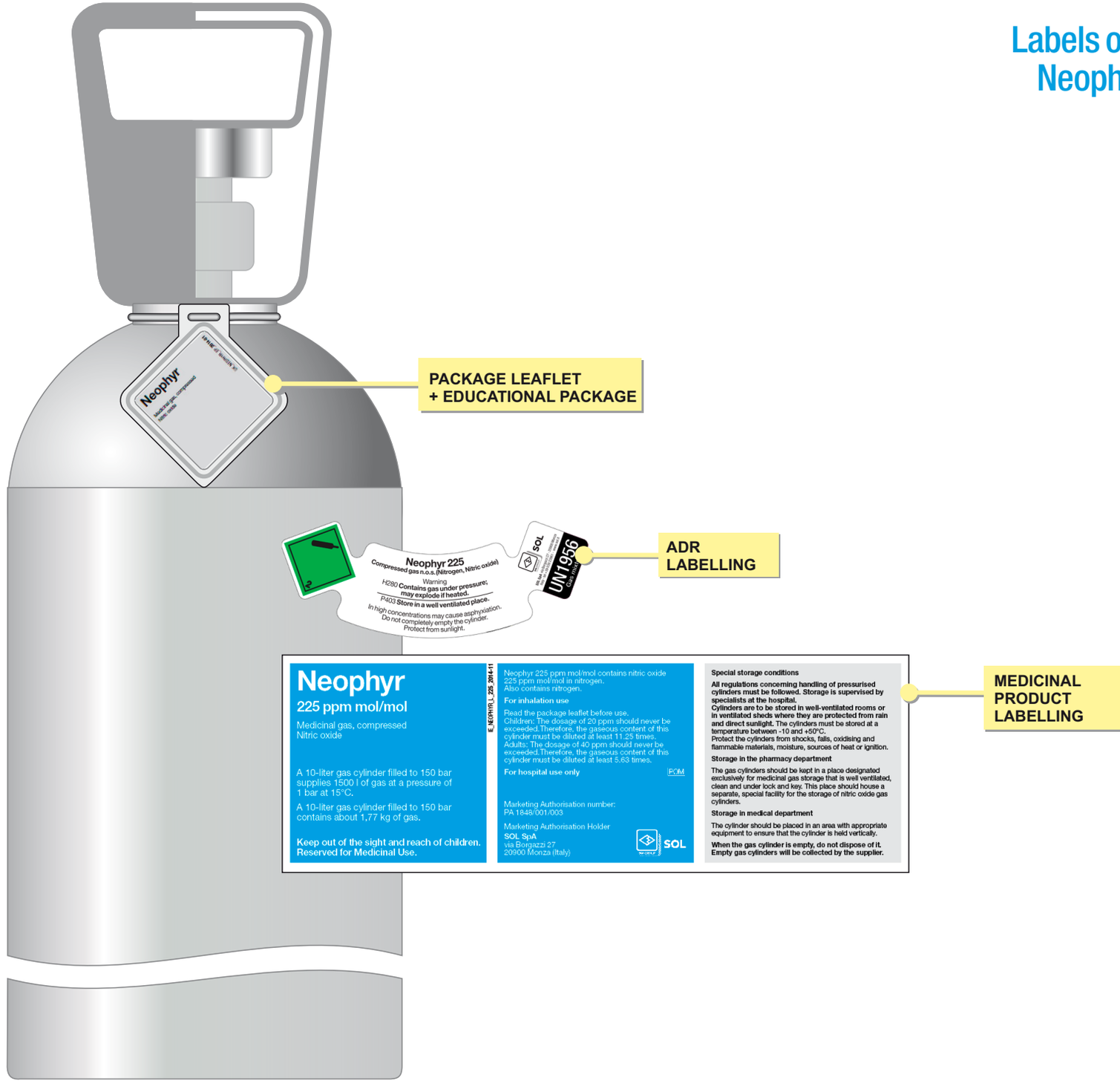
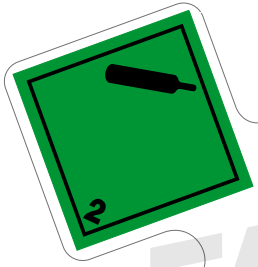
Labels on cylinders
Neophyr - Ireland



IE_Neophyr_A_225_**2014-11**



Neophyr 225

Compressed gas n.o.s. (Nitrogen, Nitric oxide)

Warning

H280 **Contains gas under pressure; may explode if heated.**

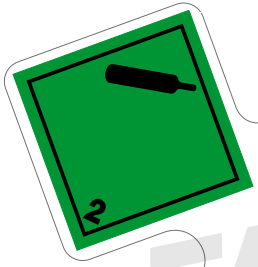
P403 **Store in a well ventilated place.**

In high concentrations may cause asphyxiation.
Do not completely empty the cylinder.
Protect from sunlight.

SOL SpA via Bergamo,27 - 20900 Monza
Italy - tel. +39 039 2396 1 - www.sol.it

UN1956
Gas mixture

IE_Neophyr_A_450_**2014-11**



Neophyr 450

Compressed gas n.o.s. (Nitrogen, Nitric oxide)

Warning

H280 **Contains gas under pressure; may explode if heated.**

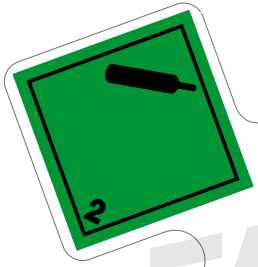
P403 **Store in a well ventilated place.**

In high concentrations may cause asphyxiation.
Do not completely empty the cylinder.
Protect from sunlight.

SOL
SOL SpA via Bergamo 27 - 20900 Monza
Italy - tel. +39 039 23961 - www.sol.it

UN1956
Gas mixture

IE_Neophyr_A_1000_**2014-11**



Neophyr 1000

Compressed gas n.o.s. (Nitrogen, Nitric oxide)

Warning

H280 **Contains gas under pressure; may explode if heated.**

P403 **Store in a well ventilated place.**

In high concentrations may cause asphyxiation.
Do not completely empty the cylinder.
Protect from sunlight.

SOL

SOL SpA via Bergamo 27 - 20900 Monza
Italy - tel. +39 039 2367 1 - www.sol.it

UN1956
Gas mixture

Neophyr

225 ppm mol/mol

Medicinal gas, compressed
Nitric oxide

A 10-liter gas cylinder filled to 150 bar supplies 1500 l of gas at a pressure of 1 bar at 15°C.

A 10-liter gas cylinder filled to 150 bar contains about 1,77 kg of gas.

Keep out of the sight and reach of children.
Reserved for Medicinal Use.

IE_NEOPHYR_L_225_2014-11

Neophyr 225 ppm mol/mol contains nitric oxide 225 ppm mol/mol in nitrogen.
Also contains nitrogen.

For inhalation use

Read the package leaflet before use.
Children: The dosage of 20 ppm should never be exceeded.Therefore, the gaseous content of this cylinder must be diluted at least 11.25 times.
Adults: The dosage of 40 ppm should never be exceeded.Therefore, the gaseous content of this cylinder must be diluted at least 5.63 times.

For hospital use only POM

Marketing Authorisation number:
PA 1848/001/003

Marketing Authorisation Holder
SOL SpA
via Borgazzi 27
20900 Monza (Italy)

SOL
SOLGROUP

Special storage conditions

All regulations concerning handling of pressurised cylinders must be followed. Storage is supervised by specialists at the hospital.
Cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight. The cylinders must be stored at a temperature between -10 and +50°C.
Protect the cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

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 medical department

The cylinder should be placed in an area with appropriate equipment to ensure that the cylinder is held vertically.

When the gas cylinder is empty, do not dispose of it. Empty gas cylinders will be collected by the supplier.

Neophyr

450 ppm mol/mol

Medicinal gas, compressed
Nitric oxide

A 10-liter gas cylinder filled to 150 bar supplies 1500 l of gas at a pressure of 1 bar at 15°C.

A 10-liter gas cylinder filled to 150 bar contains about 1,77 kg of gas.

Keep out of the sight and reach of children.
Reserved for Medicinal Use.

IE_NEOPHYR_L_450_2014-11

Neophyr 450 ppm mol/mol contains nitric oxide 450 ppm mol/mol in nitrogen.
Also contains nitrogen.

For inhalation use

Read the package leaflet before use.
Children: The dosage of 20 ppm should never be exceeded.Therefore, the gaseous content of this cylinder must be diluted at least 22.5 times.
Adults: The dosage of 40 ppm should never be exceeded.Therefore, the gaseous content of this cylinder must be diluted at least 11.25 times.

For hospital use only POM

Marketing Authorisation number:
PA 1848/001/002

Marketing Authorisation Holder
SOL SpA
via Borgazzi 27
20900 Monza (Italy)

SOL
SOLGROUP

Special storage conditions

All regulations concerning handling of pressurised cylinders must be followed. Storage is supervised by specialists at the hospital.
Cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight. The cylinders must be stored at a temperature between -10 and +50°C.
Protect the cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

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 medical department

The cylinder should be placed in an area with appropriate equipment to ensure that the cylinder is held vertically.

When the gas cylinder is empty, do not dispose of it. Empty gas cylinders will be collected by the supplier.

Neophyr

1000 ppm mol/mol

Medicinal gas, compressed
Nitric oxide

A 10-liter gas cylinder filled to 150 bar supplies 1500 l of gas at a pressure of 1 bar at 15°C.

A 10-liter gas cylinder filled to 150 bar contains about 1,77 kg of gas.

Keep out of the sight and reach of children.
Reserved for Medicinal Use.

IE_NEOPHYR_L_1000_2014-11

Neophyr 1000 ppm mol/mol contains nitric oxide 1000 ppm mol/mol in nitrogen.
Also contains nitrogen.

For inhalation use

Read the package leaflet before use.
Children: The dosage of 20 ppm should never be exceeded.Therefore, the gaseous content of this cylinder must be diluted at least 50 times.
Adults: The dosage of 40 ppm should never be exceeded.Therefore, the gaseous content of this cylinder must be diluted at least 25 times.

For hospital use only POM

Marketing Authorisation number:
PA 1848/001/001

Marketing Authorisation Holder
SOL SpA
via Borgazzi 27
20900 Monza (Italy)

SOL
SOLGROUP

Special storage conditions

All regulations concerning handling of pressurised cylinders must be followed. Storage is supervised by specialists at the hospital.
Cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight. The cylinders must be stored at a temperature between -10 and +50°C.
Protect the cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

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 medical department

The cylinder should be placed in an area with appropriate equipment to ensure that the cylinder is held vertically.

When the gas cylinder is empty, do not dispose of it. Empty gas cylinders will be collected by the supplier.

Neophyr

1000 ppm mol/mol

Medicinal gas, compressed
Nitric oxide

A **2-liter** gas cylinder filled to 150 bar supplies 300 l of gas at a pressure of 1 bar at 15°C.

A **2-liter** gas cylinder filled to 150 bar contains about 0,35 kg of gas.

Keep out of the sight and reach of children.
Reserved for Medicinal Use.

IE_NEOPHYR_L_1000/2_2015-08

Neophyr 1000 ppm mol/mol contains nitric oxide 1000 ppm mol/mol in nitrogen.
Also contains nitrogen.

For inhalation use

Read the package leaflet before use.
Children: The dosage of 20 ppm should never be exceeded.Therefore, the gaseous content of this cylinder must be diluted at least 50 times.
Adults: The dosage of 40 ppm should never be exceeded. Therefore, the gaseous content of this cylinder must be diluted at least 25 times.

For hospital use only

POM

Marketing Authorisation number:
PA 1848/001/001

Marketing Authorisation Holder
SOL SpA
via Borgazzi 27
20900 Monza (Italy)

SOL
SOLGROUP

Special storage conditions

All regulations concerning handling of pressurised cylinders must be followed. Storage is supervised by specialists at the hospital.
Cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight. The cylinders must be stored at a temperature between -10 and +50°C.
Protect the cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

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 medical department

The cylinder should be placed in an area with appropriate equipment to ensure that the cylinder is held vertically.

When the gas cylinder is empty, do not dispose of it. Empty gas cylinders will be collected by the supplier.

The following information is intended for medical or healthcare professionals only.

Neophyr
225 ppm mol/mol
450 ppm mol/mol
1000 ppm mol/mol

IE_NEOPHYR P_ 2016-01

Medicinal gas, compressed
Nitric oxide
225 ppm, 450 ppm, 1000 ppm mol/mol

1. NAME OF THE MEDICINAL PRODUCT

Neophyr 225 ppm mol/mol medicinal gas, compressed
Neophyr 450 ppm mol/mol medicinal gas, compressed
Neophyr 1000 ppm mol/mol medicinal gas, compressed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitric oxide 225ppm mol/mol.
Nitric oxide 450ppm mol/mol.
Nitric oxide 1000ppm mol/mol.

For Nitric oxide (NO) 225 ppm mol/mol
Nitric oxide (NO) 0.225 ml in
Nitrogen (N_2) 999.775 ml.

For Nitric oxide (NO) 450 ppm mol/mol
Nitric oxide (NO) 0.450 ml in
Nitrogen (N_2) 999.55 ml.

For Nitric oxide (NO) 1000 ppm mol/mol
Nitric oxide (NO) 1 ml in
Nitrogen (N_2) 999 ml.

A 2-liter gas cylinder filled to 150 bar supplies 300 l of gas at a pressure of 1 bar at 15°C.
A 10-liter gas cylinder filled to 150 bar supplies 1500 l of gas at a pressure of 1 bar at 15°C.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Medicinal gas, compressed.
Colourless and odourless gas.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Neophyr, in conjunction with ventilatory support and other appropriate active substances, is indicated:
For the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.

As part of the treatment of perioperative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

4.2 Posology and method of administration

Persistent Pulmonary Hypertension in the Newborn (PPHN)
Prescription of nitric oxide should be supervised by a physician experienced in neonatal intensive care.
Prescription should be limited to those neonatal units that have received adequate training in the use of a nitric oxide delivery system. Neophyr should only be delivered according to a neonatologist's prescription.
Neophyr should be used in ventilated newborn infants expected to require support >24 hours.
Neophyr should be used only after respiratory support has been optimised. This includes optimising tidal volume/pressures and lung recruitment (surfactant, high frequency ventilation, and positive end expiratory pressure).

Pulmonary hypertension associated with heart surgery
Prescription of nitric oxide should be supervised by a physician experienced in cardiothoracic anaesthesia & intensive care. Prescription should be limited to those cardio-thoracic units that have received adequate training in the use of a nitric oxide delivery system. Neophyr should only be delivered according to an anaesthetist's or intensive care physician's prescription.

Posology
The posology will be determined in accordance with the medical condition of the patient.
Due to the potential risk of NO_2 formation, continuous monitoring of NO_2 must be performed.

Persistent Pulmonary Hypertension in the Newborn (PPH)
Newborns > 34 weeks gestation: The maximum recommended dose of Neophyr 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 at 5 ppm 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% ($FiO_2 < 0.60$).
The treatment can be pursued up to 96 hours or until the oxygen de-saturation is resolved and the patient is ready for gradual withdrawal from Neophyr treatment. The duration of the treatment should be limited to 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.

Weaning
Attempts to wean Neophyr should be made after the ventilator support is substantially decreased or after 96 hours of therapy. When the decision is made to discontinue inhaled nitric oxide therapy, the dose should be reduced to 1 ppm for 30 minutes to one hour. If there is no change in oxygenation during administration of Neophyr at 1 ppm, the FiO_2 should be increased by 10%, the Neophyr is discontinued, and the neonates monitored closely for signs of hypoxaemia. If oxygenation falls >20%, Neophyr therapy should be resumed at 5 ppm and discontinuation of Neophyr therapy should be reconsidered after 12 to 24 hours. Infants who cannot be weaned off Neophyr by 4 days should undergo careful diagnostic work-up for other diseases.

Pulmonary hypertension associated with heart surgery
Neophyr should be used only after conservative support has been optimised. Neophyr should be administered under close monitoring of hemodynamics and oxygenation.

Newborn infants, infants and toddlers, children and adolescents, ages 0-17 years
The starting dose of inhaled nitric oxide is 10 ppm(parts per million) of inhaled gas.
The dose may be increased up to 20 ppm if the lower dose has not provided sufficient clinical effects. The lowest effective dose should be administered and the dose should be weaned down to 5 ppm provided that the pulmonary artery pressure and systemic arterial oxygenation remain adequate at this lower dose.
Clinical data supporting the suggested dose in the age range 12-17 years is limited.

Adults
The starting dose of inhaled nitric oxide is 20 ppm (parts per million) of inhaled gas.
The dose may be increased up to 40 ppm if the lower dose has not provided sufficient clinical effect. The lowest effective dose should be administered and the dose should be weaned down to 5 ppm provided that the pulmonary artery pressure and systemic arterial oxygenation remain adequate at this lower dose.
The effects of inhaled nitric oxide are rapid, decrease in pulmonary artery pressure and improved oxygenation is seen within 5-20 minutes. In case of insufficient response the dose may be titrated after a minimum of 10 minutes.
Consideration should be given to discontinuation of treatment if no beneficial physiological effects are apparent after a 30-minute trial of therapy.
Treatment may be initiated at any time point in the perioperative course to lower pulmonary pressure.
In clinical studies treatment was often initiated before separation from Cardio Pulmonary Bypass.
Inhaled NO has been given for time periods up to 7 days in the perioperative setting, but common treatment times are 24 -48 hours.

Weaning
Attempts to wean Neophyr should be commenced as soon as the hemodynamics have stabilised in conjunction to weaning from ventilator and inotropic support. The withdrawal of inhaled nitric oxide therapy should be performed in a stepwise manner. The dose should be incrementally reduced to 1 ppm for 30 minutes with close observation of systemic and central pressure, and then turned off.

Weaning should be attempted at least every 12 hours when the patient is stable on a low dose of Neophyr.
Too rapid weaning from inhaled nitric oxide therapy carries the risk of a re-bound increase in pulmonary artery pressure with subsequent circulatory instability.

Additional 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.
The safety and efficacy of inhaled nitric oxide in premature infants less than 34 weeks of gestation has not yet been established, no recommendation or posology can be made.

Method of administration
For inhalation use.
Modalities of administration of Neophyr 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 and after the humidifier. The administration system should supply a constant concentration of inhaled Neophyr, notwithstanding the ventilation equipment and ventilation modality utilised.
In order to avoid errors in the dosage, the concentration of Neophyr 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 1 ppm, the dose of Neophyr 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 Neophyr (± 2 ppm of the prescribed dose), NO_2 (maximum 1 ppm) and FiO_2 (± 0.05).
If an unexpected change in the concentration of Neophyr 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 Neophyr 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.
Neophyr 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.

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 tract; 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 Neophyr and/or FiO_2 must be reduced.
If there is an unexpected change in Neophyr concentration, the delivery system should be assessed for malfunction and the analyser should be recalibrated.

Monitoring the formation of methaemoglobin (MetHb)
Following its inhalation, the terminal compounds of nitric oxide that arrive in the systemic circulation are primarily methaemoglobin and nitrate. The nitrate is fundamentally excreted through the urinary system and the methaemoglobin is reduced by the methaemoglobin reductase.
Newborns and infants have diminished levels of MetHb reductase activity compared to adults; therefore the methaemoglobin concentrations in the blood must be monitored. The level of MetHb must be measured within 1 hour of the start of Neophyr therapy using an analyser that correctly distinguishes the fetal hemoglobin from the MetHb. If the MetHb is > 2.5%, the dose of Neophyr will have to be reduced 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.
In adults undergoing heart surgery, methaemoglobin level should be measured within one hour of the initiation of Neophyr therapy. If the fraction of methaemoglobin rises to a level that potentially compromises adequate oxygen delivery, the Neophyr dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered.

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 NO_2 below 1.5 ppm.
Continuous monitoring of atmospheric levels of NO_2 is mandatory.

Training in administration
The key elements that need to be covered in training hospital personnel are as follows.

Correct set-up and connections
- Connections to the gas cylinder and to the ventilator patient breathing circuit

Operation
- Pre-use check list procedure (a series of steps required immediately prior to each patient initiation to ensure that the system is working properly and that the system is purged of NO_2)
- Setting the device for the correct concentration of nitric oxide to be administered
- Setting the NO, NO_2 and O_2 monitors for high and low alarm limits
- Using the manual backup delivery system
- Procedures for correctly switching gas cylinders and purging system
- Troubleshooting alarms
- NO, NO_2 and O_2 monitor calibration
- Monthly system performance check-up procedures

4.3 Contraindications

- Newborns with known dependency to right-left blood shunt or newborns with significant left-right shunt.
- Patients with congenital or acquired deficiency of methaemoglobin reductase (MetHb reductase) or glucose 6 phosphate dehydrogenase (G6PD).
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Precautions to avoid exposures during inhaled Neophyr therapy
- Follow Standard Operating Procedures when preparing and using Neophyr.
- 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.

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 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 recommended 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).

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 Neophyr administration, the following possibilities should be considered:
- 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 (Aao_2>600) after 4 hours of iNO therapy indicate an urgent need to initiate ECMO therapy.
- In a non-response situation to the administration of Neophyr, 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 Neophyr treatment. The gradual withdrawal of inhaled nitric oxide must take place with caution (See 4.2 Posology and method of administration: Withdrawal).
- 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 Neophyr treatment.

Monitoring the ventricular function
With regards to interventricular or interauricular communication, the inhalation of Neophyr 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.
Inhaled nitric oxide should be used with caution in patients with complex heart defect, where high pressure in the pulmonary artery is of importance for maintaining circulation.
Inhaled nitric oxide should also be used with caution in patients with compromised left ventricular function and elevated baseline pulmonary capillary pressure (PCWP) as they may be at an increased risk of developing cardiac failure (e.g. pulmonary oedema).
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 haemostasis
Tests 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 bleeding complications observed in random controlled trials on new-borns.
A monitoring of the bleeding times is recommended during the course of Neophyr 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.

Discontinuation of therapy
The Neophyr dose should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO_2). Deterioration in oxygenation and elevation in PAP may also occur in neonates with no apparent response to Neophyr.
Weaning from inhaled nitric oxide should be performed with caution. For patients transported to other facilities for additional treatment, who need to continue with inhaled nitric oxide, arrangements should be made to ensure the continuous supply of inhaled nitric oxide during transportation. The physician should have access at the bedside to a reserve nitric oxide delivery system.

Package leaflet:
Information for the user

Neophyr
225 ppm mol/mol
450 ppm mol/mol
1000 ppm mol/mol

IE_NEOPHYR P_ 2016-01

Medicinal gas, compressed
Nitric oxide
225 ppm, 450 ppm, 1000 ppm mol/mol

Read all of this leaflet carefully before you start using 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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4

In this leaflet:

1. WHAT NEOPHYR IS AND WHAT IT IS USED FOR

Neophyr must be administered exclusively by healthcare professionals and it is only for strict hospital use.

Neophyr is indicated in the following conditions:
- newborn babies with lung failure associated with high blood pressure in the lungs, a condition known as hypoxic respiratory failure. When inhaled, this gas mixture can improve the flow of blood through the lungs, which may help to increase the amount of oxygen that reaches your baby's blood.
- newborn babies, babies, children, teenagers 0-17 years and adults with high blood pressure in the lungs, connected with heart surgery. This gas mixture can improve heart function and increase the flow of blood through the lungs.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE NEOPHYR

Do not use Neophyr
- If you (as the patient) or your child (as the patient) are allergic (hypersensitive) to nitric oxide or any of the other ingredients of this medicine (listed in section 6).
- If you have been told that you (as the patient) or your child (as the patient) have an abnormal circulation within the heart.
- If you (as the patient) or your child (as the patient) have congenital or acquired deficiency of methemoglobin reductase (MetHb reductase) or glucose 6 phosphate dehydrogenase (G6PD).

Warnings and precautions
Talk to your doctor before using Neophyr.
Inhaled nitric oxide may not always be effective and thus other therapies may be considered necessary for you or your child.
Inhaled nitric oxide may influence the oxygen carrying capacity of the blood. This will be monitored by blood samples and if required the dose of inhaled nitric oxide must be reduced.
Nitric oxide may react with oxygen forming nitrogen dioxide that may cause airway irritation. Your or your child's doctor will undertake monitoring of nitrogen dioxide and in case of elevated values the Neophyr therapy will be adjusted, decreased accordingly.
Inhaled nitric oxide may have a mild but influence on the platelets (components that help the blood to clot) of you or your child and any signs of bleeding and or haematoma should be observed.
If you see any signs or symptoms that may be associated to bleeding you should directly inform the doctor.
No effect of inhaled nitric has been documented in newborn babies with a malformation where the diaphragm is not fully complete, so called 'congenital diaphragmatic hernia'.
In newborn babies with special malformations of the heart, 'what doctors calls congenital heart defects' inhaled nitric oxide may cause a worsening of the circulation.

Children
Neophyr should not be used in preterm baby < 34 weeks of gestational age.

Other medicines and Neophyr
The doctor will decide when to treat you or your child with Neophyr and with other medicines, and will carefully supervise the treatment.
Tell your doctor if you (as the patient) or your child (as the patient) are taking, have recently taken or might take any other medicine.
Some medicines can affect the ability of blood to carry oxygen. These include prilocaine (a local anaesthetic used for pain relief in association to minor painful procedures e.g. suturing, and minor surgical or diagnostic procedures) or glyceryl trinitrate (used to treat chest pain). Your doctor will take care to check that the blood can carry enough oxygen when you are taking these medicines.

Pregnancy, breast-feeding and fertility
Neophyr should not be used during pregnancy unless clearly necessary, such as in situations of life support.
Exposure to nitric oxide in humans during lactation should be avoided.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

3. HOW TO USE NEOPHYR

Your doctor will decide the correct dose of Neophyr and will administer Neophyr to you or your child's lungs through a system designed for delivering this gas. This delivery system will ensure that the correct amount of nitric oxide is delivered by diluting Neophyr with an oxygen/air mixture immediately before giving it to you.For you or your child's safety, the delivery systems intended for administration of Neophyr are fitted with devices that constantly measure the amount of nitric oxide, oxygen and nitrogen dioxide (a chemical formed when nitric oxide and oxygen are mixed) being delivered to the lungs.
Your doctor will decide how long you or your child should be treated with Neophyr.
Neophyr is given in dose of 10 to 20 ppm, (maximal dose 20 ppm in children and 40 ppm in adults) parts per million of the gas that you or your child inhale. The lowest effective dose will be sought.
Therapy is usually required for about 4 days in newborn infants with lung failure associated with high blood pressure in the lungs. In children and adults with high blood pressure in the lungs, connected with heart surgery, Neophyr is usually given for 24-48 hours. However, therapy with Neophyr may last longer.

If you receive more Neophyr than you should
Too much of inhaled nitric oxide may influence the oxygen carrying capacity of the blood. This will be monitored by blood samples and if required the Neophyr dose will be decreased and the administration of medicines such as vitamin C, methylene blue, or eventually blood transfusion, in order to improve the oxygen carrying capacity, may be considered.

If you stop receiving Neophyr
Treatment with Neophyr should not be stopped suddenly. Low blood pressure or a rebound increase in pressure in the lungs has been known to occur if treatment with Neophyr is stopped suddenly without first lowering the dose.

At the end of treatment, the doctor will slowly lower the amount of Neophyr being given to you or your child, so that the circulation in the lungs is able to adjust to oxygen/air without Neophyr. Thus it may take a day or two before you or your child is off Neophyr therapy.
If you have any further questions on the use of this medicine ask your doctor or other healthcare professionals.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will notice and closely monitor any side effects. It is not likely that you will experience these side effects yourself.

Side effects that are very commonly seen *(affects more than 1 user in 10)* in association with Neophyr therapy include:
• Low platelet count, abnormally low potassium concentration in the blood (hypokalemia), low blood pressure, airless or collapsed lung, abnormally high amounts of bile pigment (bilirubin) in the blood.

Side effects that may be seen but the frequency is not known *(frequency cannot be estimated from the available data)* are:
• Rebound high blood pressure in the lungs (increase in pulmonary artery pressure), and too low amount of oxygen in the blood (oxygen desaturation/hypoxemia) due to sudden withdrawal of the treatment, increase in methemoglobin, thus reduced oxygen carrying capacity.
• Accidental ambient air exposure to nitric oxide, e.g. leakage from equipment or cylinder may cause headache.

You should directly inform the personnel if you experience headache while being in close proximity to your child receiving Neophyr.
If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.

If you have any further questions on the use of this product ask your doctor or other healthcare professionals.

Reporting of side effects
if you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel. +353 1 6764971
Fax. +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

5. HOW TO STORE NEOPHYR

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

Neophyr therapy should only be used and handled by hospital personnel.
• Neophyr cylinders should be stored secured in order to avoid falling and thus potentially causing harm.
• Neophyr should be used and administered only by personnel specially trained in the use and handling of Neophyr.

All regulations concerning handling of pressurised cylinders must be followed.
Storage is supervised by specialists at the hospital. Gas cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight.
The cylinders must be stored at a temperature between -10 and +50°C.

Protect the cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

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 medical department
The cylinder should be placed in an area with appropriate equipment to ensure that the cylinder is held vertically.

When the cylinder is empty, do not dispose of it. Empty cylinders will be collected by the supplier. Do not use this medicine after the expiry date which is stated on the gas cylinder label. The expiry date refers to the last day of that month.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

What Neophyr contains
• The active substance is nitric oxide
225 ppm mol/mol, 450 ppm mol/mol or 1000 ppm mol/mol
• The other ingredient is nitrogen

What Neophyr looks like and contents of the pack
Gas cylinders with a capacity of 2l (Neophyr 1000 ppm mol/mol).
A 2-liter gas cylinder filled to 150 bar contains about 0,35 kg of gas.
Or
Gas cylinders with a capacity of 10l (Neophyr 225 ppm mol/mol, Neophyr 450 ppm mol/mol, Neophyr 1000 ppm mol/mol).
A 10-liter gas cylinder filled to 150 bar contains about 1,77 kg of gas.

Aluminum alloy cylinders have a white painted body and a turquoise-painted shoulder.
They are equipped with a stainless steel residual pressure valve with a specific ISO 5145 (2004) type outlet connector.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
SOL SpA
via Borgazzi 27,
20900 Monza (Italy)

Manufacturer
SOL S.p.A.
via Libertà 247
20900 Monza
Italy

This medicinal product is authorized in the Member States of the EEA under the following names:
Austria: Neophyr
Belgium: Neophyr
Bulgaria: Neophyr
Germany: Neophyr
Ireland: Neophyr
Italy: Neophyr
Luxemburg: Neophyr
The Netherlands: Neophyr
Romania: Neophyr
United Kingdom: Neophyr

This leaflet was last revised in 01/2016.

Formation of methaemoglobin
A large portion of nitric oxide for inhalation is absorbed systemically. The end medicinal products of nitric oxide that enter the systemic circulation are predominantly methaemoglobin and nitrate. The concentrations of methaemoglobin in the blood should be monitored, see section 4.2.

Formation of NO_2
NO_2 rapidly forms in gas mixtures containing nitric oxide and O_2, and nitric oxide may in this way cause airway inflammation and damage. The dose of nitric oxide should be reduced if the concentration of nitrogen dioxide exceeds 0.5 ppm.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. A clinically significant interaction with other medicinal products used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data.

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 may cause airway inflammation and damage. There are also animal data suggesting an increased susceptibility to airway infections upon exposure to low levels of NO_2. 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 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 Neophyr with regards to the risk of developing methaemoglobinaemia.

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

Prilocaine, whether administered as oral, parenteral, or topical formulations may cause methaemoglobinaemia. Care must be taken when Neophyr is given at the same time as medicinal products containing prilocaine.
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, steroids, surfactants and high frequency ventilation, 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.
The combined used with other vasodilators (e.g. sildenafil) is not extensively studied.
Available data suggest additive effects on central circulation, pulmonary artery pressure and right ventricular performance. Inhaled nitric oxide combination with other vasodilators acting by the cGMP or cAMP systems should be done with caution.
Although controlled studies have not been done, food interactions have not been noticed in clinical trials in patients with prolonged ambulatory administration.

4.6 Fertility, pregnancy and lactation

Fertility
No fertility studies have been performed.

Pregnancy
The effect of the administration of Neophyr in pregnant women is unknown. Animal studies are insufficient (see section 5.3).
The potential risk for humans is unknown. Neophyr should not be used during pregnancy unless clearly necessary, such as in situations of life support.

Lactation
It is not known whether Neophyr passes into human breast milk. The excretion of Neophyr in milk has not been studied in animals. Exposure to nitric oxide in humans during lactation should be avoided.

4.7 Effects on ability to drive and use machines

Infants and hospitalized patient: Not relevant.

4.8 Undesirable effects

Summary of safety profile
Abrupt discontinuation of the administration of inhaled nitric oxide may cause rebound reaction; decrease in oxygenation and increase in central pressure and subsequent decrease in systemic blood pressure. Rebound reaction is the most commonly adverse reaction in association with the clinical use of Neophyr. The rebound may be seen early as well as late during therapy.
In one clinical study (NINOS), treatment groups were similar with respect to the incidence and severity of intracranial haemorrhage, Grade IV haemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary haemorrhage, or gastrointestinal haemorrhage.

Tabulated list of adverse reactions
The adverse reactions listed are derived from CINGRI study, review of public domain scientific literature and post marketing safety surveillance (the table below shows adverse reactions that occurred in at least 5% of patients receiving iNO in the CINRGI study). Adverse reactions are listed according to MedDRA frequency convention: 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).

Description of selected adverse reactions
Inhaled nitric oxide therapy may cause an increase in methaemoglobin.

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

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel. +353 1 6764971
Fax. +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

System organ class	Very common	Common	Not known
Blood and lymphatic system disorders	Thrombocytopenia	-	-
Metabolism and nutrition disorders	Hypokalemia	-	-
Nervous system disorders	-	-	Headache*
Vascular diorders	Hypotension	-	Pulmonary artery pressure increased**, Hypotension**
Respiratory, thoracic and mediastinal disorders	Atelectasis	-	-
Hepatobiliary disorders	Hyperbilirubinemia	-	-
Investigations	-	-	Methaemo globin increased, Hypoxemia**

* Post-Marketing Safety Surveillance (PMSS) data, symptom experienced by personnel associated to accidental environmental exposure

** PMSS data, effects associated with acute withdrawal of the medicinal product, and dose errors associated with the delivery system. Rapid rebound reactions such as intensified pulmonary vasoconstriction after sudden withdrawal of inhaled nitric oxide therapy has been described, precipitating cardiovascular collapse.

4.9 Overdose

Overdose with Neophyr will be manifest by elevations in methaemoglobin and NO_2.
Elevated NO_2 may cause acute lung injury.
Elevations in methaemoglobinaemia reduce the oxygen delivery capacity of the circulation.
In clinical studies, NO_2 levels > 3 ppm or methaemoglobin levels > 7% were treated by reducing the dose of, or discontinuing, iNO.
Methaemoglobinaemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other respiratory system products, ATC code R07AX01.
Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the haeme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide produces selective pulmonary vasodilation.

iNO appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.
Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. In neonates with PPHN, iNO can improve oxygenation (as indicated by significant increases in PaO_2).
The efficacy of iNO has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies.
In the NINOS trial, 235 neonates with hypoxic respiratory failure were randomised to receive 100% O_2 with (n=114) or without (n=121) nitric oxide most with an initial concentration of 20 ppm with weaning as possible to lower doses with a median duration of exposure of 0 hours. The objective of this double-blind, randomised, placebo controlled trial was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO). Neonates with less than a full response at 20 ppm were evaluated for a response to 80 ppm nitric oxide or control gas.
The combined incidence of death and/or initiation of ECMO (the prospectively defined primary endpoint) showed a significant advantage for the nitric oxide treated group (46% vs. 64%, p=0.006). Data further suggested a lack of additional benefit for the higher dose of nitric oxide. The adverse events collected occurred at similar incidence rates in both groups.
Follow-up exams at 18-24 months of age were similar between the two groups with respect to mental, motor, audiologic, and neurologic evaluations.
In the CINRGI trial, 186 term- and near-term neonates with hypoxic respiratory failure were randomised to receive either iNO (n=97) or nitrogen gas (placebo; n=89) with an initial dose of 20 ppm weaning to 5 ppm in 4 to 24 hours with median duration of exposure of 44 hours. The prospectively defined primary endpoint was the receipt of ECMO. Significantly fewer neonates in the iNO group required ECMO compared to the control group (31% vs 57%, p<0.001). The iNO group had significantly improved oxygenation as measured by PaO_2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with , 2(2%) were withdrawn from study drug due to methaemoglobin levels >4%. The frequency and number of adverse events were similar in the two study groups.
In patients undergoing heart surgery, an increase in pulmonary artery pressure due to pulmonary vasoconstriction is frequently seen. Inhaled nitric oxide has been shown to selectively reduce pulmonary vascular resistance and reduce the increased pulmonary artery pressure. This may increase the right ventricular ejection fraction. These effects in turn lead to improved blood circulation and oxygenation in the pulmonary circulation.
In the INOT27 trial, 795 preterm infants (GA<29 weeks) with hypoxic respiratory failure were randomised to receive either iNO (n=395) in a dose of 5 ppm or nitrogen (placebo n=400), beginning within the first 24 hours of life and treated for at least 7 days, up to 21 days. The primary outcome, of the combined efficacy endpoints of death or BPD at 36 weeks GA, was not significantly different between groups, even with adjustment for gestational age as a covariate (p = 0.40), or with birth weight as a covariate (p = 0.41). The overall occurrence of intraventricular haemorrhage was 114 (28.9%) among the iNO treated as compared to 91 (22.9%) among the control neonates. The overall number of death at week 36 was slightly higher in the iNO group; 53/395 (13.4%) as compared to control 42/397 (10.6%). The INOT25 trial, studying the effects of iNO in hypoxic preterm neonates, did not show improvement in alive without BDP. No difference in the incidence of IVH or death was however observed in this study.
The BALLR1 study, also evaluating the effects of iNO in preterm neonates, but initiating iNO at 7 days and in a dose of 20 ppm, found a significant increase in neonates alive without BPD at gestational week 36, 121 (45% vs 95 (35.4%) p<0.028. No signs of any increase adverse effects was noted in this study.
Nitric oxide chemically reacts with oxygen to form nitrogen dioxide.
Nitric oxide has an unpaired electron, which makes the molecule reactive. In biological tissue, nitric oxide may form peroxynitrite with superoxide (O_2^-), an unstable compound which may cause tissue damage through further redox reactions. In addition, nitric oxide has affinity to metalloproteins and may also react with SH-groups in protein forming nitrosyl compounds. The clinical significance of the chemical reactivity of nitric oxide in tissue is unknown. Studies show that nitric oxide exhibits pulmonary pharmacodynamic effects at intra-airway concentrations as low as 1 ppm.
The European Medicines Agency has waived the obligation to submit the results of studies with iNO in all subsets of the paediatric population in persistent pulmonary hypertension and other pulmonary heart disease (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of nitric oxide has been studied in adults. Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with haemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhaemoglobin to produce methaemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhaemoglobin to transiently form nitrosylhaemoglobin, which is converted to nitrogen oxides and methaemoglobin upon exposure to oxygen.
Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhaemoglobin to produce methaemoglobin and nitrate.
Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methaemoglobin and nitrate.
Methaemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. Methaemoglobin concentrations increase during the first 8 hours of nitric oxide exposure. The mean methaemoglobin levels remained below 1% in the placebo group and in the 5 ppm and 20 ppm iNO groups, but reached approximately 5% in the 80 ppm iNO group. Methaemoglobin levels > 7% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methaemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients; but one patient did not exceed 7% until 40 hours.Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for > 70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

5.3 Preclinical safety data

Effects seen in single and repeat dose-toxicity studies in rodents were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Toxicity is related to anoxia resulting from elevated methaemoglobin levels.
No reproductive and developmental toxicity studies have been performed.
A battery of genotoxicity tests has demonstrated mutagenic potential of nitric oxide in some in vitro test systems and no clastogenic effect in the in vivo system. This is possibly related to the formation of mutagenic nitrosamines, DNA alterations or impairment of DNA repair mechanisms. A low incidence in uterine adenocarcinomas in rats following daily exposure to the recommended human dose for two years was tentatively considered treatment related. The significance of these findings for clinical 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 following materials should not be used or be present in any equipment/device(s) used in nitric oxide administration: Butylrubber, Polyamide and Polyurethane.

6.3 Shelf life

1 year (2l gas cylinder)
3 years (10l gas cylinder)

6.4 Special precautions for storage

All regulations concerning handling of pressurised cylinders must be followed.
Storage is supervised by the specialists at the hospital. Cylinders are to be stored in well-ventilated rooms or in ventilated sheds where they are protected from rain and direct sunlight.
The cylinders must be stored at a temperature between -10 and +50°C.
Protect the cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

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 medical department
The cylinder should be placed in an area with appropriate equipment to ensure that the cylinder is held vertically.

Transport of gas cylinders
The gas cylinders should be transported with appropriate material in order to protect them from the risk of shocks and falls.During inter- or within-hospital transfers of patients treated with Neophyr, the gas cylinders should be securely stowed away in order to hold the gas cylinders vertically and to avoid the risk of falls or untimely modifying output. Particular attention should be also turned to the fastening of the pressure regulator so as to avoid the risk of accidental failures.

Do not use Neophyr after the expiry date which is stated on the gas cylinder label. The expiry date refers to the last day of that month.

6.5 Nature and contents of container

Gas cylinders with a capacity of 2l.
A 2-liter gas cylinder filled to 150 bar contains about 0,35 kg of gas.
Or
Gas cylinders with a capacity of 10l.
A 10-liter gas cylinder filled to 150 bar contains about 1,77 kg of gas.
Aluminum alloy cylinders have a white painted body and a turquoise-painted shoulder.
They are equipped with a stainless steel residual pressure valve with a specific ISO 5145 (2004) type outlet connector.

6.6 Special precautions for disposal and other handling

All equipment, including connectors, tubing and circuits, used in the delivery of nitric oxide must be made of materials compatible with the gas.
From a corrosion point of view the supply system can be divided into two zones:
1) From the gas cylinder valve to the humidifier (dry gas) and
2) From the humidifier to outlet (moist gas which may contain NO_2).
Tests show that dry nitric oxide mixtures can be used with most materials. However, the presence of nitrogen dioxide and moisture creates an aggressive atmosphere. Among metallic construction materials, only stainless steel can be recommended. Tested polymers which can be used in nitric oxide administration systems include polyethylene (PE) and polypropylene (PP). Butyl rubber, polyamide, and polyurethane should not be used. Polytrifluorochloroethylene, hexafluoropropene-vinyliden copolymer and polytetrafluorethylene have been used extensively with pure nitric oxide and other corrosive gases. They were considered so inert that testing was not required.

To avoid any incidents, the following instructions must be strictly adhered to:
• check that the equipment is in working order before use.
• firmly secure the cylinders using chains or hooks in the rack to avoid any accidental falls
• do not use if the cylinder pressure is below 10 bar
• never open a valve abruptly
• do not handle a cylinder on which the valve is not protected by a bonnet cap
• use a specific ISO 5145 (2004) connector: n°29 specific NO/N_2 (100 ppm< NO < 1000 ppm) W30x2 15,2-20,8 DR
• at each new use, purge the pressure- reducer/flowmeter 3 times using the nitric oxide/nitrogen mixture
• do not attempt to repair a defective valve
• do not tighten the pressure-reducer/flowmeter using a gripper, otherwise the seal may be crushed and the administration device damaged
• evacuate exhaled gases outside (avoiding areas in which they may accumulate). Before use, it should be ensured that the room has the appropriate ventilation system for evacuating gases in the event of an accident or accidental leaks.
• as nitric oxide is colorless and odorless, it is recommended using a detection system in all rooms in which it is to be used or stored.
• personnel exposure limits (see section 4.2: Dosage and route of administration)

Instruction for cylinder disposal:
When the cylinder is empty, do not dispose of it. Empty cylinders will be collected by the supplier.

7. MARKETING AUTHORISATION HOLDER

SOL SpA
via Borgazzi 27,
20900 Monza (Italy)

8. MARKETING AUTHORISATION NUMBER(S)

Neophyr 225ppm: PA 1848/001/003
Neophyr 450ppm: PA 1848/001/002
Neophyr 1000ppm: PA1848/001/001

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12th April 2013

10. DATE OF REVISION OF THE TEXT

January 2016

Neophyr

Medicinal gas, compressed
Nitric oxide

IE_NEOPHYR_EP_2014-01

Neophyr, in conjunction with ventilatory support and other appropriate active substances, is indicated:

- *for the treatment of hypoxic newborn infants >=34 weeks gestation with clinical or echocardiographic evidence of pulmonary hypertension*
- *as part of the treatment of perioperative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.*

The risk of rebound effect and the precautions to take when discontinuing the treatment

In order to avoid the risk of rebound effect (worsening of oxygenation and increasing of pulmonary artery pressure) due to an excessively fast reduction of dosage of NO, the weaning from NO therapy should be slow and constantly monitored.
Neophyr dose should be reduced to 1 ppm for 30 minutes to one hour, keeping under strict control indicators of cardio-circulatory function (pulmonary artery pressure - PAP, central venous pressure - CVP, cardiac output - CO) and oxygenation (SpO_2).

Newborn
Attempts to wean Neophyr should be made after the ventilator support is substantially decreased or after 96 hours of therapy. When the decision is made to discontinue inhaled nitric oxide therapy, the dose should be reduced to 1 ppm for 30 minutes to one hour.
If there is no change in clinical parameters during administration of Neophyr at 1 ppm, the FiO_2 should be increased by 10 %, the Neophyr is discontinued, and the neonates monitored closely for signs of hypoxaemia.
If a worsening of clinical parameters occurs, Neophyr therapy should be resumed at 5 ppm and discontinuation of Neophyr therapy should be reconsidered after 12 to 24 hours.
Infants who cannot be weaned off Neophyr by 4 days should undergo careful diagnostic work-up for other diseases.

Adults
Attempts to wean Neophyr should be commenced as soon as the hemodynamics have stabilised in conjunction to weaning from ventilator and inotropic support.
The withdrawal of inhaled nitric oxide therapy should be performed in a stepwise manner.
The dose should be incrementally reduced to 1 ppm for 30 minutes with close observation of systemic and central pressure, and then turned off. Weaning should be attempted at least every 12 hours when the patient is stable on a low dose of Neophyr.

The risk of abrupt discontinuation of Neophyr therapy in the event of critical failure of the delivery system and how to prevent it

In order to prevent an abrupt discontinuation of Neophyr therapy because of critical failure of the delivery device, the device should possess the following technical features:

- be CE marked in compliance with 93/42/EEC Directive
- be equipped with 2 gas cylinders, one in use and one as back-up
- be equipped with an automatic switch-over system, which allows automatic switch on back-up cylinder when the first one is empty
- be equipped with clearly visible pressure gauges, so clinical staff can be immediately aware of empty cylinder
- In case of 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.
- Neophyr 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.

Additionally, a CE marked according to 93/42/EEC Directive pressure regulator with integrated flowmeter should be available as emergency unit, in order to have an emergency delivery device.

The monitoring of Methaemoglobin level

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

Newborns and infants have diminished levels of MetHb reductase activity compared to adults; therefore the methaemoglobin concentrations in the blood must be monitored.
The level of MetHb must be measured within 1 hour of the start of Neophyr therapy using an analyser that correctly distinguishes the fetal hemoglobin from the MetHb.
If the MetHb is > 2.5%, the dose of Neophyr will have to be reduced 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.

In adults undergoing heart surgery, methaemoglobin level should be measured within one hour of the initiation of Neophyr therapy. If the fraction of methaemoglobin rises to a level that potentially compromises adequate oxygen delivery, the Neophyr dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered.

The monitoring of NO_2 formation

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 tract;
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 Neophyr and/or FiO_2 must be reduced.
If there is an unexpected change in Neophyr concentration, the delivery system should be assessed for malfunction and the analyser should be recalibrated.

NO_2 monitoring during the therapy must be always carried out: this is the only way to guarantee that NO_2 level is kept as lowest as possible.
NO delivering device should be natively equipped with NO_2 continuous monitoring system, otherwise an additional NO_2 monitor must be present.
In order to minimise the duration of contact between NO and air/oxygen, minimizing therefore the production of NO_2, the following measurements should be applied:

- NO injection line should be connected to inspiratory limb, after the humidifier (where present)
- distance between NO injection point and gas sampling line going into monitor should be, when possible, longer than 60 centimetres and shorter than 90 centimetres. This distance permits an optimal dilution of NO but keeps the formation of NO_2 at minimal level by reducing contact time between NO and oxygen.

The potential risk of bleeding and haemostasis disorders

Tests 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 bleeding complications observed in random controlled trials on new-borns.
A monitoring of the bleeding times is recommended during the course of Neophyr 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.

The potential risks if used in combination with other vasodilators which act on cGMP or cAMP

The combined used with other vasodilators (e.g. sildenafil) is not extensively studied. Available data suggest additive effects on central circulation, pulmonary artery pressure and right ventricular performance. Inhaled nitric oxide combination with other vasodilators acting by the cGMP or cAMP systems should be done with caution.