1. NAME OF THE MEDICINAL PRODUCT

Mixture NO 800 ppm in Nitrogen - 800 ppm mol/mol inhalation gas

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitric oxide (NO) 800 ppm mol/mol.

Nitric oxide (NO) 0.8 ml in Nitrogen (N2) 999.2 ml

Drug Product	Mixture NO 800 ppm in nitrogen
Size cylinders	0.5-50 liter
Pressure	120-150 bar
quantity	$0.05M^3$-7.5 M^3

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation gas.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Mixture NO 800 ppm in Nitrogen, 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. Mixture NO 800 ppm in Nitrogen should only be delivered according to a neonatologist's prescription.
Mixture NO 800 ppm in Nitrogen should be used in ventilated newborn infants expected to require support >24 hours. Mixture NO 800 ppm in Nitrogen should be used only after respiratory support has been optimized. This

includes optimizing 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 anesthesia & 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. Mixture NO 800 ppm in Nitrogen 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 Mixture NO 800 ppm in Nitrogen 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 FiO2 (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 Mixture NO 800 ppm in Nitrogen 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 Mixture NO 800 ppm in Nitrogen 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 Mixture NO 800 ppm in Nitrogen at 1 ppm, the FiO2 should be increased by 10 %, the Mixture system discontinued, and the neonates monitored closely for signs of hypoxaemia. If oxygenation falls >20 %, Mixture therapy should be resumed at 5 ppm and discontinuation of Mixture therapy should be reconsidered after 12 to 24 hours. Infants who cannot be weaned off Mixture sustem by 4 days should undergo careful diagnostic work-up for other diseases.

Pulmonary hypertension associated with heart surgery

Mixture NO 800 ppm in Nitrogen should be used only after conservative support has been optimized. In clinical trials Mixture NO 800 ppm in Nitrogen has been given in addition to other standard treatment regimes in the peri-operative setting, including inotropic and vasoactive medicinal products. Mixture NO 800 ppm in Nitrogen 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 Mixture NO 800 ppm in Nitrogen should be commenced as soon as the haemodynamics have stabilized 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 Mixture NO 800 ppm in Nitrogen. 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 Mixture NO 800 ppm in Nitrogen 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.
Mixture NO 800 ppm in Nitrogen 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 Mixture NO concentration irrespective of the ventilator. With a continuous flow neonatal ventilator, this may be achieved by infusing a low flow of Mixture NO 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 Mixture NO 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 Mixture NO 800 ppm in Nitrogen (± 2 ppm of the prescribed dose), NO_2 (1 ppm), and FiO_2 (± 0.05).
The Mixture NO 800 ppm in Nitrogen 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. Mixture NO 800 ppm in Nitrogen 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/m3) in most countries and the corresponding limit for NO_2 is 2-3 ppm (4-6 mg/m3).

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 NO2)
- Setting the device for the correct concentration of nitric oxide to be administered
- Setting the NO, NO2 and O2 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, NO2 and O2 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 Mixture NO 800 ppm in Nitrogen therapy, using an analyser which can reliably distinguish between foetal haemoglobin and methaemoglobin. If it is > 2.5 %, the Mixture NO 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 Mixture NO therapy. If the fraction of methaemoglobin rises to a level that potentially compromises adequate oxygen delivery, the Mixture NO dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered.

Monitoring formation of nitrogen dioxide (NO2)
Immediately prior to each patient initiation, proper procedure must be applied to purge the system of NO2. The NO2 concentration should be maintained as low as possible and always < 0.5 ppm. If the NO2 is > 0.5 ppm, the delivery system should be assessed for malfunction, the NO2 analyser should be recalibrated, and the Mixture NO 800 ppm in Nitrogen and/or FiO2 should be reduced if possible. If there is an unexpected change in Mixture NO 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 Mixture NO 800 ppm in Nitrogen, 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 Mixture NO 800 ppm in Nitrogen, 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-toright 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 Mixture NO dose should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO2). Deterioration in oxygenation and elevation in PAP may also occur in neonates with no apparent response to Mixture NO 800 ppm in Nitrogen. 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 Mixture NO 800 ppm in Nitrogen 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 Mixture NO 800 ppm in Nitrogen on the risk of developing methaemoglobinemia with nitric oxide donor substances, including

sodium nitroprusside and nitroglycerin .Mixture NO 800 ppm in Nitrogen 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 Mixture NO 800 ppm in Nitrogen is given at the same time as medicinal products containing prilocaine.

In the presence of oxygen, nitric oxide is rapidly oxidized to derivatives which are toxic to the bronchial epithelium and alveolo-capillary membrane. Nitrogen dioxide (NO2) 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 NO2. During treatment with nitric oxide, the NO2 concentration should be < 0.5 ppm in the nitric oxide dose range < 20 ppm.
If at any time the NO2 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.
Mixture NO 800 ppm in Nitrogen 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 Mixture NO 800 ppm in Nitrogen. 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 Mixture NO 800 ppm in Nitrogen 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	Thrombocytopenia[a]		Methaemoglobinaemia[a]	-	-	
Cardiac disorders	-		-	-	-	Bradycardia[b] (following abrupt discontinuation of therapy)
Vascular disorders	-	Hypotension[a, bd]	-	-	-	
Respiratory, thoracic and mediastinal disorders	-	Atelectasis[a]	-	-	-	Hypoxiab,[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 Mixture NO 800 ppm in Nitrogen will be manifest by elevations in methaemoglobin and NO2. Elevated NO2 may cause acute lung injury. Elevations in methaemoglobinaemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO2 levels > 3 ppm or methaemoglobin levels > 7 % were treated by reducing the dose of, or discontinuing, Mixture NO 800 ppm in Nitrogen.
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.
Mixture NO 800 ppm in Nitrogen appears to increase the partial pressure of arterial oxygen (PaO2) 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, mixture can improve oxygenation (as indicated by significant increases in PaO2).

The efficacy of Mixture NO 800 ppm in Nitrogen 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 % O2 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 Mixture NO 800 ppm in Nitrogen (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 Mixture NO 800 ppm in Nitrogen group required ECMO compared to the control group (31 % vs. 57 %, p<0.001). The Mixture NO 800 ppm in Nitrogen group had significantly improved oxygenation as measured by PaO2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with Mixture NO 800 ppm in Nitrogen, 2(2 %) were withdrawn from study drug due to methaemoglobin levels >4 %. The frequency and number of adverse events were similar in the two study groups.

In patients undergoing heart surgery, an increase in pulmonary artery pressure due to pulmonary vasoconstriction is frequently seen. Inhaled nitric oxide has been shown to selectively reduce pulmonary vascular resistance and reduce the increased pulmonary artery pressure. This may increase the right ventricular ejection fraction. These effects in turn lead to improved blood circulation and oxygenation in the pulmonary circulation.

In the INOT27 trial, 795 preterm infants (GA<29 weeks) with hypoxic respiratory failure were randomised to receive either Mixture NO (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 Mixture NO treated as compared to 91 (22.9 %) among the control neonates. The overall number of death at week 36 was slightly higher in the NO group; 53/395 (13.4 %) as compared to control 42/397 (10.6 %). The INOT25 trial, studying the effects of NO 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 Mixture NO in preterm
neonates, but initiating mixture NO 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 (O2 -), 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 Mixture NO 800 ppm in Nitrogen 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 NO groups, but reached approximately 5 % in the 80 ppm NO 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 NO2, see section 4.5.

6.3 Shelf life

12 months

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 Mixture NO 800 ppm, 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

Drug Product	Mixture NO 800 ppm in nitrogen
Size cylinders	5-50 liter
Pressure	120-150 bar

Material of construction	Aluminum
Cylinder Valve	CGA 660/CGA330

6.6 Special precautions for disposal and other handling

Instructions for use/handling Mixture NO 800 ppm in Nitrogen
When connecting a Mixture NO 800 ppm in Nitrogen 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
- 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. Among metallic construction materials, only stainless steel can be recommended.

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 NO2/NOx must not exceed set national occupational exposure limits. Accidental exposure to Mixture NO 800 ppm in Nitrogen in hospital staff has been associated with adverse events (see section 4.8).

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

Maxima Air Separation Center LTD
10 Haogen st.P.O.B, 4124 Ashdod 7714101 . Israel

8. MARKETING AUTHORISATION NUMBER(S)

Information for Maxima use only

10. DATE OF REVISION OF THE TEXT

25/01/2017

SPC based on Inomax SPC EMA approved for Linde Healthcare AB, Sweden