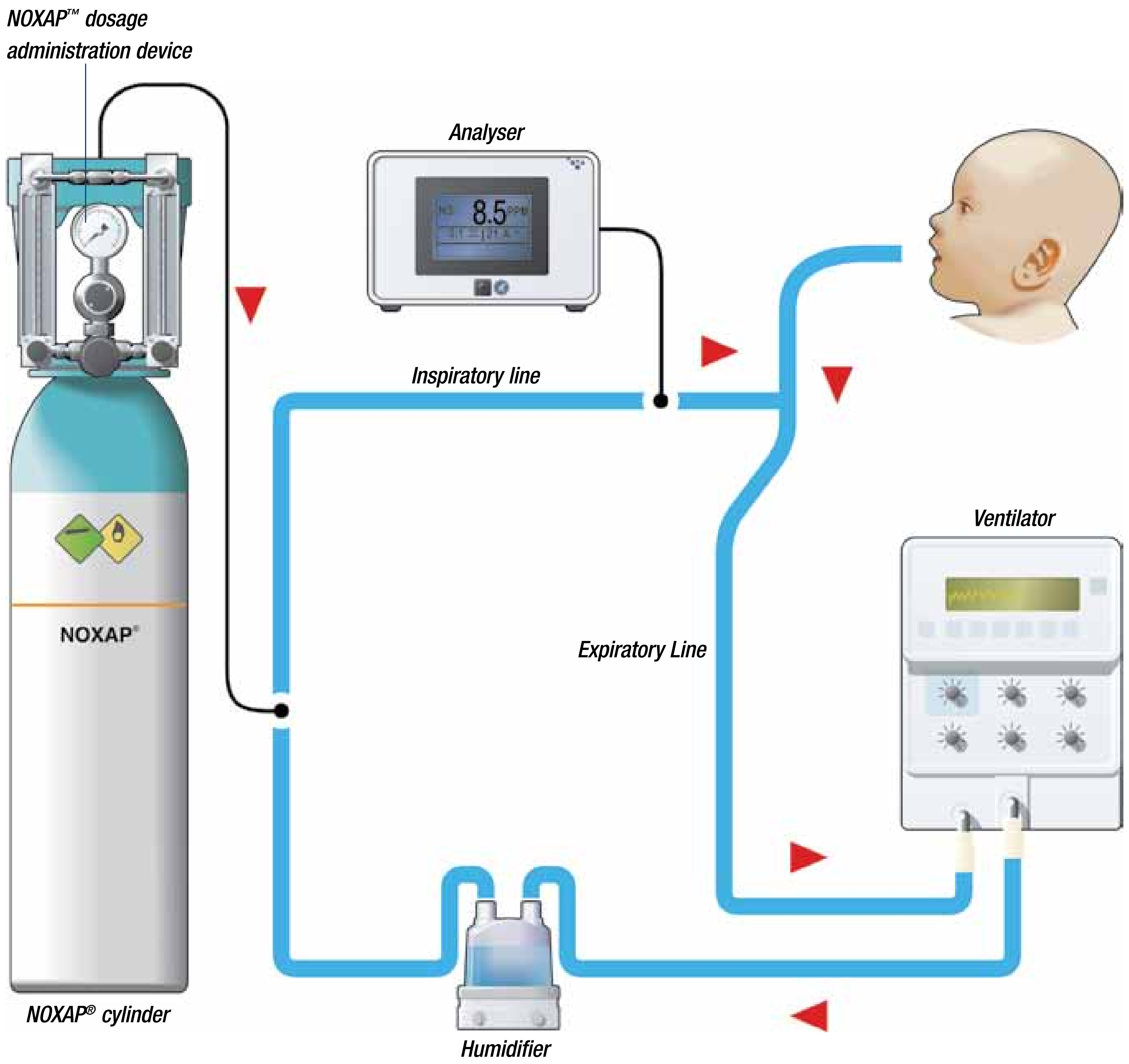
10 litres (2 m3) & 20 litres (4 m3) and in the following dosages: 800 ppm & 200 ppm mol/mol

Key benefits

Application

Allows safe and precise delivery of nitric oxide using conventional ventilators from as low as 2 ppm at 0.5 l/min to 20 ppm at 6 l/min.

NOXAP® management scheme



Duration table for 20 litres NOXAP® cylinders

NOXAP® 200 ppm Dose 20 ppm		NOXAP® 800 ppm Dose 20 ppm	
Ventilator flow (l/min)	Cylinder time use (days)	Ventilator flow (l/min)	Cylinder time use (days)
1	25	1	108.3
5	5	5	21.7
10	2.5	10	10.8
15	1.7	15	7.2
20	1.3	20	5.4
25	1	25	4.3
30	0.8	30	3.6

Table of the physical characteristics of NOXAP® cylinders

Cylinder	Dosage (ppm)	Capacity (l)	Gas Capacity (m3)	Diameter (mm)	Height (mm)	Weight (kg)	Pressure (bars)
B10	200	10	2	145	1123	12,88	200
B20	200	20	4	205	1089	23,05	200
B10	800	10	2	145	1123	12,88	200
B20	800	20	4	205	1089	23,05	200

Countries	Connection
Belgium	DIN 477 nº6
France	Type C
Germany	DIN 477 nº14
Netherlands	DIN 477 nº8
Portugal	Type M
Spain	Type M
Czech Republic	DIN 477 nº14
United Kingdom	CGA 330

NOXAP cylinder (available in 10l and 20l, 200ppm and 800ppm)

Medical devices using NOXAP

NOXAP™ dosage administration device:

Application

- Can be used with NOXAP 800 ppm and 200 ppm
- Can be used with conventional and high frequency ventilators

High Precision

- Double-state high pressure regulator
- Fixed outlet pressure
- Duplex flow meters:
  - First flow meter for low flows
  - Second flow meter for high flows

Safe and Easy to use

- Fixed outlet pressure
- The flow meters can be regulated and adjusted independently by means of a flow dial

NOXAP ™ dosage administration device: nitric oxide pressure regulator / flow meter

NOXAP ™ medical NO & NO_2 analyser: Uninterrupted NO & NO_2 monitoring

NOXAP™ NO and NO_2 analyser

Application

- Measures NO, NO_2 and O_2 in real time
- Can be used with any type of invasive ventilator

Easy to use

- Simple maintenance and calibration
- Light and portable
- Powered by batteries
- Fast start-up

Safer

- Acoustic and visual alarms (high level for NO and NO_2 and low level for NO and O_2)
- Long duration battery

NOXAP™ mobile delivery system
A complete solution for simple and safe use of nitric oxide

Application

- Can be used with NOXAP® 800 ppm and 200 ppm
- Complete solution for simple and safe usage of nitric oxide
- Mobile system for easy transport of the patient within the hospital
- Can be used with conventional and high frequency ventilators

High Precision

- Double-state high pressure regulator
- Duplex flow meters:
  - First flow meter for low flows
  - Second flow meter for high flows

NOXAP ™ mobile delivery system: Complete NO delivery system

Easy to use

- The flow meters can be regulated and adjusted by one flow dial
- Tray for carrying NO/NO_2 analyser, and other elements

Safer

- Uninterrupted administration of nitric oxide
- Reserve cylinder that guarantees a continuous delivery

Summary of NOXAP® 800 ppm

Summary of product characteristics

1. Name of the medicinal product
NOXAP 800 ppm mol/mol, medicinal gas, compressed

2. Qualitative and quantitative composition
Nitric oxide (NO) 800 ppm mol/mol
Nitric oxide (NO) 0. 8 ml in Nitrogen (N2) 999.2 ml
A 5 litre cylinder filled at 200 bar contains 945 litres (=0.945m3)
of gas under pressure at 1 bar and 15°C
A 10 litre cylinder filled at 200 bar contains 1890 litres (=1.890m3)
of gas under pressure at 1 bar and 15°C
A 20 litre cylinder filled at 200 bar contains 3780 litres (=3.780m3)
of gas under pressure at 1 bar and 15°C
A 40 litre cylinder filled at 200 bar contains 7560 litres (=7.560m3)
of gas under pressure at 1 bar and 15°C
For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Medicinal gas, compressed.
Odourless and colourless gas.

4. Clinical particulars

4.1 Therapeutic indications
Treatment of newborns > 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and reduce the need for extracorporeal membrane oxygenation.

4.2 Posology and method of administration
Nitric Oxide should only be prescribed by a physician qualified in the use of the nitric oxide and administered by experienced staff qualified in the use of nitric oxide.

Posology
The posology will be determined in accordance with the medical condition of the patient.
The maximum recommended dose of NOXAP is 20 ppm and this dose should not be exceeded.

Newborns
NOXAP should be used only after respiratory support is optimal. NOXAP should be used in ventilated infants expected to require support >24 hours.

For improved response to NOXAP in hypoxic respiratory failure , , it is necessary to ensure an optimal alveolar recruitment through the adjustment of tidal pressure and volume, the use of surfactants, high frequency ventilation and ventilation with positive pressure at the end of exhalation.

Newborns > 34 weeks gestation: The maximum recommended dose of NOXAP is 20 ppm and this dose should not be exceeded. Starting as soon as possible, and in the first 4-24 hours of therapy, the dosage must be reduced gradually to 5 ppm or less, titrating it to the needs of the individual patient, as long as the clinical parameters (oxygenation, arterial pulmonary pressure) are within the desired limits. Inhaled nitric oxide therapy must be maintained until an improvement in the oxygenation is observed in the newborn in such as way that the fraction of inhaled oxygen is diminished to below 60% (FiO2 < 0.60).

The treatment can be pursued until the oxygen de-saturation is resolved and the patient is ready for gradual withdrawal from NOXAP treatment. The duration of the treatment should be limited be as short as possible. , The duration is variable, but typically, less than 4 days. If there is no response to the inhaled nitric oxide, consult section 4.4

Aditional information on special populations:
No relevant information for dosage adjustment recommendation on special populations, such as renal/hepatic impairment or geriatric, has been found. Therefore caution is recommended in these populations.

Weaning
The administration of NOXAP must not be interrupted suddenly due to the risk of a 'rebound' effect. NOXAP treatment should only be stopped once the clinical symptoms that initiated its indication are stabilised to within satisfactory levels and in cases of hypoxic respiratory insufficiency, when the requirements for assisted ventilation (FiO_2 and PEEP) are substantially diminished or after 96 hours of treatment.

When the decision to interrupt the inhaled nitric oxide therapy has been taken, the dosage must be reduced to 1 ppm over a period of 30 minutes to one hour.

In cases of hypoxic respiratory failure, if there are no changes in oxygenation during the administration of NOXAP at 1 ppm, the FiO_2 will be increased by 10%-20% and the administration of NOXAP will be interrupted. The patient will have to be carefully monitored for any signs of hypoxemia. If oxygenation falls by more than 20%, NOXAP therapy will have to be resumed at 5 ppm and its interruption will be assessed 12 to 24 hours later. When it is not possible to stop NOXAP treatment after 4 days, the new-born will have to be submitted to an exhaustive diagnostic study in search of concomitant illnesses.

Method of administration
Modalities of administration of NOXAP can modify the toxicity profile of the drug. Administration recommendations have to be followed.

Nitric oxide is normally administered by inhalation in patients via mechanical ventilation after it has been diluted with a mix of oxygen/air using a nitric oxide administration device that has been approved for clinical use as per the European Community standards (CE marked). Direct endotracheal administration without dilution is contra-indicated due to the risk of local lesion of the mucous membrane when it comes into contact with the gas.

NO must correctly mix with other gases in the ventilator circuit. It is advisable to ensure the least amount of contact time possible between the nitric oxide and the oxygen in the inspiratory circuit in order to limit the risk of the formation of toxic oxidation derivatives in the inhaled gas. It is therefore recommended dilution of nitric oxide is administered in the inspiratory branch of the ventilation circuit or above the Y piece. This should be at least 15 cm from the patient's mouth, to allow sufficient space for a homogeneous mix to occur with the gas from the ventilator. When used in continuous administration mode; . NOXAP should be introduced after the humidifier and as close to the patient as possible.

The administration system must supply a constant concentration of inhaled NOXAP, notwithstanding the ventilation equipment utilised.

- In the case of newborns on a continuous flow ventilator, NOXAP can be administered via a continuous flow in the inhalation branch of the ventilator circuit.
- In the case of patients on intermittent flow ventilation, the use of continuous flows of NO can generate greater concentrations of NO_2, as well as the accumulation of a small quantity of NO in the inspiratory branch of the circuit during the exhalation of the patient, as it is a source of a greater concentration of NO and a lower concentration of FiO_2. In order to avoid this, the administration system of nitric oxide in the intermittent flow ventilation system will have to avoid these concentration peaks. Synchronised sequential administration in the inspiratory phase is recommended.
- As opposed to NO administration through respiratory support ventilators, the main problem with anaesthesia apparatus is the recirculation of the exhaled air, therefore it must be equipped with a selective filter for the NO_2. If nitric oxide is administer intraoperatively through the operating room ventilator system, the breathing circuit has to be equipped with an in-line oxygen analyzer downstream as well as a monitor NO and NO_2 attached as close to the patient as possible to monitor the delivered concentration of oxygen and NO. Delivered inhaled NO concentration has to be controlled by adjusting the ratio of NO flow to ventilator flow or automatically through an integrated administration system. The NO added into the inspiratory limb must take into consideration the NO still present before the injection of supplemental NO, in order to maintain a stable NO concentration and a low NO_2 concentration. Delivery of inhaled NO should take place in the inspiratory limb or just before the soda lime canister. It is recommended to use higher fresh gas flow rates to minimize the effect of NO absorption by the soda lime. All exhaled gases have to be scavenged appropriately. The exhaust gas of the breathing circuit has to be scavenged via a selective soda-lime absorber for NO_2.
- Mode of administration within the framework of functional explorations of pulmonary arterial hypertension Mode d'administration dans le cadre des explorations fonctionnelles de l'hypertension artérielle pulmonaire
  An air mixture/oxygen will be managed with a flow of about 10 liters/min. In an inspiratory circuit comprising a balloon of 5 liters acting as mixing tube, the arrival of NOXAP in the inspiratory circuit will be carried out upstream of the mixing tube, the patient breathing through a mask connected to the circuit by a part in T. An oxygen analyzer will be connected to the inspiratory circuit downstream from the balloon. With each increase in the concentration of NO in the inspiratory circuit, the fraction of oxygen delivered by the mixer will be increased in order to maintain a fraction of oxygen constant in the air inspired. This mode of administration makes it possible to ensure a time of contact between NOXAP and the 5 second old oxygen. The flow of NOXAP on the outlet side of the bottle will have to be adjusted using a manodetentor limited to 1,5 liter/minute and provided with a flowmeter of precision.
- The administration of NOXAP for diagnostic use in patients that have not been intubated with spontaneous respiration can be carried out using a continuous or intermittent method, directly from the cylinder through a precision flow regulator and a mixing system and using appropriate facial masks.

In order to avoid errors in the dosage, the concentration of NOXAP inhaled must be continually regulated in the inhalation branch of the circuit close to the patient, and near the tip of the endotracheal tube. The concentration of nitrogen dioxide (NO_2) and FiO_2 must also be regulated in the same place using a calibrated and EC-approved monitoring apparatus.

The concentration of NO_2 in the inhaled mix must be as low as possible. If the concentration of NO_2 exceeds 0.5 ppm, the dose of NOXAP and/or FiO_2 must be reduced, ruling out any possible malfunction in the administration system.

For the safety of the patient, appropriate alarms must be configured for NOXAP (± 2 ppm of the prescribed dose), NO_2 (maximum 0.5 ppm) and FiO_2 (± 0.05).

If an unexpected change in the concentration of NOXAP is produced, the administration system will have to be checked for defects and the analyser will have to be calibrated again.

The pressure of the NOXAP gas cylinder must be monitored in order to allow the gas cylinder to be changed without interruptions or changes to the treatment. There must also be a reserve supply of gas cylinders to allow changes at the appropriate moment.

In case of failure of the system or a cut in the electricity supply, there must be an emergency battery electricity supply and a back-up system for the administration of the nitric oxide. The electricity supply of the monitoring equipment must be independent of the function of the administration device.

NOXAP therapy must be available for mechanical and manual ventilation, during transportation of the patient and during resuscitation. The doctor must have access near the head of the patient to place a reserve nitric oxide administration system.

Exposure limits for hospital personnel
The maximum exposure limit (average exposure) of hospital personnel to nitric oxide has been determined by labour legislation and is 25 ppm over a period of 8 hours (30 mg/m3) and the corresponding limit for NO_2 is 2-3 ppm (4-6 mg/m3) in the majority of European countries. Extrapolating these limits to intensive care units where the inhalation of NO can be administered for a period of 24 hours, it would be prudent to keep the atmospheric levels of NO2 below 1.5 ppm. Continuous monitoring of atmospheric levels of NO_2 is mandatory.

Monitoring of the formation of Nitrogen Dioxide
Nitrogen dioxide (NO_2) forms rapidly in gaseous mixtures that contain nitric oxide and O_2.

Nitric oxide, in reaction with oxygen, will produce nitrogen dioxide (NO_2) in variable quantities depending on the NO and O_2 concentrations. NO_2 is a toxic gas that can provoke an inflammatory reaction in the respiratory tracts; it is for this reason that its production must be closely monitored.

Immediately before starting the treatment on each patient, it is necessary to apply the appropriate procedures to purge the system of NO_2. The NO_2 concentration must be kept as low as possible and always < 0.5 ppm. If NO_2 is > 0.5 ppm, the administration system must be checked for defects, the NO_2 analyser must be recalibrated and, if possible, the levels of NOXAP and/or FiO_2 must be reduced.

Monitoring the formation of methemoglobin (MetHb)
Following its inhalation, the terminal compounds of nitric oxide that arrive in the systemic circulation are primarily methemoglobin and nitrate. The nitrate is fundamentally excreted through the urinary system and the methemoglobin is reduced by the methemoglobin reductase.

Newborns have diminished levels of MetHb reductase activity compared to adults; therefore the methemoglobin concentrations in the blood must be monitored. The level of MetHb must be measured within 4 hours of the start of NOXAP therapy using an analyser that correctly distinguishes the fetal hemoglobin from the MetHb. If the MetHb is > 2.5%, the dose of NOXAP will have to be reduced. If it exceeds 5%, the administration of nitric oxide must be suspended and the necessity for the administration of reducing agents such as methylene blue will be assessed. Although considerable increases in the level of MetHb are infrequent, since the level is low during the first determination, it is advisable to repeat the MetHb measurements every 12-24 hours thereafter.

4.3 Contraindications
- New-borns with known dependency to right-left blood shunt or newborns with significant left-right shunt.
- Patients with congenital or acquired deficiency of methemoglobin reductase (MetHb reductase) or glucose 6 phosphate dehydrogenase (G6PD).
- Hypersensitivity to the active substance or any of the excipients

4.4 Special warnings and precautions for use

Precautions to avoid exposures during inhaled NOXAP therapy
- Follow Standard Operating Procedures when preparing and using NOXAP
- Install scavenging systems on ventilators to capture the patient's exhaled breath
- Take air samples when training therapists on how to use the iNO treatment.
- Portable personal alarm devices, which warn staff if environmental levels of NO or NO_2 rise above occupational safety limits, can be provided.

Precautions to avoid accidental emptying of a gas cylinder and further actions
A spontaneous leak of nitric oxide from a gas cylinder is very rare due the exhaustive controls in the filling areas. Accidental release can happen if the cylinder falls heavily such that the valve is damaged and release occurs. This would be an exceptional case because gas cylinders and valve packages must comply with EN 962 Cylinder Valve Protection & Tests. To avoid that
- Hospital staff must always secure the gas cylinder in an upright position and ensure it is firmly secured to prevent it from falling over or being knocked-over.
- The gas cylinders have to be handl with care, ensuring that they are not abruptly jolted or dropped.
- Only move gas cylinders using an appropriate type and size of vehicles and equipment for such a purpose.
- If an accidental release happens, gaseous NO leaks can be detected by a characteristic orange-brown colour and a sharp sweet and metallic smell. The recommend actions are to evacuate the room and open windows to the outside.
- In cabinet or closet stores, a fan exhausting directly to the outside should be installed to maintain a negative pressure within the cylinder storage area.
- Installation of NO and N2 monitoring systems for continuous monitoring of NO and N2 concentrations in enclosed NO gas cylinder storage areas and respiratory care areas to alert employees in case of an accidental release could be useful (Nitrogen gas could displace the ambient air and reduce the oxygen level in the environment).

Training prior administration of the product
Specialised professional units and teams should be properly trained on Standard Operating Procedures for the use of the nitric oxide administration system prior administration.

The key elements that must be included in the training of the hospital staff are as follows:
- Knowledge of the correct method of establishing the configuration and connections between the NOXAP gas cylinder, the administration equipment and the assisted ventilation equipment of the patient.
- Operational aspects
- Consult the check list before use (a series of steps to be undertaken immediately before starting the treatment on each patient in order to guarantee that the system functions correctly and that the NO_2 has been purged from the system).
- Configuration of the apparatus for administering the concentration of nitric oxide
- Configuration of the maximum and minimum limits of the alarm in the NO, NO_2 and O_2 monitoring equipment.
- Use of the manual reserve administration system
- Correct procedures for changing the gas cylinder and purging the system
- Breakdown alarms.
- Calibration of the NO, NO_2 and O_2 monitoring equipment.
- Monthly checking procedures for the system.

Evaluation of the treatment response
In newborns >34 week gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a proportion of patients that receive inhaled NO therapy do not respond to the treatment. The range of non-responders varies between 30% and 45% depending on the pre-established clinical values for favourable response. Conventional response indicators include a 20% increase in oxygenation index and/or a 20% reduction in pulmonary arterial pressure. In children, a lower response in oxygenation in new-borns with meconium aspiration syndrome has been indicated. Furthermore, the efficacy of the use of inhaled NO in patients with congenital diaphragmatic hernia has not been demonstrated in clinical trials.

If the clinical response is not considered to be adequate after 4-6 hours of NOXAP administration, the following possibilities should be studied:

- If the patient's condition continues to deteriorate or there is no improvement, the situation having been defined by pre-established criteria, the employment of a rescue system such as an ECMO will be considered, if it is indicated and possible. Persistently high levels of oxygenation index (>20) or alveolar-arterial oxygen gradient (Aao2>600) after 4 hours of iNO therapy indicate an urgent need to initiate ECMO therapy.
- In a non-response situation to the administration of NOXAP, the treatment must be suspended, but it must not be interrupted suddenly as it may provoke an increase in the pulmonary arterial pressure (PAP) and/or deterioration in blood oxygenation (PaO_2). Both situations may also occur in new-borns showing no obvious response to the NOXAP treatment. The gradual withdrawal of inhaled nitric oxide must take place with caution (See 4.2 Posology and method of administration: Weaning).
- In the case of patients that are to be transferred to another hospital, the supply of nitric oxide during the transportation of the patient must be guaranteed in order to avoid any deterioration in their state of health due to a sudden interruption of NOXAP treatment.

Monitoring the ventricular function
With regards to interventricular or interauricular communication, the inhalation of NOXAP causes an increase in the left-right shunt due to the vasodilator effect of the nitric oxide in the lung.
The increase in pulmonary blood flow in patients with left ventricular dysfunction can lead to cardiac insufficiency and the formation of pulmonary oedema. Careful monitoring of cardiac output, left atrial pressure, or pulmonary capillary wedge pressure is important in this situation. It is therefore recommended that before administering nitric oxide, a catheterization of the pulmonary artery or an echocardiographic examination of the central haemodynamics is carried out.

For identifying recipients for heart transplant in dilated cardiomyopathy patients, intravenous vasodilator and inotropic therapy contribute to better ventricular compliance and prevent further elevation in left-sided filling pressures resulting from enhanced pulmonary venous return.

Monitoring the haemostasis
The test in animals have demonstrated that NO can interact with the haemostasis provoking an increase in the bleeding time. The data in adult humans is contradictory, and there has been no increase in significant hemorrhagic complications observed in random controlled trials on new-borns .

A monitoring of the bleeding times is recommended during the course of NOXAP administration for a period of more than 24 hours in patients that suffer numerical or functional anomalies of the platelets, a deficit in the coagulation factors or that are undergoing anticoagulant treatment.

4.5 Interaction with other medicinal products and other forms of interaction
Oxygen: In the presence of oxygen, nitric oxide oxidises rapidly forming derivatives that are toxic for the bronchiolar epithelium and the alveolo-capillar membrane. Nitrogen dioxide (NO_2) is the main compound that is formed and during the treatment with nitric oxide, the concentration of NO_2 must be < 0.5 ppm in the dose interval of < 20 ppm of nitric oxide. If, at any time, the concentration of NO_2 exceeds 1 ppm, the dose of nitric oxide must be reduced immediately. See the information on monitoring NO2 in section 4.2.

NO donors: The donor compounds of nitric oxide, including sodium nitroprusside and nitroglycerine, can have an additive effect to NOXAP increasing the risk of developing methemoglobinemia.

There is a higher risk to develop methemoglobinemia if drugs that increase the methemoglobin concentrations are administrated along with nitric oxide (e.g. alkyl nitrates, sulphonamides and prilocaine). As a consequence, medicinal products that increase methemoglobin must be used with caution during inhaled nitric oxide therapy.

Synergic effects have been reported with the administration of vasoconstrictors (almitrine, phenylephrine), prostacyclin and phosphodiesterase inhibitors, without increasing adverse effects.

Inhaled nitric oxide has been used concomitantly with tolazoline, dopamine, dobutamine, norepinephrine, steroids and surfactants, with no drug interactions observed.

Experimental studies suggest that nitric oxide and also nitrogen dioxide can react chemically with the surfactant and its proteins without proven clinical consequences.

Although controlled studies have not been done, food interactions have not been noticed in clinical trials in patients with prolonged ambulatory administration.

4.6 Pregnancy and lactation

Pregnancy
The effect of the administration of NOXAP in pregnant women is unknown.Animal studies are insufficient (see section 5.3). However, harmful effects may be expected as methemoglobin is considered detrimental to the foetus and nitric oxide has shown genotoxic potential (see section 5.3) by inducing structural alterations on DNA. The potential risk for humans is unknown.

NOXAP should not be used during pregnancy unless clearly necessary, such as in situations of life support.

Lactation
It is not known whether the product NOXAP passes into human breast milk. The excretion of NOXAP in milk has not been studied in animals. Passive exposure to nitric oxide during pregnancy and lactation in humans should be avoided

4.7 Effects on ability to drive and use machines
Infants and hospitalized patients: Not applicable.

4.8 Undesirable effects
Known adverse reactions have been classified for the various organ systems. Classification based on frequency is not readily possible because structured studies have not been conducted for this. Where, based on the literature, it has been possible to perform a reasonable estimate of frequency, this is indicated in the summary below.

Description of frequencies: very common (>1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

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

Blood system disorders
Methemoglobinemia: The development of methemoglobinemia is dose-dependent, being a frequent complication in the inhalation of NO at high concentrations. Increased levels of methemoglobin will produce tissue hypoxia.

The formation of methemoglobin > 5% with inhaled nitric oxide concentrations <20 ppm are very rare (<1/10,000).

In pediatric population, newborns have a diminished MetHb reductase activity and therefore may run the risk of developing methemoglobinemia.

Haemostasis: Although preclinical studies with nitric oxide on animals and in vitro have shown inhibition of the platelet aggregation, clinical studies on humans have been contradictory. However, in controlled clinical trials carried out, no significant differences have been found between the control group and the treatment group with regards to hemorrhagic complications.

General disorders and administration site conditions
No response: The range of responsiveness to the treatment varies between 30% to 45% of the cases.

Formation of NO_2: The reaction between NO and O_2 to form NO_2 are fast with high concentrations of NO, but slow with the concentrations used in the treatments with inhaled nitric oxide. In animals, elevated levels of NO2 (>10 ppm) produce pulmonary edema, alveolar hemorrhage, changes in the activity of the surfactant, hyperplasia of alveolar cells, intrapulmonary accumulation of fibrin, neutrophils and macrophages, and death. Also, the inhalation of NO_2 during prolonged periods has been related to degeneration of pulmonary interstitial cells and moderate emphysematous changes.

The inhalation of 2 ppm NO_2 in humans increases the alveolar permeability and the reactivity of the air ways.

Significant elevations of NO_2 levels have not been found at low therapeutic doses (< 20 ppm) of inhaled NO, as well as evidence of clinical toxicity by NO_2 in most of the clinical trials, being a very rare (<1/10.000)complication. The NO_2 concentration must be always maintained as low as possible and < 0,5 ppm.

Rebound effect: Following sudden interruption to the inhaled nitric oxide therapy, rapid rebound reactions are very frequent (>1/10), such as intensified pulmonary vasoconstriction and hypoxaemia, which precipitate cardiopulmonary collapse.

The retirement of NO after its prolonged inhalation is associated with transitory pulmonary hypertension, for approximately one hour, in all patients.

Clinically it has been observed that after 10 to 30 hours of treatment with inhaled nitric oxide, an abrupt retirement of NO will produce approximately 75% of the patient rebound symptoms, mainly alterations of the gaseous exchange with reduction of oxygen saturation to different degrees. In a third of them, hemodynamic instability will take place. The reduction of PaO2 will be greater with greater concentrations of administered NO. For that reason the reduction to 1 ppm of the nitric oxide inhalation before its retirement seems to diminish the reduction of the PaO2.

Long term adverse effects: From all the controlled studies carried out, there is no evidence of adverse reactions of the treatment provoking the need for re-hospitalisation, special medical services, pulmonary disease or neurological sequelae.

4.9 Overdose
NOXAP overdose is manifested as increases in methemoglobin and NO_2 levels.

- **"Symptoms and Treatment"**

High levels of NO_2 can cause acute pulmonary injury.

Increased levels of methemoglobin reduce the capacity to transport oxygen in the circulation. In clinical studies, levels of NO_2 > 3 ppm or levels of methemoglobin > 7% were treated by reducing the dose of inhaled nitric oxide or by interrupting its administration.

Methemoglobinemia that does not respond to reduction or interruption of the treatment can be treated intravenously with vitamin C, methylene blue or by blood transfusion, depending on the clinical situation.

5 Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Other respiratory system products.

ATC code: R07AX01

- **Mechanism of action**

Nitric oxide is a substance that is produced by many cells of the organism.

It relaxes the vascular smooth muscle by binding it to the heme part of cytosolic guanylate cyclase, activating the guanylate cyclase and increasing the intracellular levels of cyclic guanosine 3'.5'-monophosphate, which in turn causes vasodilatation. The inhalation of of nitric oxide produces pulmonary vasodilatation.

- **Pharmacodynamic effects**

The therapeutic importance of inhaled nitric oxide, is that it produces selective pulmonary vasodilation with minimum systemic cardiovascular effects. The pulmonary selective vasodilation of nitric oxide is because of its fast inactivation by means of its reaction with the heme groups. The average life in vivo of NO is only of a few seconds.

Nitric oxide increases the partial pressure of arterial oxygen (PaO_2) by dilating the pulmonary vessels in the better ventilated areas of the lung, redistributing the pulmonary blood flow away from the pulmonary regions with low ventilation/perfusion (V/Q) indexes to regions with normal indexes. Studies show that its pharmacodynamic effects appear in the lung at concentrations as low as 1 ppm inside the air way.

- **Efficacy and safety**

Clinical trials have confirmed in different pathological processes the ability from inhaled nitric oxide to diminish the pulmonary vascular resistance and to increase the oxygenation.

The efficacy of inhaled nitric oxide has been investigated in newborns with hypoxic respiratory failure with different aetiology. In the case of newborns with persistent pulmonary hypertension, the inhalation of NO improves oxygenation and reduces the risk of needing oxygenation through extracorporeal membrane. In the meta-analysis of randomized clinical trials, in infants without congenital diaphragmatic hernia with persistent pulmonary hypertension of the newborn (n=548), inhalation of NO reduces the need for ECMO (relative risk: 0.73; 95% Cl: 0.60 to 0.90) and improves the oxygenation (PaO2 by a mean of 53.3 mm Hg; 95% Cl: 44.8 to 61.4; oxygenation index by a mean of -12.2; 95% Cl: -14.1 to -9.9). In newborns with hypoxic respiratory failure, in the meta-analysis, 2000 (n=989), the inhalation of NO improves the PaO2 with a difference of 46.4 Torr compared with controls (95% Cl, 34.2, 58.5) and significantly decreases the oxygenation index by 10.7 compared with controls (95% Cl, -14.1, -7.4). The incidence of death or need for extracorporeal membrane oxygenation (ECMO) was significantly reduced by treatment with iNO, relative risk 0.72 compared to control (95% Cl, 0.6, 0.87). Increase of complications related to the use of inhaled NO were not observed in either of the two meta-analyses.

The inhalation of nitric oxide has demonstrated efficacy, safety and selectivity in the evaluation of the pulmonary vascular responsiveness in patients with cardiac failure and children with cardiac congenital diseases, used during cardiac catheterization.

Several clinical trials have demonstrated that in children with high risk of pulmonary hypertension, routine use of inhaled NO after congenital cardiac surgery, lessen the risk of hypertensive crisis and shorten the postoperative course. In adults, the use of NO as adjuvant treatment in cardiac surgery, in controlled clinical trials, has been shown efficacy in the treatment of pulmonary hypertension and improves the blood oxygenation in patients under left ventricular assist device, coronary by-pass, and weaning cardiopulmonary by-pass in the cardiac transplant.

5.2 Pharmacokinetic properties
The pharmacokinetics of nitric oxide has been studied in adults.

Nitric oxide, in the dilution procedure before its administration, reacts chemically with oxygen to form nitrogen dioxide, a toxic substance for the body.

Nitric oxide is absorbed systemically following inhalation. The major part passes through the pulmonary capillary bed where it combines with the hemoglobin, which is saturated with 60% - 100% of oxygen. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. With a low saturation level of oxygen, the nitric oxide can combine with deoxyhemoglobin to form transitory nitrosylhemoglobin, which turns into nitrogen oxides and methemoglobin when exposed to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrate respectively, which interact with the oxyhemoglobin to produce methemoglobin and nitrate. Therefore, the final products of nitric oxide that arrive in the systemic circulation are primarily methemoglobin and nitrate.

The formation of methemoglobin depends on the exposure time and concentrations to nitric oxide. The concentrations of methemoglobin increase during the first 8 hours of treatment with inhaled nitric oxide. Methemoglobin levels > 7% have been observed in patients who received high doses of NO (80 ppm).

Nitrate has been identified as the predominant metabolite of nitric oxide excreted in the urine, representing > 70% of the inhaled nitric oxide dose. The kidney eliminates the plasma nitrate at a similar rate to glomerular filtration.

5.3 Preclinical safety data
Single-dose studies on rodents indicate that the lethal dose is around 300 ppm of nitric oxide or above.

Repeated-dose studies show that the rodents can survive exposure to nitric oxide of up to sustained levels of nitric oxide of around 250 ppm. Death is secondary to anoxia derived from high levels of methaemoglobin.

From the studies carried out on dogs, it is possible to deduce that the lethal concentration varies around 640 ppm of NO exposure for 4 hours, while exposure to 320 ppm of NO is not lethal.

Levels of methaemoglobin higher than 30% have been recorded in animals that died due to NO exposure. The recuperation from methaemoglobinaemia is rapid, in less than 24 hours, a full recovery has been recorded. At levels of 80 ppm NO administered for 3 hours, no increase of methaemoglobin was observed in sheep.

In biological tissue, nitric oxide can form peroxinitrite (ˉOONO) to react with superoxide (O2-), an unstable substance that can damage the tissue through further redox reactions.

Furthermore, nitric oxide has an affinity for metal proteins and might also react with sulfhydryl groups (-SH) in proteins, giving rise to nitrosyl compounds. The clinical importance of the chemical reactivity of nitric oxide in the tissue is unknown.

Bleeding time: In a study conducted on rabbits and healthy humans, it has been found that inhaled nitric oxide approximately doubles the bleeding time.

No studies on toxicity to reproduction or carcinogenicity have been conducted.

Mutagenicity and genotoxicity: Various preclinical genotoxicity tests with nitric oxide show a positive genotoxic potential. Part of its toxicity is mediated by peroxinitrite. Although DNA damage has not been demonstrated in human cells following in vivo exposure, preclinical in vitro and in vivo studies (bacteria and mice), have demonstrated NO-induced chromosomal alterations. This is possibly related to the formation of mutagenic nitrosamines, DNA alteration or impairment of DNA repair mechanisms. The significance of these findings for clinical use in neonates and the potential for effects on the germ cells are unknown.

6 Pharmaceutical particulars

6.1 List of excipients
Nitrogen.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal product/equipment/devices except those mentioned in section 6.6.

The equipments/devices should not be administered simultaneously: Butylrubber, Polyamide and Polyurethane.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Follow all the rules regarding the handling of pressurised containers.

Store in the original gas cylinder.
Do not transfer contents from original gas cylinder to another gas cylinder.
Store cylinders vertically in well-ventilated rooms.
Protect the cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

The installation of a nitric oxide duct system is prohibited with a cylinder distribution system, a fixed network or terminal units.

Storage in the pharmacy department
The gas cylinders should be kept in a place designated exclusively for medicinal gas storage that is well ventilated, clean and under lock and key. This place should house a separate, special facility for the storage of nitric oxide gas cylinders.

Storage in the medical department
The gas cylinders should be stored in a place with the appropriate equipment to ensure that it stays in a vertical position.

6.5 Nature and contents of container
NOXAP is stored in high pressure gas cylinders made out of aluminium or aluminium with an external elastomers layer). The valves which close the gas cylinders are made out of stainless steel. The pack sizes of thes gas cylinders are 5L, 10L, 20L and 40L.

NOXAP is filled as a gas in these gas cylinders to a pressure of 200bar.

Pack sizes (litres)	Filling Pressure (bar)	Litres Quantity of the mixture 800 ppm NO/N_2	m3 Quantity of the mixture 800 ppm NO/N_2
5	200	945	0.945
10	200	1890	1.890
20	200	3780	3.780
40	200	7560	7.560

The colour coding of the gas cylinder is a turquoise blue shoulder on a white gas cylinder body.

6.6 Special precautions for disposal and other handling

General
All personnel handling NOXAP gas cylinders should have adequate knowledge of the properties of this gas, any necessary precautions to take, the steps to follow in the event of an emergency and the correct operational procedures for its installation.

Transport of gas cylinders
The gas cylinders should be transported with the appropriate equipment to ensure that they are protected from the risk of jolts or drops. When patients undergoing NOXAP treatment are being transferred between different hospitals or within the same, the gas cylinders should be separated and properly secured so that they maintain a vertical position and do not run the risk of drops or inopportune changes to the administration of the medicine. Special attention should be paid to the pressure regulator fixing in order to avoid the risk of accidental breakdowns.

Preparation for use
- The valves of the gas cylinder should be opened slowly.
- The valves of the gas cylinder or of any associated equipment should never be lubricated and should always be kept free of oils and grease.
- When connecting equipment to the gas cylinders, never use excessive force.

Utilisation of the gas cylinders
To avoid any type of incident, the following instructions should always be respected:
- Handle the gas cylinders with care, ensuring that they are not abruptly jolted or dropped.
- Only move the gas cylinders using an appropriate type and size lorry for such a purpose.
- Medicinal gases should only be used for medicinal purposes.
- Always ensure the material is in good condition before use.
- If the pressure is less than 10 bar, do not use the gas cylinder.
- Do not use the gas cylinder if its valve is not protected by a cap or cover.
- The valve should not be opened in an abrupt manner.
- Do not attempt to repair the valve if it is defective.
- A specific connection should be used, as well as a pressure regulator that allows a pressure equivalent to at least 1.5 of the maximum functioning pressure of the gas cylinder.
- In order to ensure that NO2 is not inhaled, purge the pressure regulator with a mixture of nitrogen/nitric oxide before each new use.
- The pressure regulator should not be gripped with pliers or pincers since this could damage the gasket.
- Whilst in use, the gas cylinder should be firmly secured in an appropriate support for this type of gas cylinder in order to avoid an accidental drop.
- Release the gas discharged outdoors. It is advisable to ensure possible ventilation at all times which is adequate for the evacuation of the gas in the event of an untimely accident or leak.
- Smoking or sources of ignition are not permitted in the area where the gas cylinders are stored or in the pipe vents.
- After use, close the valves of the gas cylinders with moderate force and release the residual pressure in the regulator.
- Ensure that the valve of the gas cylinder is always closed when not in use.

Compatibility
All the equipment, including tubes, connections and circuits, that are used in nitric oxide administration should be manufactured with materials that are compatible with the gas. As far as corrosion is concerned, the supply system can be divided into two areas: 1) from the gas cylinder valve to the humidifier (dry gas) and 2) from the humidifier to the vent (moist gas that may contain NO2). Evidence shows that the dry NO mixtures can be used with the majority of the materials. Nevertheless, the presence of nitrogen dioxide and humidity create an aggressive atmosphere. Only stainless steel is recommended out of the materials made of metal. Polyethylene (PE) and polypropylene (PP) are two polymers, among others, that have been tested and can be used in nitric oxide administration systems. Polytrifluorochloro ethylene, the hexafluoropropene-vinylidene copolymer and polytetrafluorethylene have been used with pure nitric oxide and other corrosive gases and are considered inert.

Instructions for the disposal of the gas cylinders
- Do not throw away empty gas cylinders. They should be sent immediately to an empty cylinder warehouse or an appropriate storage area for collection by the supplier.

7 Marketing authorisation holder
To be completed nationally.

8 Marketing authorisation number
To be completed nationally

9 Date of first authorisation
To be completed nationally

10 Date of revision of the text
October 2009

Summary of NOXAP® 200 ppm

Summary of product characteristics

1. Name of the medicinal product

NOXAP 200 ppm mol/mol, medicinal gas, compressed

2. Qualitative and quantitative composition

Nitric oxide (NO) 200 ppm mol/mol
Nitric oxide (NO) 0.2 ml in Nitrogen (N2) 999.8 ml
A 5 litre cylinder filled at 200 bar contains 945 litres (=0.945m3)
of gas under pressure at 1 bar and 15°C
A 10 litre cylinder filled at 200 bar contains 1890 litres (=1.890m3
)of gas under pressure at 1 bar and 15°C
A 20 litre cylinder filled at 200 bar contains 3780 litres (=3.780m3)
of gas under pressure at 1 bar and 15°C
A 40 litre cylinder filled at 200 bar contains 7560 litres (=7.560m3)
of gas under pressure at 1 bar and 15°C
For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Medicinal gas, compressed.
Odourless and colourless gas.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of newborns > 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and reduce the need for extracorporeal membrane oxygenation.

4.2 Posology and method of administration

Nitric Oxide should only be prescribed by a physician qualified in the use of the nitric oxide and administered by experienced staff qualified in the use of nitric oxide.

Posology

The posology will be determined in accordance with the medical condition of the patient.
The maximum recommended dose of NOXAP is 20 ppm and this dose should not be exceeded.

Newborns

NOXAP should be used only after respiratory support is optimal. NOXAP should be used in ventilated infants expected to require support >24 hours.

For improved response to NOXAP In hypoxic respiratory failure, it is necessary to ensure an optimal alveolar recruitment through the adjustment of tidal pressure and volume, the use of surfactants, high frequency ventilation and ventilation with positive pressure at the end of exhalation.

— Newborns > 34 weeks gestation: The maximum recommended dose of NOXAP is 20 ppm and this dose should not be exceeded. Starting as soon as possible, and in the first 4-24 hours of therapy, the dose must be reduced gradually to 5 ppm or less, titrating it to the needs of the individual patient, as long as the clinical parameters (oxygenation, arterial pulmonary pressure) are within the desired limits. Inhaled nitric oxide therapy must be maintained until an improvement in the oxygenation is observed in the newborn in such as way that the fraction of inhaled oxygen is diminished to below 60% (FiO2 < 0.60).

The treatment can be pursued until the oxygen de-saturation is resolved and the patient is ready for gradual withdrawal from NOXAP treatment. The duration of the treatment should be limited be as short as possible. The duration is variable, but typically less than 4 days. If ttthere is no response to the inhaled nitric oxide, consult section 4.4

Aditional information on special populations:

No relevant information for dosage adjustment recommendation for special populations, such as renal/hepatic impairment, has been found. Therefore caution is recommended in these populations.

Weaning

The administration of NOXAP must not be interrupted suddenly due to the risk of a 'rebound' effect. NOXAP treatment should only be stopped once the clinical symptoms that initiated its indication are stabilised within satisfactory levels and in cases of hypoxic respiratory insufficiency, when the requirements for assisted ventilation (FiO_2 and PEEP) are substantially diminished or after 96 hours of treatment.

When the decision to interrupt the inhaled nitric oxide therapy has been taken, the dosage must be reduced to 1 ppm over a period of 30 minutes to one hour.

In cases of hypoxic respiratory failure, if there are no changes in oxygenation during the administration of NOXAP at 1 ppm, the FiO2 will be increased by 10%-20% and the administration of NOXAP will be interrupted. The patient will have to be carefully monitored for any signs of hypoxemia. If oxygenation falls by more than 20%, NOXAP therapy will have to be resumed at 5 ppm and its interruption will be assessed 12 to 24 hours later. When it is not possible to stop NOXAP treatment after 4 days, the new-born will have to be submitted to an exhaustive diagnostic study in search of concomitant illnesses.

Method of administration

Modalities of administration of NOXAP can modify the toxicity profile of the drug. Administration recommendations have to be followed.

Nitric oxide is normally administered by inhalation in patients via mechanical ventilation after it has been diluted with a mix of oxygen/air using a nitric oxide administration device that has been approved for clinical use as per the European Community standards (CE marked). Direct endotracheal administration without dilution is contra-indicated due to the risk of local lesion of the mucous membrane when it comes into contact with the gas.

NO must correctly mix with other gases in the ventilator circuit. It is advisable to ensure the least amount of contact time possible between the nitric oxide and the oxygen in the inspiratory circuit in order to limit the risk of the formation of toxic oxidation derivatives in the inhaled gas. It is therefore recommended dilution of nitric oxide is administered in the inspiratory branch of the ventilation circuit or above the Y piece. This should be at least 15 cm from the patient's mouth, to allow sufficient space for a homogeneous mix to occur with the gas from the ventilator. When used in continuous administration mode, NOXAP should be introduced after the humidifier and as close to the patient as possible.

The administration system must supply a constant concentration of inhaled NOXAP, notwithstanding the ventilation equipment utilised.

–In the case of newborns on a continuous flow ventilator, NOXAP can be administered via a continuous flow in the inhalation branch of the ventilator circuit.

–In the case of patients on intermittent flow ventilation, the use of continuous flows of NO can generate greater concentrations of NO_2, as well as the accumulation of a small quantity of NO in the inspiratory branch of the circuit during the exhalation of the patient, as it is a source of a greater concentration of NO and a lower concentration of FiO_2. In order to avoid this, the administration system of nitric oxide in the intermittent flow ventilation system will have to avoid these concentration peaks. Synchronised sequential administration in the inspiratory phase is recommended.

In order to avoid errors in the dosage, the concentration of NOXAP inhaled must be continuously regulated in the inhalation branch of the circuit close to the patient and near the tip of the endotracheal tube. The concentration of nitrogen dioxide (NO2) and FiO2 must also be regulated in the same place using a calibrated and EC-approved monitoring apparatus.

The concentration of NO2 in the inhaled mix must be as low as possible. If the concentration of NO2 exceeds 0.5 ppm, the dose of NOXAP and/or FiO2 must be reduced, after ruling out any possible malfunction in the administration system.

For the safety of the patient, appropriate alarms must be configured for NOXAP (± 2 ppm of the prescribed dose), NO2 (maximum 0.5 ppm) and FiO2 (± 0.05).

If an unexpected change in the concentration of NOXAP is produced, the administration system will have to be checked for defects and the analyser will have to be calibrated again.

The pressure of the NOXAP gas cylinder must be monitored in order to allow the gas cylinder to be changed without interruptions or changes to the treatment. There must also be a reserve supply of gas cylinders to allow changes at the appropriate moment.

In case of failure of the system or a cut in the electricity supply, there must be an emergency battery electricity supply and a back-up system for the administration of the nitric oxide. The electricity supply of the monitoring equipment must be independent of the function of the administration device.

NOXAP therapy must be available for mechanical and manual ventilation, during transportation of the patient and during resuscitation. The doctor must have access near the head of the patient to place a reserve nitric oxide administration system.

Exposure limits for hospital personnel

The maximum exposure limit (average exposure) of hospital personnel to nitric oxide has been determined by labour legislation and is 25 ppm over a period of 8 hours (30 mg/m3) and the corresponding limit for NO2 is 2-3 ppm (4-6 mg/m3) in the majority of European countries. Extrapolating these limits to intensive care units where the inhalation of NO can be administered for a period of 24 hours, it would be prudent to keep the atmospheric levels of NO2 below 1.5 ppm. Continuous monitoring of atmospheric levels of NO2 is mandatory.

Monitoring of the formation of Nitrogen Dioxide

Nitrogen dioxide (NO_2) forms rapidly in gaseous mixtures that contain nitric oxide and O_2.

Nitric oxide, in reaction with oxygen, will produce nitrogen dioxide (NO_2) in variable quantities depending on the NO and O_2 concentrations. NO2 is a toxic gas that can provoke an inflammatory reaction in the respiratory tracts; it is for this reason that its production must be closely monitored.

Immediately before starting the treatment on each patient, it is necessary to apply the appropriate procedures to purge the system of NO_2. The NO_2 concentration must be kept as low as possible and always < 0.5 ppm. If NO2 is > 0.5 ppm, the administration system must be checked for defects, the NO_2 analyser must be recalibrated and, if possible, the levels of NOXAP and/or FiO_2 must be reduced.

Monitoring the formation of methemoglobin (MetHb)

Following its inhalation, the terminal compounds of nitric oxide that arrive in the systemic circulation are primarily methemoglobin and nitrate. The nitrate is excreted through the urinary system and the methemoglobin is reduced by methemoglobin reductase.

Newborns have diminished levels of MetHb reductase activity compared to adults; therefore the methemoglobin concentrations in the blood must be monitored. The level of MetHb must be measured within 4 hours of the start of NOXAP therapy using an analyser that correctly distinguishes the fetal hemoglobin from the MetHb. If the MetHb is > 2.5%, the dose of NOXAP will have to be reduced. If it exceeds 5%, the administration of nitric oxide must be suspended and the necessity for the administration of reducing agents such as methylene blue will be assessed. Although considerable increases in the level of MetHb are infrequent, since the level is low during the first determination, it is advisable to repeat the MetHb measurements every 12-24 hours thereafter.

4.3 Contraindications

- New-borns with known dependency to right-left blood shunt or newborns with significant left-right shunt.
- Patients with congenital or acquired deficiency of methemoglobin reductase (MetHb reductase) or glucose 6 phosphate dehydrogenase (G6PD).
- Hypersensitivity to the active substance or any of the excipients

4.4 Special warnings and precautions for use

Precautions to avoid exposures during inhaled NOXAP therapy

- Follow Standard Operating Procedures when preparing and using NOXAP
- Install scavenging systems on ventilators to capture the patient's exhaled breath
- Take air samples when training therapists on how to use the iNO treatment.
- Portable personal alarm devices, which warn staff if environmental levels of NO or NO_2 rise above occupational safety limits, can be provided.

Precautions to avoid accidental emptying of a gas cylinder and further actions

A spontaneous leak of nitric oxide from a gas cylinder is very rare due the exhaustive controls in the filling areas. Accidental release can happen if the cylinder falls heavily such that the valve is damaged and release occurs. This would be an exceptional case because gas cylinders and valve packages must comply with EN 962 Cylinder Valve Protection & Tests. To avoid this problem:

- Hospital staff must always secure the gas cylinder in an upright position and ensure it is firmly secured to prevent it from falling over or being knocked-over.
- The gas cylinders have to be handled with care, ensuring that they are not abruptly jolted or dropped.
- Only move gas cylinders using an appropriate type and size of vehicles and equipment for such a purpose.
- If an accidental release happens, gaseous NO leaks can be detected by a characteristic orange-brown colour and a sharp sweet and metallic smell. The recommend actions are to evacuate the room and open windows to the outside.
- In cabinet or closet stores, a fan exhausting directly to the outside should be installed to maintain a negative pressure within the cylinder storage area.
- Installation of NO and N_2 monitoring systems for continuous monitoring of NO and N_2 concentrations in enclosed NO gas cylinder storage areas and respiratory care areas to alert employees in case of an accidental release could be useful. (Nitrogen gas could displace the ambient air and reduce the oxygen level in the environment).

Training prior administration of the product

Specialised professional units and teams should be properly trained on Standard Operating Procedures for the use of the nitric oxide administration system prior administration.

The key elements that must be included in the training of the hospital staff are as follows:

- Knowledge of the correct method of establishing the configuration and connections between the NOXAP gas cylinder, the administration equipment and the assisted ventilation equipment of the patient.
- Operational aspects
- Consult the check list before use (a series of steps to be undertaken immediately before starting the treatment on each patient in order to guarantee that the system functions correctly and that the NO_2 has been purged from the system).
- Configuration of the apparatus for administering the concentration of nitric oxide
- Configuration of the maximum and minimum limits of the alarm in the NO, NO_2 and O_2 monitoring equipment.
- Use of the manual reserve administration system
- Correct procedures for changing the gas cylinder and purging the system
- Breakdown alarms.
- Calibration of the NO, NO_2 and O_2 monitoring equipment.
- Monthly checking procedures for the system.

Evaluation of the treatment response

In newborns >34 week gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a proportion of patients that receive inhaled NO therapy do not respond to the treatment. The range of non-responders varies between 30% and 45% depending on the pre-established clinical values for favourable response. Conventional response indicators include a 20% increase in oxygenation index and/or a 20% reduction in pulmonary arterial pressure. In children, a lower response in oxygenation in new-borns with meconium aspiration syndrome has been indicated. Furthermore, the efficacy of the use of inhaled NO in patients with congenital diaphragmatic hernia has not been demonstrated in clinical trials.

If the clinical response is not considered to be adequate after 4-6 hours of NOXAP administration, the following possibilities should be studied:

- If the patient's condition continues to deteriorate or there is no improvement, the situation having been defined by pre-established criteria, the employment of a rescue system such as an ECMO will be considered, if it is indicated and possible. Persistently high levels of oxygenation index (>20) or alveolar-arterial oxygen gradient (Aao2>600) after 4 hours of iNO therapy indicate an urgent need to initiate ECMO therapy. In a non-response situation to the administration of NOXAP, the treatment must be suspended, but it must not be interrupted suddenly as it may provoke an increase in the pulmonary arterial pressure (PAP) and/or deterioration in blood oxygenation (PaO2). Both situations may also occur in new-borns showing no obvious response to NOXAP treatment. The gradual withdrawal of inhaled nitric oxide must take place with caution (See 4.2 Posology and method of administration: Weaning).
- In the case of patients that are to be transferred to another hospital, the supply of nitric oxide during the transportation of the patient must be guaranteed in order to avoid any deterioration in their state of health due to a sudden interruption of NOXAP treatment.

Monitoring the ventricular function

With regards to interventricular or interauricular communication, the inhalation of NOXAP causes an increase in the left-right shunt due to the vasodilator effect of the nitric oxide in the lung.

The increase in pulmonary blood flow in patients with left ventricular dysfunction can lead to cardiac insufficiency and the formation of pulmonary oedema. Careful monitoring of cardiac output, left atrial pressure, or pulmonary capillary wedge pressure is important in this situation. It is therefore recommended that before administering nitric oxide, a catheterization of the pulmonary artery or an echocardiographic examination of the central haemodynamics is carried out.

Monitoring the haemostasis

The test in animals have demonstrated that NO can interact with the haemostasis provoking an increase in the bleeding time. The data in adult humans is contradictory, and there has been no increase in significant hemorrhagic complications observed in random controlled trials on new-borns .

A monitoring of the bleeding times is recommended during the course of NOXAP administration for a period of more than 24 hours in patients that suffer numerical or functional anomalies of the platelets, a deficit in the coagulation factors or that are undergoing anticoagulant treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Oxygen: In the presence of oxygen, nitric oxide oxidises rapidly forming derivatives that are toxic for the bronchiolar epithelium and the alveolo-capillar membrane. Nitrogen dioxide (NO_2) is the main compound that is formed and during the treatment with nitric oxide, the concentration of NO_2 must be < 0.5 ppm in the dose interval of < 20 ppm of nitric oxide. If, at any time, the concentration of NO2 exceeds 1 ppm, the dose of nitric oxide must be reduced immediately. See the information on monitoring NO_2 in section 4.2.

NO donors: The donor compounds of nitric oxide, including sodium nitroprusside and nitroglycerine, can have an additive effect to NOXAP with regards to the risk of developing methemoglobinemia.

There is a higher risk to develop methemoglobinemia if drugs that increase the methemoglobin concentrations are administrated along with nitric oxide (e.g. alkyl nitrates, sulphonamides and prilocaine). As a consequence, medicinal products that increase methemoglobin must be used with caution during inhaled nitric oxide therapy.

Synergic effects have been reported with the administration of vasoconstrictors (almitrine, phenylephrine), prostacyclin and phosphodiesterase inhibitors, without increasing adverse effects.

Inhaled nitric oxide has been used concomitantly with tolazoline, dopamine, dobutamine, norepinephrine, steroids and surfactants, with no drug interactions observed.

Experimental studies suggest that nitric oxide and also nitrogen dioxide can react chemically with the surfactant and its proteins without proven clinical consequences.

Although controlled studies have not been done, food interactions have not been noticed in clinical trials in patients with prolonged ambulatory administration.

4.6 Pregnancy and lactation

Pregnancy

The effect of the administration of NOXAP in pregnant women is unknown. Animal studies are insufficient (see section 5.3). However, harmful effects may be expected as methemoglobin is considered detrimental to the foetus and nitric oxide has shown genotoxic potential (see section 5.3) by inducing structural alterations on DNA. The potential risk for humans is unknown.

NOXAP should not be used during pregnancy unless clearly necessary, such as in situations of life support.

Lactation

It is not known whether the product NOXAP passes into human breast milk. The excretion of NOXAP in milk has not been studied in animals. Passive exposure to nitric oxide during pregnancy and lactation in humans should be avoided.

4.7 Effects on ability to drive and use machines

Infants and hospitalized patients: Not applicable.

4.8 Undesirable effects

Known adverse reactions have been classified for the various organ systems. Classification based on frequency is not readily possible because structured studies have not been conducted for this. Where, based on the literature, it has been possible to perform a reasonable estimate of frequency, this is indicated in the summary below.

Description of frequencies: very common (>1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

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

Blood system disorders

Methemoglobinemia: The development of methemoglobinemia is dose-dependent, being a frequent complication in the inhalation of NO at high concentrations. Increased levels of methemoglobin will produce tissue hypoxia.

The formation of methemoglobin > 5% with inhaled nitric oxide concentrations <20 ppm are very rare (<1/10,000).

In pediatric population, newborns have a diminished MetHb reductase activity and therefore may run the risk of developing methemoglobinemia.

Haemostasis: Although preclinical studies with nitric oxide on animals and in vitro have shown inhibition of the platelet aggregation, clinical studies on humans have been contradictory. However, in controlled clinical trials carried out, no significant differences have been found between the control group and the treatment group with regards to hemorrhagic complications.

General disorders and administration site conditions

No response: The range of responsiveness to the treatment varies between 30% to 45% of the cases.

Formation of NO_2: The reaction between NO and O_2 to form NO_2 are fast with high concentrations of NO, but slow with the concentrations used in the treatments with inhaled nitric oxide. In animals, elevated levels of NO_2 (>10 ppm) produce pulmonary edema, alveolar hemorrhage, changes in the activity of the surfactant, hyperplasia of alveolar cells, intrapulmonary accumulation of fibrin, neutrophils and macrophages, and death. Also, the inhalation of NO_2 during prolonged periods has been related to degeneration of pulmonary interstitial cells and moderate emphysematous changes.

The inhalation of 2 ppm NO_2 in humans increases the alveolar permeability and the reactivity of the air ways.

Significant elevations of NO_2 levels have not been found at low therapeutic doses (< 20 ppm) of inhaled NO, as well as evidence of clinical toxicity by NO_2 in most of the clinical trials, being a very rare (<1/10,000) complication. The NO_2 concentration must be always maintained as low as possible and < 0,5 ppm.

Rebound effect: Following sudden interruption to the inhaled nitric oxide therapy, rapid rebound reactions are very frequent (>1/10), such as intensified pulmonary vasoconstriction and hypoxemia, which precipitate cardiopulmonary collapse.

The retirement of NO after its prolonged inhalation is associated with transitory pulmonary hypertension, for approximately one hour, in all patients.

Clinically it has been observed that after 10 to 30 hours of treatment with inhaled nitric oxide, an abrupt retirement of NO will produce approximately 75% of the patient rebound symptoms, mainly alterations of the gaseous exchange with reduction of oxygen saturation to different degrees. In a third of them, hemodynamic instability will take place. The reduction of PaO_2 will be greater with greater concentrations of administered NO. For that reason the reduction to 1 ppm of the nitric oxide inhalation before its retirement seems to diminish the reduction of the PaO_2.

Long term adverse effects: From all the controlled studies carried out, there is no evidence of adverse reactions of the treatment provoking the need for re-hospitalisation, special medical services, pulmonary disease or neurological sequelae.

4.9 Overdose

NOXAP overdose is manifested as increases in methemoglobin and NO_2 levels.

• "Symptoms and Treatment"

High levels of NO_2 can cause acute pulmonary injury.

Increased levels of methemoglobin reduce the capacity to transport oxygen in the circulation. In clinical studies, levels of NO_2 > 3 ppm or levels of methemoglobin > 7% were treated by reducing the dose of inhaled nitric oxide or by interrupting its administration.

Methemoglobinemia that does not respond to reduction or interruption of the treatment can be treated intravenously with vitamin C, methylene blue or by blood transfusion, depending on the clinical situation.

5 Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products.

ATC code: R07AX01

• Mechanism of action

Nitric oxide is a substance that is produced by many cells of the organism.

It relaxes the vascular smooth muscle by binding it to the heme part of cytosolic guanylate cyclase, activating the guanylate cyclase and increasing the intracellular levels of cyclic guanosine 3'.5'-monophosphate, which in turn causes vasodilatation. The inhalation of nitric oxide produces pulmonary vasodilatation.

• Pharmacodynamic effects

The therapeutic importance of inhaled nitric oxide, is that it produces selective pulmonary vasodilation with minimum systemic cardiovascular effects. The pulmonary selective vasodilation of nitric oxide is because of its fast inactivation by means of its reaction with the heme groups. The average life in vivo of NO is only of a few seconds.

Nitric oxide increases the partial pressure of arterial oxygen (PaO_2) by dilating the pulmonary vessels in the better ventilated areas of the lung, redistributing the pulmonary blood flow away from the pulmonary regions with low ventilation/perfusion (V/Q) indexes to regions with normal indexes. Studies show that its pharmacodynamic effects appear in the lung at concentrations as low as 1 ppm inside the air way.

• Efficacy and safety

Clinical trials have confirmed in different pathological processes the ability from inhaled nitric oxide to diminish the pulmonary vascular resistance and to increase the oxygenation.

The efficacy of inhaled nitric oxide has been investigated in newborns with hypoxic respiratory failure with different aetiology. In the case of newborns with persistent pulmonary hypertension, the inhalation of NO improves oxygenation and reduces the risk of needing oxygenation through extracorporeal membrane. In the meta-analysis of randomized clinical trials in infants without congenital diaphragmatic hernia with persistent pulmonary hypertension of the newborn (n=548), inhalation of NO reduces the need for ECMO (relative risk: 0.73; 95% CI: 0.60 to 0.90) and improves the oxygenation (PaO2 by a mean of 53.3 mm Hg; 95% CI: 44.8 to 61.4; oxygenation index by a mean of -12.2; 95% CI: -14.1 to -9.9). In newborns with hypoxic respiratory failure, in the meta-analysis (n=989), the inhalation of NO improves the PaO2 with a difference of 46.4 Torr compared with controls (95% CI, 34.2, 58.5) and significantly decreases the oxygenation index by 10.7 compared with controls (95% CI, -14.1, -7.4). The incidence of death or need for extracorporeal membrane oxygenation (ECMO) was significantly reduced by treatment with iNO, relative risk 0.72 compared to control (95% CI, 0.6, 0.87). Increase of complications related to the use of inhaled NO were not observed in either of the two meta-analyses.

5.2 Pharmacokinetic properties

The pharmacokinetics of nitric oxide has been studied in adults.

Nitric oxide, in the dilution procedure before its administration, reacts chemically with oxygen to form nitrogen dioxide, a toxic substance for the body.

Nitric oxide is absorbed systemically following inhalation. The major part passes through the pulmonary capillary bed where it combines with the hemoglobin, which is saturated with 60% - 100% of oxygen. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. With a low saturation level of oxygen, the nitric oxide can combine with deoxyhemoglobin to form transitory nitrosylhemoglobin, which turns into nitrogen oxides and methemoglobin when exposed to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrate respectively, which interact with the oxyhemoglobin to produce methemoglobin and nitrate. Therefore, the final products of nitric oxide that arrive in the systemic circulation are primarily methemoglobin and nitrate.

The formation of methemoglobin depends on the exposure time and concentrations to nitric oxide. The concentrations of methemoglobin increase during the first 8 hours of treatment with inhaled nitric oxide. Methemoglobin levels > 7% have been observed in patients who received high doses of NO (80 ppm).

Nitrate has been identified as the predominant metabolite of nitric oxide excreted in the urine, representing > 70% of the inhaled nitric oxide dose. The kidney eliminates the plasma nitrate at a similar rate to glomerular filtration.

5.3 Preclinical safety data

Single-dose studies on rodents indicate that the lethal dose is around 300 ppm of nitric oxide or above.

Repeated-dose studies show that the rodents can survive exposure to nitric oxide of up to sustained levels of nitric oxide of around 250 ppm. Death is secondary to anoxia derived from high levels of methaemoglobin.

From the studies carried out on dogs, it is possible to deduce that the lethal concentration varies around 640 ppm of NO exposure for 4 hours, while exposure to 320 ppm of NO is not lethal.

Levels of methaemoglobin higher than 30% have been recorded in animals that died due to NO exposure. The recuperation from methaemoglobinaemia is rapid; in less than 24 hours, a full recovery has been recorded. At levels of 80 ppm NO administered for 3 hours, no increase of methaemoglobin was observed in sheep.

In biological tissue, nitric oxide can form peroxinitrite (˙OONO) to react with superoxide (O_2-), an unstable substance that can damage the tissue through further redox reactions.

Furthermore, nitric oxide has an affinity for metal proteins and might also react with sulfhydryl groups (-SH) in proteins, giving rise to nitrosyl compounds. The clinical importance of the chemical reactivity of nitric oxide in the tissue is unknown.

Bleeding time: In a study conducted on rabbits and healthy humans, it has been found that inhaled nitric oxide approximately doubles the bleeding time.

No studies on toxicity to reproduction or carcinogenicity have been conducted.

Mutagenicity and genotoxicity: Various preclinical genotoxicity tests with nitric oxide show a positive genotoxic potential. Part of its toxicity is mediated by peroxinitrite. Although DNA damage has not been demonstrated in human cells following in vivo exposure, preclinical in vitro and in vivo studies (bacteria and mice), have demonstrated NO-induced chromosomal alterations. This is possibly related to the formation of mutagenic nitrosamines, DNA alterations or impairment of DNA repair mechanisms. The significance of these findings for clinical use in neonates and the potential for effects on the germ cells are unknown.

6 Pharmaceutical particulars

6.1 List of excipients

Nitrogen.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal product/equipment/devices except those mentioned in section 6.6.

The equipments/devices should not be administered simultaneously: Butylrubber, Polyamide and Polyurethane.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Follow all the rules regarding the handling of pressurised containers:

Store in the original gas cylinder.

Do not transfer contents from original gas cylinder to another gas cylinder. Store cylinders vertically in well-ventilated rooms.
Protect the cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.
The installation of a nitric oxide duct system is prohibited with a cylinder distribution system, a fixed network or terminal units.

Storage in the pharmacy department

The gas cylinders should be kept in a place designated exclusively for medicinal gas storage that is well ventilated, clean and under lock and key. This place should house a separate, special facility for the storage of nitric oxide gas cylinders.

Storage in the medical department

The gas cylinders should be stored in a place with the appropriate equipment to ensure that it stays in a vertical position.

6.5 Nature and contents of container

NOXAP is stored in high pressure gas cylinders made out of aluminium or aluminium with an external elastomers layer. The valves which close the gas cylinders are made of stainless steel. The pack sizes of the gas cylinders are 5L, 10L, 20L, 40L

NOXAP is filled as a gas in these gas cylinders to a pressure of 200bar.

Pack sizes (litres)	Filling Pressure (bar)	Litres Quantity of the mixture 800 ppm NO/N_2	m3 Quantity of the mixture 800 ppm NO/N_2
5	200	945	0.945
10	200	1890	1.890
20	200	3780	3.780
40	200	7560	7.560

The colour coding of the gas cylinder is a turquoise blue shoulder on a white gas cylinder body.

6.6 Special precautions for disposal and other handling

General

All personnel handling NOXAP gas cylinders should have adequate knowledge of the properties of this gas, any necessary precautions to take, the steps to follow in the event of an emergency and the correct operational procedures for its installation.

Transport of gas cylinders

The gas cylinders should be transported with the appropriate equipment to ensure that they are protected from the risk of jolts or drops. When patients undergoing NOXAP treatment are being transferred between different hospitals or within the same, the gas cylinders should be separated and properly secured so that they maintain a vertical position and do not run the risk of drops or inopportune changes to the administration of the medicine. Special attention should be paid to the pressure regulator fixing in order to avoid the risk of accidental breakdowns.

Preparation for use

- The valves of the gas cylinder should be opened slowly.
- The valves of the gas cylinder or of any associated equipment should never be lubricated and should always be kept free of oils and grease.
- When connecting equipment to the gas cylinders, never use excessive force.

Utilisation of the gas cylinders

To avoid any type of incident, the following instructions should always be respected:

- Handle the gas cylinders with care, ensuring that they are not abruptly jolted or dropped.
- Only move the gas cylinders using an appropriate type and size lorry for such a purpose.
- Medicinal gases should only be used for medicinal purposes.
- Always ensure the material is in good condition before use.
- If the pressure is less than 10 bar, do not use the gas cylinder.
- Do not use the gas cylinder if its valve is not protected by a cap or cover.
- The valve should not be opened in an abrupt manner.
- Do not attempt to repair the valve if it is defective.
- A specific connection should be used, as well as a pressure regulator that allows a pressure equivalent to at least 1.5 of the maximum functioning pressure of the gas cylinder.
- In order to ensure that NO_2 is not inhaled, purge the pressure regulator with a mixture of nitrogen/nitric oxide before each new use.
- The pressure regulator should not be gripped with pliers or pincers since this could damage the gasket.
- Whilst in use, the gas cylinder should be firmly secured in an appropriate support for this type of gas cylinder in order to avoid an accidental drop.
- Release the gas discharged outdoors. It is advisable to ensure possible ventilation at all times which is adequate for the evacuation of the gas in the event of an untimely accident or leak.
- Smoking or sources of ignition are not permitted in the area where the gas cylinders are stored or in the pipe vents.
- After use, close the valves of the gas cylinders with moderate force and release the residual pressure in the regulator.
- Ensure that the valve of the gas cylinder is always closed when not in use.

Compatibility

All the equipment, including tubes, connections and circuits, that are used in nitric oxide administration should be manufactured with materials that are compatible with the gas. As far as corrosion is concerned, the supply system can be divided into two areas: 1) from the gas cylinder valve to the humidifier (dry gas) and 2) from the humidifier to the vent (moist gas that may contain NO_2). Evidence shows that the dry NO mixtures can be used with the majority of the materials. Nevertheless, the presence of nitrogen dioxide and humidity create an aggressive atmosphere. Only stainless steel is recommended out of the materials made of metal. Polyethylene (PE) and polypropylene (PP) are two polymers, among others, that have been tested and can be used in nitric oxide administration systems. Polytrifluorochloro ethylene, the hexafluoropropene-vinylidene copolymer and polytetrafluorethylene have been used with pure nitric oxide and other corrosive gases and are considered inert.

Instructions for the disposal of the gas cylinders

- Do not throw away empty gas cylinders. They should be sent immediately to an empty cylinder warehouse, or an appropriate storage area for collection by the supplier.

7 Marketing authorisation holder

To be completed nationally.

8 Marketing authorisation number

To be completed nationally

9 Date of first authorisation

To be completed nationally

10 Date of revision of the text

October 2009

tell me more
www.airproducts.com/noxap

Air Products PLC
2 Millennium Gate
Westmere Drive
Crewe
Cheshire
CW1 6AP
Tel: 0800 389 0202

tell me more
www.airproducts.com

239-10-010-GB