ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

INOmax 400 ppm mol/mol medicinal gas, compressed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitric oxide (NO) 400 ppm mol/mol.

A 2 litre gas cylinder filled at 155 bar absolute brings 307 litres of gas under pressure of 1 bar at 15°C.
A 10 litre gas cylinder filled at 155 bar absolute brings 1535 litres of gas under pressure of 1 bar at 15°C.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Medicinal gas, compressed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INOmax, 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 peri- and post-operative 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. INOmax should only be delivered according to a neonatologist's prescription.

INOmax should be used in ventilated newborn infants expected to require support >24 hours. INOmax 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. INOmax should only be delivered according to an anaesthetist's or intensive care physician's prescription.

Posology

Persistent Pulmonary Hypertension in the Newborn (PPHN)
The maximum recommended dose of INOmax is 20 ppm and this dose should not be exceeded. In the pivotal clinical trials, the starting dose was 20 ppm. Starting as soon as possible and within 4-24 hours of therapy, the dose should be weaned to 5 ppm provided that arterial oxygenation is adequate at this lower dose. Inhaled nitric oxide therapy should be maintained at 5 ppm until there is improvement in the neonate's oxygenation such that the FiO_2 (fraction of inspired oxygen) < 0.60.

Treatment can be maintained up to 96 hours or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy. The duration of therapy is variable, but typically less than four days. In cases of failure to respond to inhaled nitric oxide, see section 4.4.

Weaning
Attempts to wean INOmax 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 INOmax at 1 ppm, the FiO_2 should be increased by 10 %, the INOmax is discontinued, and the neonates monitored closely for signs of hypoxaemia. If oxygenation falls >20 %, INOmax therapy should be resumed at 5 ppm and discontinuation of INOmax therapy should be reconsidered after 12 to 24 hours. Infants who cannot be weaned off INOmax by 4 days should undergo careful diagnostic work-up for other diseases.

Pulmonary hypertension associated with heart surgery
INOmax should be used only after conservative support has been optimised. In clinical trials INOmax has been given in addition to other standard treatment regimes in the peri-operative setting, including inotropic and vasoactive medicinal products. INOmax should be administered under close monitoring of haemodynamics and oxygenation.

Newborn infants, infants and toddlers, children and adolescents, ages 0-17 years
The starting dose of inhaled nitric oxide is 10 ppm(part 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 (part per million) of inhaled gas. The dose may be increased up to 40 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.

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 peri-operative 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 peri-operative setting, but common treatment times are 24 -48 hours.

Weaning
Attempts to wean INOmax should be commenced as soon as the haemodynamics 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 INOmax.

Too rapid weaning from inhaled nitric oxide therapy carries the risk of a re-bound increase in pulmonary artery pressure with subsequent circulatory instability.

Paediatric population
The safety and efficacy of INOmax in premature infants less than 34 weeks of gestation has not yet been established. Currently available data are described in section 5.1 but no recommendation or posology can be made.

Method of administration
For endotracheopulmonary use.

Nitric oxide is delivered to the patient via mechanical ventilation after dilution with an oxygen/air mixture using an approved (CE-marked) nitric oxide delivery system. Before initiation of therapy, during set-up, secure that the device setting is in agreement with the cylinder gas concentration.

The delivery system must provide a constant inhaled INOmax concentration irrespective of the ventilator. With a continuous flow neonatal ventilator, this may be achieved by infusing a low flow of INOmax into the inspiratory limb of the ventilator circuit. Intermittent flow neonatal ventilation may be associated with spikes in nitric oxide concentration. The nitric oxide delivery system for intermittent flow ventilation should be adequate to avoid spikes in nitric oxide concentration.

The inspired INOmax concentration must be measured continuously in the inspiratory limb of the circuit near the patient. The nitrogen dioxide (NO_2) concentration and FiO_2 must also be measured at the same site using calibrated and approved (CE-marked) monitoring equipment. For patient safety, appropriate alarms must be set for INOmax (± 2 ppm of the prescribed dose), NO_2 (1 ppm), and FiO_2 (± 0.05). The INOmax gas cylinder pressure must be displayed to allow timely gas cylinder replacement without inadvertent loss of therapy and backup gas cylinders must be available to provide timely replacement. INOmax therapy must be available for manual ventilation such as suctioning, patient transport, and resuscitation.

In the event of a system failure or a wall-outlet power failure, a backup battery power supply and reserve nitric oxide delivery system should be available. The power supply for the monitoring equipment should be independent of the delivery device function.

The upper limit of exposure (mean exposure) to nitric oxide for personnel defined by worker's legislation is 25 ppm for 8 hours (30 mg/m^3) in most countries and the corresponding limit for NO_2 is 2-3 ppm (4-6 mg/m^3).

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

Monitoring formation of methaemoglobin (MetHb)
Neonates and infants are known to have diminished MetHb reductase activity compared to adults. Methaemoglobin level should be measured within one hour after initiation of INOmax therapy, using an analyser which can reliably distinguish between foetal haemoglobin and methaemoglobin. If it is > 2.5 %, the INOmax dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered. Although it is unusual for the methaemoglobin level to increase significantly if the first level is low, it is prudent to repeat methaemoglobin measurements every one to two days.

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

Monitoring formation of nitrogen dioxide (NO_2)
Immediately prior to each patient initiation, proper procedure must be applied to purge the system of NO_2. The NO_2 concentration should be maintained as low as possible and always < 0.5 ppm. If the NO_2 is > 0.5 ppm, the delivery system should be assessed for malfunction, the NO_2 analyser should be recalibrated, and the INOmax and/or FiO_2 should be reduced if possible. If there is an unexpected change in INOmax concentration, the delivery system should be assessed for malfunction and the analyser should be recalibrated.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Neonates known to be dependent on right-to-left, or significant left-to-right, shunting of blood.

4.4 Special warnings and precautions for use

Inadequate response
If it is judged that clinical response is inadequate at 4-6 hours after starting INOmax, the following should be considered.
For patients who are to be referred to another hospital, to prevent worsening of their condition on acute discontinuation of INOmax, the availability of nitric oxide during transport should be assured. Rescue, such as Extra Corporeal Membrane Oxygenation (ECMO) where available, should be considered based on continued deterioration or failure to improve, defined by criteria based on local circumstances.

Special patient populations
In clinical trials, no efficacy has been demonstrated with the use of inhaled nitric oxide in patients with congenital diaphragmatic hernia.

Treatment with inhaled nitric oxide might aggravate cardiac insufficiency in a situation with left-to-right shunting. This is due to unwanted pulmonary vasodilation caused by inhaled nitric oxide, resulting in a further increase of already existing pulmonary hyperperfusion thus potentially giving raise to forward or backward failure. It, therefore, is recommended that prior to the administration of nitric oxide, pulmonary artery catheterisation or echocardiographic examination of central haemodynamics be performed. 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).

Discontinuation of therapy
The INOmax 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 INOmax. 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.

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.

Effects on platelets
Animal models have shown that nitric oxide may interact with haemostasis, resulting in an increased bleeding time. Data in adult humans are conflicting, and there has been no increase in bleeding complications in randomised controlled trials in term and near-term neonates with hypoxic respiratory failure.

Regular monitoring of haemostasis and measurement of bleeding time is recommended during the administration of INOmax for more than 24 hours to patients with functional or quantitative platelet anomalies, a low coagulation factor or receiving anticoagulation treatment.

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. There may be an additive effect with INOmax on the risk of developing methaemoglobinemia with nitric oxide donor substances, including sodium nitroprusside and nitroglycerin. INOmax has been safely administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation.

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.

There is an increased risk of methaemoglobin formation if substances with a known tendency to increase methaemoglobin concentrations are administered concomitantly with nitric oxide (e.g. alkyl nitrates and sulphonamides). Substances known to cause increased methaemoglobin levels should thus be used with caution during therapy with inhaled nitric oxide. Prilocaine, whether administered as oral, parenteral, or topical formulations may cause methaemoglobinaemia. Care must be taken when INOmax is given at the same time as medicinal products containing prilocaine.

In the presence of oxygen, nitric oxide is rapidly oxidised to derivatives which are toxic to the bronchial epithelium and alveolo-capillary membrane. Nitrogen dioxide (NO_2) is the main substance 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 treatment with nitric oxide, the NO_2 concentration should be < 0.5 ppm in the nitric oxide dose range < 20 ppm. If at any time the NO_2 concentration exceeds 1 ppm, the nitric oxide dose should immediately be reduced. See section 4.2 for information on monitoring for NO_2.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of nitric oxide in pregnant women. The potential risk for humans is unknown.

It is unknown whether nitric oxide is excreted in human milk.

INOmax should not be used during pregnancy or breastfeeding.

No fertility studies have been performed.

4.7 Effects on ability to drive and use machines

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 INOmax. 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 table below presents adverse reactions (ADRs) that have been reported with the use of INOmax from either the CINRGI trial of 212 neonates or post marketing experience in neonates (≤1 months of age)). The displayed frequency categories use the following 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).

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders	Thrombo-cytopenia[a]	-	Methaemoglobinaemia[a]	-	-	-
Cardiac disorders	-	-	-	-	-	Bradycardia[b] (following abrupt discontinuation of therapy)
Vascular disorders	-	Hypotension[a,b,d]	-	-	-	-
Respiratory, thoracic and mediastinal disorders	-	Atelectasis[a]	-	-	-	Hypoxia[b,d] Dyspnoea[c] Chest Discomfort[c] Dry throat[c]
Nervous system disorders	-	-	-	-	-	Headache[c] Dizziness[c]

a: Identified from the clinical trial
b: Identified from Post Marketing experience
c: Identified from Post-Marketing experience, experienced by healthcare personnel following accidental exposure
d: Post Marketing Safety Surveillance (PMSS) data, effects associated with acute withdrawal of the medicinal product, and /or delivery system failures. Rapid rebound reactions such as intensified pulmonary vasoconstriction and hypoxia after sudden withdrawal of inhaled nitric oxide therapy has been described, precipitating cardiovascular collapse.

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 the national reporting system listed in Appendix V

4.9 Overdose

Overdose with INOmax 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, INOmax.

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.
INOmax 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, INOmax can improve oxygenation (as indicated by significant increases in PaO_2).

The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of aetiologies.

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 40 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 and without lung hypoplasia were randomised to receive either INOmax (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 INOmax group required ECMO compared to the control group (31 % vs. 57 %, $p<0.001$). The INOmax 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 INOmax, 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 vaso-constriction 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 INOmax (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 BPD. 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 were 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 INOmax 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 INOmax groups, but reached approximately 5 % in the 80 ppm INOmax 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 in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Acute toxicity is related to anoxia resulting from elevated methaemoglobin levels.

Nitric oxide is genotoxic in some test systems. No evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 20 h/day for up to two years. Higher exposures have not been investigated.

No reproduction toxicity studies have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nitrogen

6.2 Incompatibilities

In the presence of oxygen NO rapidly forms NO_2, see section 4.5.

6.3 Shelf life

3 years

6.4 Special precautions for storage

All regulations concerning handling of pressure vessels must be followed.

Store gas cylinders indoors in well-ventilated rooms or outdoors in ventilated sheds where they are protected from rain and direct sunlight.

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

Storage in the pharmacy department
The gas cylinders should be stored in an airy, clean and locked place, for storage of medicinal gas only. Inside this place, a separate premise should be dedicated to the storage of nitric oxide gas cylinders.

Storage in the medical department
The gas cylinder should be put in an equipped site with appropriate material in order to hold the gas cylinder vertically.

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

6.5 Nature and contents of container

Pack sizes:

A 2 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a standard valve hand-wheel.

A 2 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a INOmeter device equipped valve hand-wheel.

A 10 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a standard valve hand-wheel.

A 10 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a INOmeter device equipped valve hand-wheel.

6.6 Special precautions for disposal and other handling

Instructions for use/handling INOmax
When connecting an INOmax cylinder to the delivery system, always secure that the cylinder concentration is of the same concentration for which the system is configured.

In order to avoid all incidents, the following instructions should be absolutely respected.
- the good condition of the material should be checked before use
- the gas cylinders should be fixedly stowed away in order to avoid untimely fall
- the valve should be fully open when used but not be opened with violence
- a defective valve should neither be used nor be repaired. Return to distributor / manufacturer
- a gas cylinder whose valve is not protected by a cap or a shell should not be used
- a specific connection, with a 30 mm thread which is designated for medical use, complying with ISO 5145 and a pressure regulator which admits a pressure at least equal to 1.5 the maximum operating pressure (155 bar) of the gas cylinder should be used
- the pressure regulator should be purged by the nitrogen-nitric oxide mixture before each new use in order to preclude nitrogen dioxide inhalation
- the pressure regulator should not be tightened with pliers, at the risk of crushing the gasket

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 polytetraflourethylene have been used extensively with pure nitric oxide and other corrosive gases. They were considered so inert that testing was not required.

The installation of a nitric oxide pipeline system with supply station of gas cylinders, fixed network and terminal units is forbidden.

There is in general no need for scavenging of excess gas, the work place ambient air quality should however be considered and trace concentrations of NO or NO_2/NOx must not exceed set national occupational exposure limits. Accidental exposure to INOmax in hospital staff has been associated with adverse events (see section 4.8).

Cylinders equipped with a standard valve hand-wheel cannot be used with the INOmax DSIR delivery system.

Instruction for disposal of gas cylinder
When the gas cylinder is empty, it should not be discarded. Empty gas cylinders will be collected by the supplier.

7. MARKETING AUTHORISATION HOLDER

Linde Healthcare AB
Rättarvägen 3
169 68 Solna
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/194/001, EU/1/01/194/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01/08/2001
Date of last renewal: 01/06/2006

10. DATE OF REVISION OF THE TEXT

MM/YYYY

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

1. NAME OF THE MEDICINAL PRODUCT

INOmax 800 ppm mol/mol medicinal gas, compressed

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitric oxide (NO) 800 ppm mol/mol.

A 2 litre gas cylinder filled at 155 bar absolute brings 307 litres of gas under pressure of 1 bar at 15°C.
A 10 litre gas cylinder filled at 155 bar absolute brings 1535 litres of gas under pressure of 1 bar at 15°C.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Medicinal gas, compressed.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INOmax, 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 peri- and post-operative 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. INOmax should only be delivered according to a neonatologist's prescription.

INOmax should be used in ventilated newborn infants expected to require support >24 hours. INOmax 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. INOmax should only be delivered according to an anaesthetist's or intensive care physician's prescription.

Posology
Persistent Pulmonary Hypertension in the Newborn (PPHN)

The maximum recommended dose of INOmax is 20 ppm and this dose should not be exceeded. In the pivotal clinical trials, the starting dose was 20 ppm. Starting as soon as possible and within 4-24 hours of therapy, the dose should be weaned to 5 ppm provided that arterial oxygenation is adequate at this lower dose. Inhaled nitric oxide therapy should be maintained at 5 ppm until there is improvement in the neonate's oxygenation such that the FiO_2 (fraction of inspired oxygen) < 0.60.

Treatment can be maintained up to 96 hours or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy. The duration of therapy is variable, but typically less than four days. In cases of failure to respond to inhaled nitric oxide, see section 4.4.

Weaning
Attempts to wean INOmax 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 INOmax at 1 ppm, the FiO_2 should be increased by 10 %, the INOmax is discontinued, and the neonates monitored closely for signs of hypoxaemia. If oxygenation falls >20 %, INOmax therapy should be resumed at 5 ppm and discontinuation of INOmax therapy should be reconsidered after 12 to 24 hours. Infants who cannot be weaned off INOmax by 4 days should undergo careful diagnostic work-up for other diseases.

Pulmonary hypertension associated with heart surgery
INOmax should be used only after conservative support has been optimised. In clinical trials INOmax has been given in addition to other standard treatment regimes in the peri-operative setting, including inotropic and vasoactive medicinal products. INOmax should be administered under close monitoring of haemodynamics and oxygenation.

Newborn infants, infants and toddlers, children and adolescents, ages 0-17 years
The starting dose of inhaled nitric oxide is 10 ppm(part 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 (part per million) of inhaled gas. The dose may be increased up to 40 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.

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 peri-operative 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 peri-operative setting, but common treatment times are 24 -48 hours.

Weaning
Attempts to wean INOmax should be commenced as soon as the haemodynamics 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 INOmax.

Too rapid weaning from inhaled nitric oxide therapy carries the risk of a re-bound increase in pulmonary artery pressure with subsequent circulatory instability.

Paediatric population
The safety and efficacy of INOmax in premature infants less than 34 weeks of gestation has not yet been established. Currently available data are described in section 5.1 but no recommendation or posology can be made.

Method of administration
For endotracheopulmonary use.

Nitric oxide is delivered to the patient via mechanical ventilation after dilution with an oxygen/air mixture using an approved (CE-marked) nitric oxide delivery system. Before initiation of therapy, during set-up, secure that the device setting is in agreement with the cylinder gas concentration.

The delivery system must provide a constant inhaled INOmax concentration irrespective of the ventilator. With a continuous flow neonatal ventilator, this may be achieved by infusing a low flow of INOmax into the inspiratory limb of the ventilator circuit. Intermittent flow neonatal ventilation may be associated with spikes in nitric oxide concentration. The nitric oxide delivery system for intermittent flow ventilation should be adequate to avoid spikes in nitric oxide concentration.

The inspired INOmax concentration must be measured continuously in the inspiratory limb of the circuit near the patient. The nitrogen dioxide (NO_2) concentration and FiO_2 must also be measured at the same site using calibrated and approved (CE-marked) monitoring equipment. For patient safety, appropriate alarms must be set for INOmax (± 2 ppm of the prescribed dose), NO_2 (1 ppm), and FiO_2 (± 0.05). The INOmax gas cylinder pressure must be displayed to allow timely gas cylinder replacement without inadvertent loss of therapy and backup gas cylinders must be available to provide timely replacement. INOmax therapy must be available for manual ventilation such as suctioning, patient transport, and resuscitation.

In the event of a system failure or a wall-outlet power failure, a backup battery power supply and reserve nitric oxide delivery system should be available. The power supply for the monitoring equipment should be independent of the delivery device function.

The upper limit of exposure (mean exposure) to nitric oxide for personnel defined by worker's legislation is 25 ppm for 8 hours (30 mg/m^3) in most countries and the corresponding limit for NO_2 is 2-3 ppm (4-6 mg/m^3).

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

Monitoring formation of methaemoglobin (MetHb)
Neonates and infants are known to have diminished MetHb reductase activity compared to adults. Methaemoglobin level should be measured within one hour after initiation of INOmax therapy, using an analyser which can reliably distinguish between foetal haemoglobin and methaemoglobin. If it is > 2.5 %, the INOmax dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered. Although it is unusual for the methaemoglobin level to increase significantly if the first level is low, it is prudent to repeat methaemoglobin measurements every one to two days.

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

Monitoring formation of nitrogen dioxide (NO_2)
Immediately prior to each patient initiation, proper procedure must be applied to purge the system of NO_2. The NO_2 concentration should be maintained as low as possible and always < 0.5 ppm. If the NO_2 is > 0.5 ppm, the delivery system should be assessed for malfunction, the NO_2 analyser should be recalibrated, and the INOmax and/or FiO_2 should be reduced if possible. If there is an unexpected change in INOmax concentration, the delivery system should be assessed for malfunction and the analyser should be recalibrated.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Neonates known to be dependent on right-to-left, or significant left-to-right, shunting of blood.

4.4 Special warnings and precautions for use

Inadequate response
If it is judged that clinical response is inadequate at 4-6 hours after starting INOmax, the following should be considered.
For patients who are to be referred to another hospital, to prevent worsening of their condition on acute discontinuation of INOmax, the availability of nitric oxide during transport should be assured. Rescue, such as Extra Corporeal Membrane Oxygenation (ECMO) where available, should be considered based on continued deterioration or failure to improve, defined by criteria based on local circumstances.

Special patient populations
In clinical trials, no efficacy has been demonstrated with the use of inhaled nitric oxide in patients with congenital diaphragmatic hernia.

Treatment with inhaled nitric oxide might aggravate cardiac insufficiency in a situation with left-to-right shunting. This is due to unwanted pulmonary vasodilation caused by inhaled nitric oxide, resulting in a further increase of already existing pulmonary hyperperfusion thus potentially giving raise to forward or backward failure. It, therefore, is recommended that prior to the administration of nitric oxide, pulmonary artery catheterisation or echocardiographic examination of central haemodynamics be performed. 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).

Discontinuation of therapy
The INOmax 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 INOmax. 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.

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.

Effects on platelets
Animal models have shown that nitric oxide may interact with haemostasis, resulting in an increased bleeding time. Data in adult humans are conflicting, and there has been no increase in bleeding complications in randomised controlled trials in term and near-term neonates with hypoxic respiratory failure.

Regular monitoring of haemostasis and measurement of bleeding time is recommended during the administration of INOmax for more than 24 hours to patients with functional or quantitative platelet anomalies, a low coagulation factor or receiving anticoagulation treatment.

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. There may be an additive effect with INOmax on the risk of developing methaemoglobinemia with nitric oxide donor substances, including sodium nitroprusside and nitroglycerin. INOmax has been safely administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation.

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.

There is an increased risk of methaemoglobin formation if substances with a known tendency to increase methaemoglobin concentrations are administered concomitantly with nitric oxide (e.g. alkyl nitrates and sulphonamides). Substances known to cause increased methaemoglobin levels should thus be used with caution during therapy with inhaled nitric oxide. Prilocaine, whether administered as oral, parenteral, or topical formulations may cause methaemoglobinaemia. Care must be taken when INOmax is given at the same time as medicinal products containing prilocaine.

In the presence of oxygen, nitric oxide is rapidly oxidised to derivatives which are toxic to the bronchial epithelium and alveolo-capillary membrane. Nitrogen dioxide (NO_2) is the main substance 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 treatment with nitric oxide, the NO_2 concentration should be < 0.5 ppm in the nitric oxide dose range < 20 ppm. If at any time the NO_2 concentration exceeds 1 ppm, the nitric oxide dose should immediately be reduced. See section 4.2 for information on monitoring for NO_2.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of nitric oxide in pregnant women. The potential risk for humans is unknown.

It is unknown whether nitric oxide is excreted in human milk.

INOmax should not be used during pregnancy or breastfeeding.

No fertility studies have been performed.

4.7 Effects on ability to drive and use machines

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 INOmax. 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 table below presents adverse reactions (ADRs) that have been reported with the use of INOmax from either the CINRGI trial of 212 neonates or post marketing experience in neonates (≤1 months of age). The displayed frequency categories use the following 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).

System organ class	Very common	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders	Thrombo-cytopenia[a]	-	Methaemoglobinaemia[a]	-	-	-
Cardiac disorders	-	-	-	-	-	Bradycardia[b] (following abrupt discontinuation of therapy)
Vascular disorders	-	Hypotension[a,b,d]	-	-	-	-
Respiratory, thoracic and mediastinal disorders	-	Atelectasis[a]	-	-	-	Hypoxia[b,d] Dyspnoea[c] Chest Discomfort[c] Dry throat[c]
Nervous system disorders	-	-	-	-	-	Headache[c] Dizziness[c]

a: Identified from the clinical trial
b: Identified from Post-Marketing experience
c: Identified from Post-Marketing experience, experienced by healthcare personnel following accidental exposure
d: Post Marketing Safety Surveillance (PMSS) data, effects associated with acute withdrawal of the medicinal product, and /or delivery system failures. Rapid rebound reactions such as intensified pulmonary vasoconstriction and hypoxia after sudden withdrawal of inhaled nitric oxide therapy has been described, precipitating cardiovascular collapse.

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 the national reporting system listed in Appendix V

4.9 Overdose

Overdose with INOmax 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, INOmax.

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.
INOmax 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, INOmax can improve oxygenation (as indicated by significant increases in PaO_2).

The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of aetiologies.

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 40 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 and without lung hypoplasia were randomised to receive either INOmax (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 INOmax group required ECMO compared to the control group (31 % vs. 57 %, $p<0.001$). The INOmax 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 INOmax, 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 vaso-constriction 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 INOmax (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 BPD. 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 were 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 INOmax 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 INOmax groups, but reached approximately 5 % in the 80 ppm INOmax 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 in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Acute toxicity is related to anoxia resulting from elevated methaemoglobin levels.

Nitric oxide is genotoxic in some test systems.. No evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 20 h/day for up to two years. Higher exposures have not been investigated.

No reproduction toxicity studies have been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Nitrogen

6.2 Incompatibilities

In the presence of oxygen NO rapidly forms NO_2, see section 4.5.

6.3 Shelf life

3 years

6.4 Special precautions for storage

All regulations concerning handling of pressure vessels must be followed.

Store gas cylinders indoors in well-ventilated rooms or outdoors in ventilated sheds where they are protected from rain and direct sunlight.

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

Storage in the pharmacy department
The gas cylinders should be stored in an airy, clean and locked place, for storage of medicinal gas only. Inside this place, a separate premise should be dedicated to the storage of nitric oxide gas cylinders.

Storage in the medical department
The gas cylinder should be put in an equipped site with appropriate material in order to hold the gas cylinder vertically.

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

6.5 Nature and contents of container

Pack sizes:

A 2 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a standard valve hand-wheel.

A 2 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a INOmeter device equipped valve hand-wheel.

A 10 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a standard valve hand-wheel.

A 10 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a INOmeter device equipped valve hand-wheel.

6.6 Special precautions for disposal and other handling

Instructions for use/handling INOmax
When connecting an INOmax cylinder to the delivery system, always secure that the cylinder concentration is of the same concentration for which the system is configured.

In order to avoid all incidents, the following instructions should be absolutely respected.
- the good condition of the material should be checked before use
- the gas cylinders should be fixedly stowed away in order to avoid untimely fall
- the valve should be fully open when used but not be opened with violence
- a defective valve should neither be used nor be repaired. Return to distributor / manufacturer
- a gas cylinder whose valve is not protected by a cap or a shell should not be used
- a specific connection, with a 30 mm thread which is designated for medical use, complying with ISO 5145 and a pressure regulator which admits a pressure at least equal to 1.5 the maximum operating pressure (155 bar) of the gas cylinder should be used
- the pressure regulator should be purged by the nitrogen-nitric oxide mixture before each new use in order to preclude nitrogen dioxide inhalation
- the pressure regulator should not be tightened with pliers, at the risk of crushing the gasket

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 polytetraflourethylene have been used extensively with pure nitric oxide and other corrosive gases. They were considered so inert that testing was not required.

The installation of a nitric oxide pipeline system with supply station of gas cylinders, fixed network and terminal units is forbidden.

There is in general no need for scavenging of excess gas, the work place ambient air quality should however be considered and trace concentrations of NO or NO_2/NOx must not exceed set national occupational exposure limits. Accidental exposure to INOmax in hospital staff has been associated with adverse events (see section 4.8).

Cylinders equipped with a standard valve hand-wheel cannot be used with the INOmax DSIR delivery system.

Instruction for disposal of gas cylinder
When the gas cylinder is empty, it should not be discarded. Empty gas cylinders will be collected by the supplier.

7. MARKETING AUTHORISATION HOLDER

Linde Healthcare AB
Rättarvägen 3
169 68 Solna
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/194/003, EU/1/01/194/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01/08/2001
Date of last renewal: 01/06/2006

10. DATE OF REVISION OF THE TEXT

MM/YYYY

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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Linde France
Zone Industrielle de Limay Porcheville
3 avenue Ozanne
78440 Porcheville
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic Safety Update Reports
The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time

- **Additional risk minimisation measures**

Prior to launch of the new indication of the product in each Member State, the Marketing Authorisation Holder shall agree the content and format of the educational material with the national competent authority.

The Marketing Authorisation Holder (MAH) should ensure that, at launch of the new indication, all Healthcare Professionals who are expected to use and/or prescribe INOmax as part of the treatment of peri- or post- operative pulmonary hypertension in adults and children in conjunction to heart surgery are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet for INOmax

- Educational material for Healthcare Professionals

The educational material should include information on the following key elements:

- The risk of rebound effect and the precautions to take when discontinuing the treatment
- The risk of abrupt discontinuation of INOmax therapy in the event of critical failure of the delivery system and how to prevent it
- The monitoring of Methaemoglobin level
- The monitoring of NO_2 formation
- The potential risk of bleeding and haemostasis disorders
- The potential risks if used in combination with other vasodilators which act on cGMP or cAMP

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

2 litres gas cylinder

1. NAME OF THE MEDICINAL PRODUCT

INOmax 400 ppm mol/mol medicinal gas, compressed
Nitric oxide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Nitric oxide (NO) 400 ppm mol/mol.

3. LIST OF EXCIPIENTS

Also contains nitrogen.

4. PHARMACEUTICAL FORM AND CONTENTS

Medicinal gas, compressed
A 2 litre gas cylinder filled at 155 bar absolute brings 307 litres of gas under pressure of 1 bar at 15ºC.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Endotracheopulmonary use.

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Ensure that the parent or guardian has read and is aware of the indications and cautions presented in the package leaflet prior to administration to their baby.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

All regulations concerning handling of pressure vessels must be followed.

Store gas cylinders vertically in well-ventilated rooms.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Do not discard used gas cylinders. All gas cylinders should be returned to the supplier for disposal.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Linde Healthcare AB
Rättarvägen 3
169 68 Solna
Sweden

12. NUMBER(S) IN THE COMMUNITY REGISTER OF MEDICINAL PRODUCTS

EU/1/01/194/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

10 litres gas cylinder

1. NAME OF THE MEDICINAL PRODUCT

INOmax 400 ppm mol/mol medicinal gas, compressed
Nitric oxide.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Nitric oxide (NO) 400 ppm mol/mol.

3. LIST OF EXCIPIENTS

Also contains nitrogen.

4. PHARMACEUTICAL FORM AND CONTENTS

Medicinal gas, compressed
A 10 litre gas cylinder filled at 155 bar absolute brings 1535 litres of gas under pressure of 1 bar at 15ºC.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Endotracheopulmonary use

Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Ensure that the parent or guardian has read and is aware of the indications and cautions presented in the package leaflet prior to administration to their baby.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

All regulations concerning handling of pressure vessels must be followed.

Store gas cylinders vertically in well-ventilated rooms.
Protect the gas cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

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13. BATCH NUMBER

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15. INSTRUCTIONS ON USE

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18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

2 litres gas cylinder

1. NAME OF THE MEDICINAL PRODUCT

INOmax 800 ppm mol/mol medicinal gas, compressed
Nitric oxide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Nitric oxide (NO) 800 ppm mol/mol.

3. LIST OF EXCIPIENTS

Also contains nitrogen.

4. PHARMACEUTICAL FORM AND CONTENTS

Medicinal gas, compressed
A 2 litre gas cylinder filled at 155 bar absolute brings 307 litres of gas under pressure of 1 bar at 15ºC.

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15. INSTRUCTIONS ON USE

16. BRAILLE

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17. UNIQUE IDENTIFIER – 2D BARCODE

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18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

10 litres gas cylinder

1. NAME OF THE MEDICINAL PRODUCT

INOmax 800 ppm mol/mol medicinal gas, compressed
Nitric oxide.

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Also contains nitrogen.

4. PHARMACEUTICAL FORM AND CONTENTS

Medicinal gas, compressed
A 10 litre gas cylinder filled at 155 bar absolute brings 1535 litres of gas under pressure of 1 bar at 15°C.

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Endotracheopulmonary use

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7. OTHER SPECIAL WARNING(S), IF NECESSARY

Ensure that the parent or guardian has read and is aware of the indications and cautions presented in the package leaflet prior to administration to their baby.

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9. SPECIAL STORAGE CONDITIONS

All regulations concerning handling of pressure vessels must be followed.

Store gas cylinders vertically in well-ventilated rooms.
Protect the gas cylinders from shocks, falls, oxidising and flammable materials, moisture, sources of heat or ignition.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Do not discard used gas cylinders. All gas cylinders should be returned to the supplier for disposal.

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15. INSTRUCTIONS ON USE

16. BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

INOmax 400 ppm mol/mol medicinal gas, compressed
Nitric oxide

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
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4

What is in this leaflet:

1. What INOmax is and what it is used for

INOmax contains nitric oxide, a gas used for the treatment of

- 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, which may help to increase the amount of oxygen that reaches the blood.

2. What you need to know before you begin a treatment with INOmax

Do not use INOmax

- If you (as the patient) or your child (as the patient) are allergic (hypersensitive) to nitric oxide or any other ingredients of INOmax (see section 6 'further information' where the full list of ingredients is provided).

- If you have been told that you (as the patient) or your child (as the patient) have an abnormal circulation within the heart.

Warnings and precautions

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 INOmax 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 oxide 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

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

Other medicines and INOmax

The doctor will decide when to treat you or your child with INOmax and with other medicines and will carefully supervise the treatment.

Please tell your doctor if you (as the patient) or your child (as the patient) are taking or have recently taken or used any other medicines, including medicines obtained without a prescription.

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 and breastfeeding

INOmax is not recommended for use during pregnancy and breastfeeding.
Tell your doctor before treatment with INOmax if you are pregnant, think you could be pregnant or are breastfeeding

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Not relevant.

INOmax contains Nitrogen

3. How to use INOmax

Your doctor will decide the correct dose of INOmax and will administer INOmax 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 INOmax 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 INOmax 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 INOmax.

INOmax is given in dose of 10 to 20 ppm, (maximal dose 20 ppm in children and 40 ppm in adults) part 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, INOmax is usually given for 24-48 hours. However, therapy with INOmax may last longer.

If you or your child receive more INOmax 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 INOmax 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 using INOmax

Treatment with INOmax 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 INOmax is stopped suddenly without first lowering the dose.

At the end of treatment, the doctor will slowly lower the amount of INOmax being given to you or your child, so that the circulation in the lungs is able to adjust to oxygen/air without INOmax. Thus, it may take a day or two before you or your child is off INOmax therapy.

If you have any other questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
The doctor will examine you or your child closely for all side effects.

Side effects that are very commonly seen *(affects more than 1 user in 10)* in association with INOmax therapy include:
- Low platelet count.

Side effects that are commonly seen *(affects more than 1 user in 100)* in association with INOmax therapy include:
- low blood pressure, airless or collapsed lung.

Side effects that may be seen, but uncommonly *(affects between 1 user in 100 and 1 user in 1000)* are:
- increase in methaemoglobin, thus reduced oxygen carrying capacity.

Side effects that may be seen but the frequency is not known *(frequency cannot be estimated from the available data)* are:
- Bradycardia (low cardiac frequency) or too low amount of oxygen in the blood (oxygen desaturation/hypoxemia) due to sudden withdrawal of the treatment,
- Headache, dizziness, dry throat, or shortness of breath following accidental ambient air exposure to nitric oxide (e.g. leakage from equipment or cylinder).

You should directly inform the personnel if you experience headache while being in close proximity to your child receiving INOmax.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, even after you or your child leave the hospital, please tell your doctor.

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

5. How to store INOmax

Keep this medicine out of the sight and reach of children

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

INOmax therapy should only be used and handled by hospital personnel.

- INOmax cylinders should be stored secured in order to avoid falling and thus potentially causing harm.

- INOmax should be used and administered only by personnel specially trained in the use and handling of INOmax.

All regulations concerning handling of pressurised gas cylinders must be followed.
Storage is supervised by the 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.

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

Storage in the pharmacy department
The gas cylinders should be stored in an airy, clean and locked place, for storage of medicinal gas only. Inside this place, a separate premise should be dedicated to the storage of nitric oxide gas cylinders.

Storage in the medical department
The gas cylinder should be put in an equipped site with appropriate material in order to hold the cylinder vertically.

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

6. Contents of the pack and other information

What INOmax contains

The active substance in INOmax is nitric oxide 400 ppm mol/mol. A 2 litre gas cylinder filled at 155 bar absolute brings 307 litres of gas under pressure of 1 bar at 15°C. A 10 litre gas cylinder filled at 155 bar absolute brings 1535 litres of gas under pressure of 1 bar at 15°C.

The other ingredient is nitrogen.

What INOmax looks like and contents of the pack

Medicinal gas, compressed

A 2 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under

a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a standard valve hand-wheel.

A 2 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a INOmeter device equipped valve hand-wheel.

A 10 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a standard valve hand-wheel.

A 10 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a INOmeter device equipped valve hand-wheel.

INOmax is available in 2 litre and 10 litre aluminium gas cylinder.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Linde Healthcare AB
Rättarvägen 3
169 68 Solna
Sweden

Manufacturer
Linde France
Z.I. Limay Porcheville
3 avenue Ozanne
78440 Porcheville
France

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

België/Belgique/Belgien
Linde Gas Belgium N.V.
Borsbeeksebrug 34
B - 2600 Antwerpen
Tél/Tel.: +32 70 233 826
info.healthcare.be@linde.com

България
Linde Healthcare AB
Rättarvägen 3
S - 169 68 Solna
Швеция
Tel: +46 8 7311000
healthcare.se@linde.com

Česká republika
Linde Gas a.s.
U Technoplynu 1324
CZ - 198 00 Praha 9
Tel: +420 800 121 121
info.cz@linde.com

Lietuva
Linde Gas UAB
Didlaukio g. 69
LT - 08300 Vilnius
Tel.: +370 2787787
administracija.lt@linde.com

Luxembourg/Luxemburg
Linde Gas Belgium N.V.
Borsbeeksebrug 34
B - 2600 Antwerpen
Belgique/Belgien
Tél/Tel.: +32 70 233 826
info.healthcare.be@linde.com

Magyarország
Linde Gáz Magyarország Zrt.
Illatos út 11/A.
H - 1097 Budapest
Tel.: +36 30 349 2237
tunde.bencze@linde.com

Danmark
Linde Gas A/S
Lautruphøj 2-6
DK - 2750 Ballerup
Tlf: + 45 70 104 103
healthcare.dk@linde.com

Deutschland
Linde GmbH
Seitnerstraße 70
D - 82049 Pullach
Tel: +49 89 31001 0
medgas@linde.com

Eesti
AS Linde Gas
Valukoja 8
EE - 11415 Tallinn
Tel: +372 650 4500
linde.ee@linde.com

Ελλάδα
ΛΙΝΤΕ ΕΛΛΑΣ ΜΟΝ ΕΠΕ
Θέση Τρύπιο Λιθάρι
EL – 19600 Μάνδρα Αττικής
Τηλ: +30 211-1045500-510
healthcare.gr@linde.com

España
Linde Gas España, S.A.U.
Camino de Liria, s/n
E - 46530 Puzol (Valencia)
Tel: +34 900 941 857 / +34 902 426 462
lindehealthcare.spain@linde.com

France
Linde France - Activité médicale - Linde Healthcare
Z.I. Limay-Porcheville
3 avenue Ozanne
F - 78440 Porcheville
Tél:+33 810 421 000
infotherapies@linde.com

Hrvatska
GTG plin d.o.o.
Kalinovac 2/a
47000 Karlovac
Tel. +385 47 609 200
info.hr@gtg-plin.com

Ireland
BOC Ltd.
Forge, 43 Church Street West
Woking, Surrey, GU21 6HT - UK
Tel: 0800 917 4024

Malta
Linde Healthcare AB
Rättarvägen 3
S - 169 68 Solna
l-Isvezja
Tel: +46 8 7311000
healthcare.se@linde.com

Nederland
Linde Gas Therapeutics Benelux B.V.
De Keten 7
NL - 5651 GJ Eindhoven
Tel: +31 40 282 58 25
info.healthcare.nl@linde.com

Norge
Linde Gas AS
Postboks 13 Nydalen
N - 0409 Oslo
Tlf. +47 81559095
healthcare.no@linde.com

Österreich
Linde Gas GmbH
Modecenterstr.17/ Objekt 2/1.OG
A - 1110 Wien
Tel: +43(0)50.4273-2200
healthcare.at@linde.com

Polska
Linde Gaz Polska Sp. z o.o.
ul. prof. Michała Życzkowskiego 17
PL - 31-864 Krakow
Tel.: +48 (65) 511 89 30
dzialania.niepozadane.pl@linde.com

Portugal
Linde Portugal, Lda.
Av. Infante D. Henrique Lotes 21-24
P - 1800-217 Lisboa
Tel: + 351 218 310 420
linde.portugal@linde.com

România
Linde Gaz România SRL
str. Avram Imbroane nr. 9
Timisoara 300136 - RO
Tel: +40 256 300 700
healthcare.ro@linde.com

Slovenija
GTG plin d.o.o.
Bukovžlak 65/b
SI - 3000 CELJE
Tel: + 386 (0)3 42 60 746

ukcsc@inotherapy.co.uk

Ísland
Linde Gas ehf
Breiðhöfða 11
IS - 110 Reykjavik
Sími: + 354 577 3030
healthcare.is@linde.com

Italia
LINDE MEDICALE S.r.L
Via Guido Rossa 3
I - 20004 Arluno (MI)
Tel : +39 02 903731 / 800 600 633

Κύπρος
Linde Hadjikyriakos Gas Ltd
Λεωφόρος Λεμεσού 260, 2029 Στρόβολος
CY - Λευκωσία, Κύπρος.
Τηλ. +357-22482330
info.cy@linde.com

Latvija
Linde Gas SIA
Katrīnas iela 5
Rīga, LV-1045
Tel: +371 67023900
ksc.lv@linde.com

prodaja@gtg-plin.com

Slovenská republika
Linde Gas s.r.o.
Tuhovská 3
SK - 831 06 Bratislava
Tel: +421 2 49 10 25 16
healthcare.sk@linde.com

Suomi/Finland
Oy Linde Gas Ab
Itsehallintokuja 6
FI - 02600 Espoo
Puh/Tel: + 358 10 2421
hctilaus.fi@linde.com

Sverige
Linde Gas AB
Rättarvägen 3
S - 169 68 Solna
Tel: + 46 8 7311800
healthcare.se@linde.com

United Kingdom (Northern Ireland)
BOC Ltd.
Forge, 43 Church Street West
Woking, Surrey, GU21 6HT - UK
Tel: 0800 917 4024
ukcsc@inotherapy.co.uk

This leaflet was last revised in MM/YYYY.

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

PACKAGE LEAFLET: INFORMATION FOR THE USER

INOmax 800 ppm mol/mol medicinal gas, compressed
Nitric oxide

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
- If you get any of the side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What INOmax is and what it is used for

INOmax contains nitric oxide, a gas used for the treatment of

- 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, which may help to increase the amount of oxygen that reaches the blood.

2. What you need to know before you begin a treatment with INOmax

Do not use INOmax

- If you (as the patient) or your child (as the patient) are allergic (hypersensitive) to nitric oxide or any other ingredients of INOmax (see section 6 'further information' where the full list of ingredients is provided).

- If you have been told that you (as the patient) or your child (as the patient) have an abnormal circulation within the heart.

Warnings and precautions

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 INOmax 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 oxide 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

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

Other medicines and INOmax

The doctor will decide when to treat you or your child with INOmax and with other medicines and will carefully supervise the treatment.

Please tell your doctor if you (as the patient) or your child (as the patient) are taking or have recently taken or used any other medicines, including medicines obtained without a prescription.

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 and breastfeeding

INOmax is not recommended for use during pregnancy and breastfeeding. Tell your doctor before treatment with INOmax if you are pregnant, think you could be pregnant or are breastfeeding

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
Not relevant.

INOmax contains Nitrogen

3. How to use INOmax

Your doctor will decide the correct dose of INOmax and will administer INOmax 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 INOmax 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 INOmax 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 INOmax.

INOmax is given in dose of 10 to 20 ppm, (maximal dose 20 ppm in children and 40 ppm in adults) part 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, INOmax is usually given for 24-48 hours. However, therapy with INOmax may last longer.

If you or your child receive more INOmax 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 INOmax 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 using INOmax

Treatment with INOmax 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 INOmax is stopped suddenly without first lowering the dose.

At the end of treatment, the doctor will slowly lower the amount of INOmax being given to you or your child, so that the circulation in the lungs is able to adjust to oxygen/air without INOmax. Thus, it may take a day or two before you or your child is off INOmax therapy.

If you have any other questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The doctor will examine you or your child closely for all side effects.

Side effects that are very commonly seen *(affects more than 1 user in 10)* in association with INOmax therapy include:
- Low platelet count.

Side effects that are commonly seen *(affects more than 1 user in 100)* in association with INOmax therapy include:
- low blood pressure, airless or collapsed lung.

Side effects that may be seen, but uncommonly *(affects between 1 user in 100 and 1 user in 1000)* are:
- increase in methaemoglobin, thus reduced oxygen carrying capacity.

Side effects that may be seen but the frequency is not known *(frequency cannot be estimated from the available data)* are:
- Bradycardia (low cardiac frequency) or too low amount of oxygen in the blood (oxygen desaturation/hypoxemia) due to sudden withdrawal of the treatment

- Headache, dizziness, dry throat or shortness of breath following accidental ambient air exposure to nitric oxide (e.g. leakage from equipment or cylinder).

You should directly inform the personnel if you experience headache while being in close proximity to your child receiving INOmax.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, even after you or your child leave the hospital, please tell your doctor.

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

5. How to store INOmax

Keep this medicine out of the sight and reach of children

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

INOmax therapy should only be used and handled by hospital personnel.
- INOmax cylinders should be stored secured in order to avoid falling and thus potentially causing harm.

- INOmax should be used and administered only by personnel specially trained in the use and handling of INOmax.

All regulations concerning handling of pressurised gas cylinders must be followed.
Storage is supervised by the 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.

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

Storage in the pharmacy department
The gas cylinders should be stored in an airy, clean and locked place, for storage of medicinal gas only. Inside this place, a separate premise should be dedicated to the storage of nitric oxide gas cylinders.

Storage in the medical department
The gas cylinder should be put in an equipped site with appropriate material in order to hold the cylinder vertically.

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

6. Contents of the pack and other information

What INOmax contains

The active substance in INOmax is nitric oxide 800 ppm mol/mol. A 2 litre gas cylinder filled at 155 bar absolute brings 307 litres of gas under pressure of 1 bar at 15°C. A 10 litre gas cylinder filled at 155 bar absolute brings 1535 litres of gas under pressure of 1 bar at 15°C.

The other ingredient is nitrogen.

What INOmax looks like and contents of the pack

Medicinal gas, compressed

A 2 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under

a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a standard valve hand-wheel.

A 2 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a INOmeter device equipped valve hand-wheel.

A 10 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a standard valve hand-wheel.

A 10 litre aluminium gas cylinder (identification with aquamarine shoulder and white body) filled under a pressure of 155 bar, equipped with a stainless steel positive pressure (residual) valve with a specific outlet connection and a INOmeter device equipped valve hand-wheel.

INOmax is available in 2 litre and 10 litre aluminium gas cylinder.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Linde Healthcare AB
Rättarvägen 3
169 68 Solna
Sweden

Manufacturer
Linde France
Z.I. Limay Porcheville
3 avenue Ozanne
78440 Porcheville
France

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

België/Belgique/Belgien
Linde Gas Belgium N.V.
Borsbeeksebrug 34
B - 2600 Antwerpen
Tél/Tel.: +32 70 233 826
info.healthcare.be@linde.com

България
Linde Healthcare AB
Rättarvägen 3
S - 169 68 Solna
Швеция
Tel: +46 8 7311000
healthcare.se@linde.com

Česká republika
Linde Gas a.s.
U Technoplynu 1324
CZ - 198 00 Praha 9
Tel: +420 800 121 121
info.cz@linde.com

Lietuva
Linde Gas UAB
Didlaukio g. 69
LT - 08300 Vilnius
Tel.: +370 2787787
administracija.lt@linde.com

Luxembourg/Luxemburg
Linde Gas Belgium N.V.
Borsbeeksebrug 34
B - 2600 Antwerpen
Belgique/Belgien
Tél/Tel.: +32 70 233 826
info.healthcare.be@linde.com

Magyarország
Linde Gáz Magyarország Zrt.
Illatos út 11/A.
H - 1097 Budapest
Tel.: +36 30 349 2237
tunde.bencze@linde.com

Danmark
Linde Gas A/S
Lautruphøj 2-6
DK - 2750 Ballerup
Tlf: + 45 70 104 103
healthcare.dk@linde.com

Deutschland
Linde GmbH
Seitnerstraße 70
D - 82049 Pullach
Tel: +49 89 31001 0
medgas@linde.com

Eesti
AS Linde Gas
Valukoja 8
EE - 11415 Tallinn
Tel: +372 650 4500
linde.ee@linde.com

Ελλάδα
ΛΙΝΤΕ ΕΛΛΑΣ ΜΟΝ ΕΠΕ
Θέση Τρύπιο Λιθάρι
EL – 19600 Μάνδρα Αττικής
Τηλ: +30 211-1045500-510
healthcare.gr@linde.com

España
Linde Gas España, S.A.U.
Camino de Liria, s/n
E - 46530 Puzol (Valencia)
Tel: +34 900 941 857 / +34 902 426 462
lindehealthcare.spain@linde.com

France
Linde France - Activité médicale - Linde Healthcare
Z.I. Limay-Porcheville
3 avenue Ozanne
F - 78440 Porcheville
Tél:+33 810 421 000
infotherapies@linde.com

Hrvatska
GTG plin d.o.o.
Kalinovac 2/a
47000 Karlovac
Tel. +385 47 609 200
info.hr@gtg-plin.com

Ireland
BOC Ltd.
Forge, 43 Church Street West
Woking, Surrey, GU21 6HT - UK
Tel: 0800 917 4024

Malta
Linde Healthcare AB
Rättarvägen 3
S - 169 68 Solna
l-Isvezja
Tel: +46 8 7311000
healthcare.se@linde.com

Nederland
Linde Gas Therapeutics Benelux B.V.
De Keten 7
NL - 5651 GJ Eindhoven
Tel: +31 40 282 58 25
info.healthcare.nl@linde.com

Norge
Linde Gas AS
Postboks 13 Nydalen
N - 0409 Oslo
Tlf. +47 81559095
healthcare.no@linde.com

Österreich
Linde Gas GmbH
Modecenterstr.17/ Objekt 2/1.OG
A - 1110 Wien
Tel: +43(0)50.4273-2200
healthcare.at@linde.com

Polska
Linde Gaz Polska Sp. z o.o.
ul. prof. Michała Życzkowskiego 17
PL - 31-864 Krakow
Tel.: +48 (65) 511 89 30
dzialania.niepozadane.pl@linde.com

Portugal
Linde Portugal, Lda.
Av. Infante D. Henrique Lotes 21-24
P - 1800-217 Lisboa
Tel: + 351 218 310 420
linde.portugal@linde.com

România
Linde Gaz România SRL
str. Avram Imbroane nr. 9
Timisoara 300136 - RO
Tel: +40 256 300 700
healthcare.ro@linde.com

Slovenija
GTG plin d.o.o.
Bukovžlak 65/b
SI - 3000 CELJE
Tel: + 386 (0)3 42 60 746

ukcsc@inotherapy.co.uk

Ísland
Linde Gas ehf
Breiðhöfða 11
IS - 110 Reykjavik
Sími: + 354 577 3030
healthcare.is@linde.com

Italia
LINDE MEDICALE S.r.L
Via Guido Rossa 3
I - 20004 Arluno (MI)
Tel : +39 02 903731 / 800 600 633

Κύπρος
Linde Hadjikyriakos Gas Ltd
Λεωφόρος Λεμεσού 260, 2029 Στρόβολος
CY - Λευκωσία, Κύπρος.
Τηλ. +357-22482330
info.cy@linde.com

Latvija
Linde Gas SIA
Katrīnas iela 5
Rīga, LV-1045
Tel: +371 67023900
ksc.lv@linde.com

prodaja@gtg-plin.com

Slovenská republika
Linde Gas s.r.o.
Tuhovská 3
SK - 831 06 Bratislava
Tel: +421 2 49 10 25 16
healthcare.sk@linde.com

Suomi/Finland
Oy Linde Gas Ab
Itsehallintokuja 6
FI - 02600 Espoo
Puh/Tel: + 358 10 2421
hctilaus.fi@linde.com

Sverige
Linde Gas AB
Rättarvägen 3
S - 169 68 Solna
Tel: + 46 8 7311800
healthcare.se@linde.com

United Kingdom (Northern Ireland)
BOC Ltd.
Forge, 43 Church Street West
Woking, Surrey, GU21 6HT - UK
Tel: 0800 917 4024
ukcsc@inotherapy.co.uk

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