

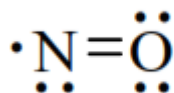
PRODUCT INFORMATION

Name of the Medicine

VasoKINOX® 450ppm (nitric oxide for inhalation), medicinal gas compressed

Pharmacotherapeutic class: Pulmonary vasodilator

Structural formula, including relative and absolute stereochemistry:



Molecular formula:

NO

Chemical Abstracts Service (CAS) registry number:

[10102-43-9]

DESCRIPTION

VasoKINOX is a colourless and odourless medicinal gas. Nitric oxide (NO), the active ingredient of VasoKINOX, is a pulmonary vasodilator. VasoKINOX is supplied in aluminium alloy gas cylinders (of 5L or 11L or 20L capacity) with a NO concentration of 450ppm mol/mol (NO 0.450 ml in Nitrogen (N₂) 999.55 ml).

A 5-litre cylinder filled to 200 bar (20,000 kPa) supplies 0.94m³ of gas at a pressure of 1 bar (101.3kPa) at 15°C

A 11-litre cylinder filled to 200 bar (20,000 kPa) supplies 2.1m³ of gas at a pressure of 1 bar (101.3kPa) at 15°C

A 20-litre cylinder filled to 200 bar (20,000 kPa) supplies 3.8m³ of gas at a pressure of 1 bar (101.3kPa) at 15°C.

PHARMACOLOGY

Mechanism of action

Nitric oxide is produced endogenously by numerous cells within the organism, including those in the vascular endothelium.

Nitric oxide induces the relaxation of vascular smooth muscles thus resulting in vasodilation by combining with cytosolic guanylate cyclase haem iron. This activates the guanylate-cyclase and increases intracellular concentrations of cyclic guanosine 3',5'-monophosphate (GMPc). An increase in intraplatelet GMPc may be responsible for platelet aggregation inhibition.

Inhaled NO (iNO) exerts a selective action on pulmonary arterial circulation due to its very short half-life and inhalation route.

Pharmacodynamics

VasoKINOX induces a reduction in pulmonary vascular resistance (PVR) and is effective only in the presence of existing vasoconstriction in the ventilated area of the lung. It improves arterial oxygenation by re-distributing pulmonary blood flow from the unventilated areas of the lung with a low ventilation/perfusion ratio (V/Q) to the ventilated areas, consequently reducing the shunt effect. The effect of iNO is dependent on alveolar recruitment.

Pharmacokinetics

Absorption and Distribution:

Inhaled NO is diffused via a systemic pathway. The largest part crosses the alveolocapillary membrane and combines with haemoglobin presenting oxygen (O₂) saturation of between 60% and 100%. At this level of O₂ saturation, iNO mainly fixes to the oxyhaemoglobin, which transforms into methaemoglobin and nitrates. When O₂ saturation is low, iNO fixes onto deoxyhaemoglobin to form an intermediate compound, nitrosylhaemoglobin, which then decomposes into nitrogen oxides and methaemoglobin in the presence of O₂.

Metabolism:

Nitric oxide reacts with O₂ and water to form nitrogen dioxide (NO₂) and nitrites, which react with oxyhaemoglobin to produce methaemoglobin and nitrates. Thus, the principal metabolites of iNO found in the systemic circulation are methaemoglobin and nitrates. The very short half-life of iNO is due to the haemoglobin circulating in the vicinity of its points of diffusion through the alveolocapillary membrane which is responsible for its deactivation.

Excretion:

Nitrates are eliminated mainly in urine whereas methaemoglobin is metabolised in several hours into haemoglobin by endogenic reductases. The nitrates excreted in urine represent over 70% of the iNO dosage.

CLINICAL TRIALS

A review of published literature was conducted studying the efficacy of iNO in the treatment of perioperative pulmonary hypertension (PHT) in both paediatric and adult patients in the context of cardiac surgery.

Paediatric Populations

The selective pulmonary anti-hypertensive effect of iNO in this population has been demonstrated in randomised studies comparing iNO with nitrogen (N₂), conventional treatment, hyperventilation, milrinone, sildenafil, prostacyclin and iloprost. The main efficacy results are seen in pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR) and PHT crisis.

A total of 12 randomised controlled trials involving a total of 456 paediatric patients (238 treated with iNO) were assessed as published study reports for the indication of perioperative PHT in conjunction with cardiac surgery. Four of these were considered key studies: Miller *et al* (2000) and Russell *et al* (1998) which were placebo-controlled double blind studies and Day *et al* (2000) and Morris *et al* (2000) which were controlled against conventional therapy. Their designs and results are detailed below.

Miller *et al* (2000) was the largest of the key studies. This double-blind study included 124 children with a median age of 3 months (range 1 to 5 months). Patients were randomised to iNO (10 ppm, n=63) or placebo (N₂, n=61). Treatment was started in a time period from “after surgery” to “just before extubation”. The primary endpoint was the number of PHT crises during treatment. Infants receiving iNO showed significantly fewer PHT crises than those receiving the placebo (median of 4 [interquartile ranges-(IQR): 0-12] versus 7 [IQR: 1-19]). Unadjusted relative risk was 0.66 [95% Confidence Intervals-(95%CI): 0.59–0.74], p<0.001. Relative risk adjusted for dispersion was 0.65 [95%CI: 0.43–0.99], p=0.045. Most of secondary endpoints also demonstrated better outcomes with iNO: the PVR index measured every 12 hours during study gas administration was significantly lower in the iNO group (p<0.001) and patients treated with iNO reached extubation criteria significantly sooner than patients receiving the placebo (80 hours [IQR: 38-121] versus 122 hours [IQR: 63-164], p=0.019).

Russell *et al* (1998) was a double blind study that included 40 children (age range 2 days to 6.5 years) with pre-operative PHT (mean PAP (mPAP) > 50% of mean systemic arterial pressure (mSAP)) undergoing cardiac surgery for congenital heart defects. Patients were randomised to receive iNO 80

ppm or placebo over 20 minutes after weaning from cardiopulmonary bypass. A significant haemodynamic effect was seen with iNO in the subset of 13 patients with elevated PAP: mean PAP was reduced by 19% (range 8-35% at 20 minutes) with iNO (n=5, p=0.008) and increased by 9% with placebo (n=8).

Day *et al* (2000) was an open study including 38 children undergoing corrective surgery or heart transplantation due to congenital heart disease. Patients were randomised to either conventional therapy (n=19; age range 1 day to 3 years) or iNO at 20 ppm (n=19; age range 1 day to 20 years). The primary endpoint was the number of patient with PHT crises during treatment. There was no significant difference in the number of patients presenting PHT crises between the two treatment groups. In comparison to baseline, significant reduction in systolic PAP (from 52±3 mmHg to 47±2 mmHg, p<0.05) was observed only in patients receiving iNO.

Morris *et al* (2000) was a crossover study that included 12 children presenting postoperative PHT (PAP>25mmHg) after biventricular repair surgery (age range 0.1 to 17.7 years). In this prospective, randomised crossover study, the patients received iNO (5 ppm for 15 minutes then 40 ppm for 15 minutes) versus control therapy (mild alkalosis (pH 7.5) induced by hyperventilation). The efficacy endpoints were cardiac output and other haemodynamic parameters. Inhaled NO and hyperventilation were both effective at lowering PAP and PVR, producing significant changes compared to baseline, but there were no significant differences between the two treatments. Compared to baseline, hyperventilation resulted in a significant increase in the mean systemic vascular resistance (SVR) index and in a significant reduction in cardiac index, and iNO did not have significant effects on systemic haemodynamics. The differences between the two treatments for SVR Index and cardiac index were not statistically significant.

In summary for the 12 randomised controlled paediatric trials, iNO was effective in reducing PAP (expressed either directly as PAP or indirectly by PVR measurement) in children with PHT in conjunction with cardiac surgery. In all studies that reported changes in PAP, the reduction of PAP was approximately 10% to 30%. In the studies that reported changes in PVR, iNO reduced the PVR index by approximately 15% to 25% and had no significant effect on SVR index. In the studies that assessed the PHT crises, iNO reduced the number of PHT crises.

Adult populations

The selective pulmonary anti-hypertensive effect of iNO in this population has been demonstrated in randomised studies comparing iNO with placebo, conventional therapy, prostaglandin, nitroprusside/nitroglycerin, prostacyclin, milrinone, and sildenafil. The main efficacy results are seen in PAP and PVR.

A total of 10 prospective randomised controlled trials involving 336 adult patients (198 treated with iNO) were assessed as published study reports for the indication of perioperative PHT in conjunction with cardiac surgery. Four of these were considered key studies: Argenziano *et al* (1998) which was a placebo-controlled double blind study and Knothe *et al* (1996), Fernandes *et al* (2011) and Rajek *et al* (2000) which were controlled against conventional therapy. Their designs and results are detailed below.

Argenziano *et al* (1998) was a placebo-controlled, double blind randomised study investigating the effects of iNO (20ppm) versus placebo (N₂) in 11 patients (mean age: 55±3 years) with PHT (mPAP>25 mmHg) implanted with a left ventricular assist device (LVAD) for advanced heart failure. Patients randomised to placebo where to be crossed over to receive iNO if no clinical response was obtained after 15 minutes. In the iNO group, PAP decreased rapidly from 35±6 mmHg to 24±4 mmHg (p=0.02) and the LVAD flow index increased from 1.9±0.2 L/min/m² to 2.7±0.3 L/min/m² (p=0.02). In the placebo group, no significant change was seen in PAP or LVAD flow index.

Knothe *et al* (1996) was a randomised open study investigating the effect of iNO (30 ppm) versus conventional therapy in 20 patients (age range 46 to 80 years) with PHT (PAP>25 mmHg) before valve replacement surgery. In the iNO group, PAP and PVR were significantly reduced (p<0.05) and returned to their baseline value after iNO was stopped. In the conventional therapy group, changes in PAP

and PVR were not statistically significant. Treatment with iNO significantly increased SVR, which remained elevated after iNO was stopped.

Fernandes *et al* (2011) was an open randomised study investigating the effect of iNO (10 ppm) versus O₂ in 29 patients (mean age 46±2 years) with severe PHT (systolic PAP>60 mmHg) undergoing mitral valve stenosis surgery. The increase in cardiac index was significantly greater ($p<0.0001$) in patients receiving iNO than in those receiving O₂ at both 24 and 48 hours. The decrease in PVR was also significantly greater ($p=0.005$) in the iNO group than in the O₂ group, but only at 48 hours. Pulmonary capillary wedge pressure and systolic PAP were significantly reduced in both groups, but the difference between groups was not significant.

Rajek *et al* (2000) was a double-blind randomised study investigating the efficacy of iNO (34 patients, mean age: 54±11 years) versus intravenous prostaglandin E1 (PGE1)(34 patients, mean age: 55±9 years) in patients with PHT (mean PVR >250 dyn/sec/cm⁵, mPAP>30 mmHg) undergoing heart transplantation. Patients were switched to the alternative study drug when PAP was consistently elevated and when weaning from cardiopulmonary bypass was difficult because of right heart failure. Pulmonary arterial pressure was decreased by approximately 30% with iNO ($p<0.0001$), but only by approximately 16% with PGE1. PVR was nearly halved in the iNO group ($p<0.0001$) but reduced by only 10% in the PGE1 group. Weaning from cardiopulmonary bypass was successful in all patients in the iNO group and failed in six patients in the PGE1 group.

In summary for the 10 randomised controlled adult trials, iNO was effective in reducing PAP (expressed either directly as PAP or indirectly by PVR measurement) in adults with PHT in conjunction with cardiac surgery. In the studies that reported changes in PAP, the reduction of PAP was approximately from 15% to 40%. In the studies that reported changes in vascular resistance, iNO reduced the PVR by approximately 35% to 65% and had no significant effect on SVR (where reported). In all studies, iNO treatment maintained or improved cardiac function. It should be noted that the adult studies have some methodological limitations such as the relatively low total number of patients included in the trials and the heterogeneity of the trials.

INDICATIONS

VasoKINOX is indicated in conjunction with ventilator support and other appropriate active substances to selectively decrease pulmonary arterial pressure in patients with perioperative pulmonary hypertension in conjunction with heart surgery

CONTRAINDICATIONS

- Hypersensitivity to the active substance or any of the excipients.
- Newborns dependent on a right-to-left shunt or with a 'malignant' left-right arterial canal.

PRECAUTIONS

DO NOT USE VasoKINOX undiluted.

VasoKINOX is delivered to the patient via mechanical ventilation after dilution with an oxygen/air mixture using an approved NO gas delivery system provided by the sponsor that meets the criteria specified in the Dosage and Administration Section. The controlled flow of 450ppm VasoKINOX is delivered to the ventilator circuit via the injector tube where it is diluted by the ventilator gas flow to the concentration set by the operator. This concentration must not exceed 20 ppm. The delivery system must provide a constant inhaled nitric oxide concentration irrespective of the ventilator.

Rebound pulmonary hypertension syndrome following abrupt discontinuation

VasoKINOX treatment must not be stopped abruptly to avoid the risk of increasing PAP and/or inducing rebound hypoxaemia (reduction in PaO₂). When patients treated with iNO are to be transported, continuous administration of iNO should be ensured throughout the transport.

Weaning from iNO must be progressive and carried out with precaution. Inhaled NO therapy should be re-instated if rebound PHT occurs (see DOSAGE AND ADMINISTRATION).

Deterioration in oxygenation and elevation in PAP may also occur in patients who are not responsive to VasoKINOX.

Methaemoglobin production:

After inhalation, the terminal compounds of nitric oxide found in the systemic circulation are mainly methaemoglobin and nitrate. Methaemoglobin concentration in the blood should be monitored in all patients.

Although a significant increase in methaemoglobin is uncommon where its initial level is low, this should be tested prior to treatment, then regularly throughout administration. If the methaemoglobin level exceeds 2.5%, the NO dosage must be reduced. If it exceeds 5%, administration must be stopped. The administration of a reducing agent such as methylene blue should be considered.

Formation of NO₂:

NO₂ rapidly forms in gas mixtures containing NO and O₂, and NO may in this way cause airway inflammation and damage. The dose of NO should be reduced if the concentration of NO₂ exceeds 0.5ppm (see DOSAGE AND ADMINISTRATION).

Special patient populations

-Left ventricular dysfunction

Inhaled nitric oxide should also be used with caution in patients with compromised left ventricular function and with elevated baseline pulmonary capillary wedge pressure as they may be at an increased risk of developing cardiac failure (e.g. pulmonary oedema). Severe hypotension, bradycardia and cardiac arrest have been reported in this patient group.

-Cardiac insufficiency

Treatment with iNO might aggravate cardiac insufficiency in a situation with left-to-right shunting. This is due to unwanted pulmonary vasodilation caused by iNO, resulting in a further increase of already existing pulmonary hyperperfusion thus potentially giving rise to forward or backward failure. It, therefore, is recommended that prior to the administration of NO, pulmonary artery catheterisation or echocardiographic examination of central haemodynamics be performed.

- Complex heart defect

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.

Haemostasis monitoring:

Regular monitoring of haemostasis and measurement of bleeding time is recommended during the administration of VasoKINOX for more than 24 hours to patients with functional or quantitative platelet anomalies, a low coagulation factor or receiving anticoagulation treatment. Animal testing has shown that iNO is likely to interfere with haemostasis and induce an increase in bleeding time. The available data for adult humans are contradictory and do not allow formal conclusions to be drawn.

Effects on fertility

No fertility studies have been performed.

Use in Pregnancy (Category B2)

Animal studies are insufficient with respect to reproductive and developmental toxicity.

It is not known if NO can cause foetal harm when administered to pregnant women or affect reproductive capacity because of a limited amount of data of the use of NO in pregnant-women.

A review summarised the use of iNO in 10 pregnant women with PHT who received iNO in late pregnancy (dose range from 5 to 80 ppm for minutes to hours). Elevation in maternal methaemoglobin levels has not been reported. No data on the effect of iNO on the foetus is available.

VasoKINOX is not recommended during pregnancy.

Use in Lactation

It is unknown whether NO/metabolites are excreted in human milk. The excretion of VasoKINOX in milk has not been studied in animals. A risk to the newborn/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue VasoKINOX therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Paediatric Use

The safety and efficacy of VasoKINOX in premature infants less than 34 weeks of gestation have not yet been established.

The maximum recommended dose in children is 20 ppm.

Clinical data supporting the suggested dose in the age range of 12-17 years is limited. The long term consequences of the use of nitric oxide in children for the approved indication have not been established.

Inhalation exposure of rats (whole body, 6 hours per day) from post-natal days 1-29 (birth to 8 days following weaning) resulted in reduced body weights and reduced body weight gain without compensatory growth over the post-natal days 1-90 period. The clinical relevance of these findings is uncertain.

Use in Adults

Clinical data supporting the use of iNO in adults is limited.

Use in the Elderly patients

No specific studies have been carried out in elderly patients.

Genotoxicity

Nitric oxide consistently induced base pair mutations in bacterial reverse mutation assays and indications of mutagenicity in mammalian cell (mouse lymphoma) forward mutation assays, most likely due to peroxynitrites and reactive O₂ species generated by oxidation of NO. Mutagenic activity of NO has been inconsistently reported in literature in other mammalian cells *in vitro*. Nitric oxide induced gene mutations in rat lung cells *in vivo*. 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.

Carcinogenicity

No carcinogenicity studies have been conducted.

INTERACTIONS WITH OTHER MEDICINES

No interaction studies have been performed.

Administration with O₂ – Formation of NO₂

In the presence of O₂, NO is rapidly oxidised to form derivatives that are toxic for the bronchial epithelium and the alveolocapillary membrane. Nitrogen dioxide is the principal compound formed. The oxidation

rate is proportional to the initial concentrations of NO and O₂ in the inhaled air, and to the duration of contact between NO and O₂. Its concentration should remain below 0.5 ppm when iNO is administered at doses of less than 20 ppm and if the measures to reduce the contact time between O₂ and NO are correctly applied. If the NO₂ concentration exceeds 1 ppm during treatment, the NO dose and/or FiO₂ must be immediately reduced. See DOSAGE AND ADMINISTRATION for recommendations concerning NO₂ monitoring.

NO donor compounds

It is possible that NO donor compounds such as sodium nitroprusside and nitroglycerin, potentiates the risk of developing methaemoglobinaemia.

There is an increased risk of methaemoglobin formation if substances with a known tendency to increase methaemoglobin concentrations, or known to produce oxidative damage to the erythrocytes, are administered concomitantly with NO (e.g. prilocaine, alkyl nitrates and sulphonamides). The effects of these agents with VasoKINOX on methaemoglobin formation can be expected to be at least additive. Substances known to cause increased methaemoglobin levels, or to produce oxidative damage to the erythrocytes, should be used with caution during therapy with iNO. Appropriate guidance should be sought before such agents are used concurrently with VasoKINOX.

Other vasodilators

Available data suggest additive effects of inhaled NO and other vasodilators acting by the cGMP or cAMP systems (Phosphodiesterase inhibitors, Prostacycline), on pulmonary vasodilator effects and right ventricular performance. Therefore, administration of iNO in combination with these drugs should be done with caution. A possible synergy between the platelet anti aggregation effects of NO and prostacyclin and its analogues is suggested but has not been clinically demonstrated or detected.

Others

Nitric Oxide has been administered with dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation.

Experimental results suggest that NO and NO₂ can react chemically with the surfactant and/or the surfactant proteins.

ADVERSE EFFECTS

Summary of safety profile

Approximately 1250 children and over 400 adults received iNO (the exact number cannot be determined) in the included publications and clinical studies conducted by the sponsor.

The most common adverse effects of iNO are as follows:

-Abrupt discontinuation of the administration of iNO may cause rebound reaction such as increased PAP and hypoxaemia, precipitating cardiovascular collapse. The rebound may be seen early as well as late during therapy. (See DOSAGE AND ADMINISTRATION/discontinuation of therapy)

- After inhalation, one of the terminal compounds of NO found in the systemic circulation is methaemoglobin, which may cause increased methaemoglobinaemia.

No additional adverse effects were identified in studies conducted by the sponsor. Published data from paediatric and adult studies in cardiac surgery support the known safety profile for iNO.

Tabulated list of adverse reactions

Published adverse reactions are listed according to MedDRA frequency convention (very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ 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	-	Methaemoglobinemia ^a	-	-	-
Metabolism and nutrition disorders		-				-
Nervous system disorders	-	-	-	-	-	Headache ^c Dizziness ^c
Vascular disorders	-	Hypotension ^{a,b,d}	-	-	-	-
Cardiac disorders	-	-	-	-	-	Bradycardia ^b (following abrupt discontinuation of therapy)
Respiratory, thoracic and mediastinal disorders	-	Atelectasis ^a				Hypoxia ^{b,d} Dyspnea ^c Chest discomfort ^c Dry throat ^c

a: Identified from clinical trials studying patients with persistent pulmonary hypertension of the newborn

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.

Most of the Adverse Effects reported are from publications, the reporting of Adverse effects was not standardised in publications and may be limited; adverse effects and figures are sourced from studies (for which not all safety data was published in detail) and post-marketing surveillance (which was not conducted by the sponsor or available to the sponsor). The incidence of adverse effects are only approximations. Not all listed adverse effects have been observed with the use of VasoKINOX by the sponsor.

Post-marketing experience

Based on post-marketing experience, accidental; exposure to iNO in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnoea and headache.

The post-marketing surveillance did not identify other adverse effects than those already listed.

DOSAGE AND ADMINISTRATION

Dosage

Prescription of NO 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 NO delivery system. VasoKINOX should only be delivered according to an anaesthetist's or intensive care physician's prescription.

VasoKINOX should be used only after respiratory support has been optimised, according to the current clinical practices. Inhaled NO is usually given in addition to other standard treatment regimes in the peri-

operative setting, including inotropic and vasoactive medicinal products. VasoKINOX should be administered under close monitoring of haemodynamics and oxygenation.

Dosage is determined by the patient's clinical condition (severity of pulmonary arterial hypertension) and patient's age.

In children and adults, the recommended starting dose of iNO is 10 ppm of inhaled gas. The lowest effective dose should be administered. The effects of iNO are rapid usually observed within 5-20 minutes. In case of insufficient response the dose may be titrated after a minimum of 10 minutes. The maximum recommended is 20 ppm.

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. The duration of treatment in this situation is variable according to the pathology, the population treated and pulmonary circulation remodelling. Inhaled NO has been given for time periods up to 7 days in the perioperative setting, but common treatment times are 24 -48 hours.

Clinical data supporting the suggested dose in the age range of 12-17 years is limited

Discontinuation of therapy

The administration of VasoKINOX must not be stopped abruptly due to the risk of rebound (see PRECAUTIONS).

Weaning

Attempts to wean iNO should be started as soon as the haemodynamics have stabilised in conjunction to weaning from ventilator and inotropic support. The withdrawal of iNO treatment should be performed in a stepwise manner and under close monitoring of PAP. Weaning should be attempted at least every 12 hours when the patient is stable on a low dose of VasoKINOX.

The following withdrawal technique can be proposed. The dosage should be incrementally reduced to 1 ppm at least 30 minutes, with close monitoring of systemic and pulmonary arterial pressures and oxygenation, and then turned off. If, following withdrawal, a rise in PAP occurs, iNO can be recommenced at the lowest effective dose.

Too rapid weaning from iNO treatment carries the risk of an increase in pulmonary artery pressure with subsequent haemodynamic instability (re-bound effect).

Administration

Method

Endotracheopulmonary use

Do not use VasoKINOX undiluted.

Nitric oxide is administered by ventilation after dilution in an air/O₂ mixture. VasoKINOX should be administered in the inspiratory limb of the ventilator, and in any case as close as possible to the patient. Direct intratracheal administration must be avoided due to the risk of local lesions occurring on contact with the mucous membrane.

Before initiation of therapy, during set-up, ensure that the device setting is in agreement with the cylinder gas concentration.

The system used to administer VasoKINOX must allow for inhalation of a stable concentration of NO, regardless of the ventilator used. Furthermore, the contact time between NO and O₂ in the inspiration circuit should be kept to a minimum to limit the risk toxic oxidation by-product production in the inhaled gas (see PRECAUTIONS). With ventilators in "continuous flow" mode (conventional or high frequency oscillatory), VasoKINOX can be administered in continuous flow mode on the inspiratory limb.

With ventilators in sequential discontinuous flow mode, the NO administration system must be capable of managing gas peak concentration. Synchronised sequential administration at the inspiratory phase is recommended to avoid NO concentration peaks and bolus effect induced by continuous administration of the gas.

Nitric oxide is usually administered through a tracheal tube or with face mask and/or nasal cannulae, with all ventilation modes. VasoKINOX can be delivered by manual ventilation under certain clinical circumstances (e.g. suction, patient transport, resuscitation) with interruption of mechanical ventilation. The effective dose is not related to the type of ventilation (manual or mechanical).

Backup gas cylinders must be available to provide timely replacement.

In case of transport of patient treated by iNO, it will be advisable to make sure of the preservation of a continuous administration of the iNO during the transport.

Training

Hospital personnel have to be trained before using VasoKINOX with respect to delivery system and treatment monitoring. The supplier provides training to relevant hospital personnel, and ongoing 24-hour, 7 days a week technical support service, on the proper use of VasoKINOX in conjunction with the nitric oxide gas delivery system.

Administration and instruction for use

To avoid any incidents, the following instructions must be strictly adhered to:

- check that the equipment is in working order before use
- firmly secure the cylinders using chains or other suitable restraining methods to avoid any accidental falls
- never open a valve abruptly: open it counter clockwise, slowly and completely, then turn the valve back a quarter of turn
- do not handle a cylinder on which the valve is not protected by a shroud and a protective guard
- use a gas specific pressure regulator to connect to the cylinder valve: n°29 NO/N₂ (100 ppm < NO < 1000 ppm) W30x2 15.2-20.8 DR (ISO 5145)
- use a pressure regulator that admits a pressure at least equal to 1.5 the maximum operating pressure (200 bar) of the gas cylinder
- at each new use, purge the pressure regulator / flowmeter using VasoKINOX
- do not attempt to repair a defective valve or pressure regulator
- do not use tools to tighten the pressure regulator/ flowmeter. This may damage the regulator seal.
- evacuate exhaled gases outside (avoiding areas in which they may accumulate). Before use, it should be ensured that the room has the appropriate ventilation system for evacuating gases in the event of an accident or accidental leaks
- as nitric oxide is colourless and odourless, it is recommended using a gas detection system in all rooms in which it is to be used or stored to monitor for excessive ambient concentrations
- personnel exposure limits should not be exceeded (see section Exposure limit for medical personnel)

Incompatibilities

All equipment, including connectors, tubing and breathing circuits, used in the delivery of iNO must be made of materials compatible with the gas. The only recommended metal is stainless steel and the only tested polymers are polyethylene (PE) and polypropylene (PP).

Monitoring of treatment

Monitoring formation of nitrogen dioxide (NO₂):

Nitrogen dioxide can form rapidly in gaseous mixtures containing NO and O₂, which may cause an inflammatory reaction and airway lesions. The concentrations of iNO, NO₂ and FiO₂ must be measured continuously in the inspiratory circuit near to the patient using the appropriate certified equipment (Australian approved medical device).

The concentration of NO₂ in the inhaled air must remain as low as possible.

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 VasoKINOX dose and/or FiO₂ should be reduced if possible (see PRECAUTIONS/formation of NO₂). If there is an unexpected change in VasoKINOX concentration, the delivery system should be assessed for malfunction and the analyser should be recalibrated.

During treatment:

For the safety of the patient, alert thresholds must be set:

- NO ± 2 ppm of the prescribed dosage,
- NO₂: 0.5 ppm
- FiO₂ ± 0.05

If at any time the NO₂ concentration exceeds 0.5 ppm, the NO dose should immediately be reduced.

For discontinuous-flow volumetric ventilators, spirometry monitoring can detect an increase in VasoKINOX flow if a difference is observed between the inspired volume and expired volume.

The pressure in the VasoKINOX cylinder must be displayed to allow for rapid replacement of an empty cylinder so as not to abruptly interrupt treatment. Replacement cylinders must be kept available nearby.

Monitoring formation of methaemoglobin:

Neonates and infants are known to have diminished methaemoglobin reductase activity compared to adults, and therefore a more rapid rise in methaemoglobin can occur in infants than in adults.

Methaemoglobin level should be measured within one hour after initiation of VasoKINOX therapy, using an analyser which can reliably distinguish between foetal haemoglobin and methaemoglobin. If methaemoglobin level is >2.5 %, the VasoKINOX 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, methaemoglobin level should be measured within one hour of the initiation of VasoKINOX therapy. If methaemoglobin level is >2.5 %, the VasoKINOX dose should be decreased and the administration of reducing medicinal products such as methylene blue may be considered.

Exposure limit for medical personnel:

The Australian National Occupational Health and Safety Commission's adapted national exposure standards for atmospheric contaminants in the occupational environment (NOHSC:1003 (1995) recommend the following exposure limits:

- NO: (TWA*): 25 ppm (31 mg/m³)
- NO₂: TWA 3 ppm (5.6mg/m³); Short term exposure limit (STEL*): 5 ppm (9.4 mg/m³)

For the above recommendations to be met, a monitoring program for NO and NO₂ content in the atmosphere must be in place.

* TWA :Time-weighted Average, STEL: Short term exposure limit

OVERDOSAGE

A VasoKINOX overdose causes an increase in methaemoglobin and NO₂ levels. A high concentration of NO₂ can provoke acute pulmonary lesions and cases of pulmonary oedema have been reported after administration of high concentrations of iNO.

Course of action in the event of accidental patient overdose:

- symptomatic treatment of respiratory disorders,
- in the event of persistent methaemoglobinaemia despite the reduction or interruption of the treatment, an intravenous injection of vitamin C or methylene blue, or blood transfusion should be considered depending on the patient's clinical condition.

Course of action in the event of massive inhalation due to accidental leaks:

- medical observation for at least 24 hours
- in the event of respiratory disorders, symptomatic treatment should be administered

For further advice on overdosage, contact the Poisons Information Centre on 131126 (Australia)

PRESENTATION AND STORAGE CONDITIONS

Presentation

VasoKINOX is available in the following sizes:

5 L: aluminium alloy cylinder (white painted body, turkish blue painted shoulder), equipped with a stainless steel residual pressure valve with a specific outlet connector.

11L: aluminium alloy cylinder (white painted body, turkish blue painted shoulder), equipped with a stainless steel residual pressure valve with a specific outlet connector.

20 L: aluminium alloy cylinder (white painted body, turkish blue painted shoulder), equipped with a stainless steel residual pressure valve with a specific outlet connector.

Storage

The cylinders must be stored at a temperature of between -10 and + 50°C.

The installation of a NO pipeline system with supply station of gas cylinders, fixed network and terminal units is forbidden.

Storage in the pharmacy department

Cylinders must be stored in a clean, well-ventilated, locked room reserved for the storage of gases for medicinal use. A specific area inside this room will be reserved for storing VasoKINOX cylinders. These should be protected so as to avoid breakage and falling. They should also be kept away from any oxidizing and combustible materials and humidity.

Storage in the user department

Cylinders must be installed in an equipped area with appropriate equipment to maintain them in a vertical position at all times. Cylinders must be protected to avoid breakage or falling and be kept away from any sources of heat or ignition, oxidizing and combustible materials and humidity.

Cylinder Transportation

Cylinders must be transported using the appropriate equipment (trolley equipped with chains, barriers or rings) to protect them from breakage or falls. During inter- or intra-hospital transfer of patients receiving NO treatment, the cylinders must be firmly secured to hold them in the vertical position and to avoid the risk of falling. Special attention must also be paid to the securing of the pressure regulator to avoid the risk of accidental breakage.

Instruction for cylinder disposal

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

POISON SCHEDULE OF THE MEDICINE

S4

Attachment 1: Product information for AusPAR Attachment 1: Product Information for Vasokinox nitric oxide Air Liquide Healthcare Pty Ltd PM-2014-04327-1-3 FINAL 15 January 2018. This Product Information was approved at the time this AusPAR was published.

DISPOSAL

Do not discard empty or damaged cylinders. These must be returned to the supplier.

NAME AND ADDRESS OF SPONSOR

AIR LIQUIDE AUSTRALIA Limited
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Melbourne, VIC,
AUSTRALIA, 3004

NAME AND ADDRESS OF SUPPLIER

AIR LIQUIDE Healthcare Australia Pty. Ltd.
Unit 5/476 Gardeners Road,
Alexandria, NSW, AUSTRALIA, 2015

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS:

16 January 2017

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