Air Liquide HEALTHCARE | KINOX™

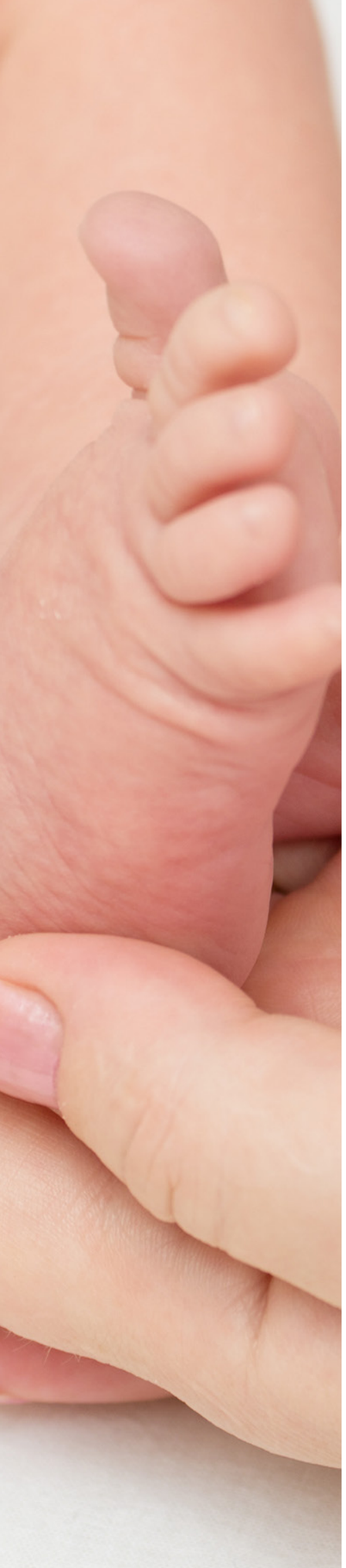
Keen on Innovation

for the administration and monitoring of inhaled NO

INHALED NO

TECHNOLOGY

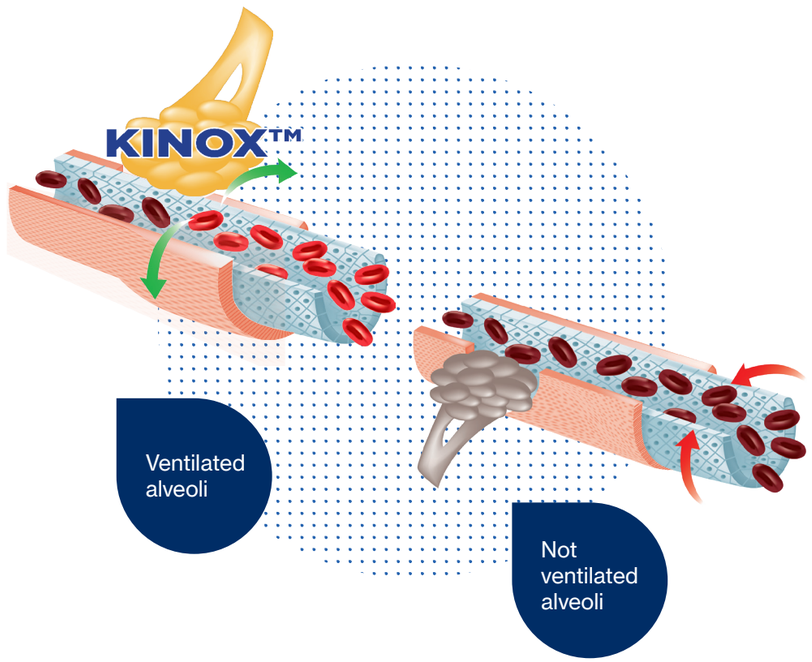
SERVICES



KINOX™ inhaled NO

KINOX™, inhaled nitric oxide, is a selective pulmonary vasodilator developed by Air Liquide Healthcare and characterized by:

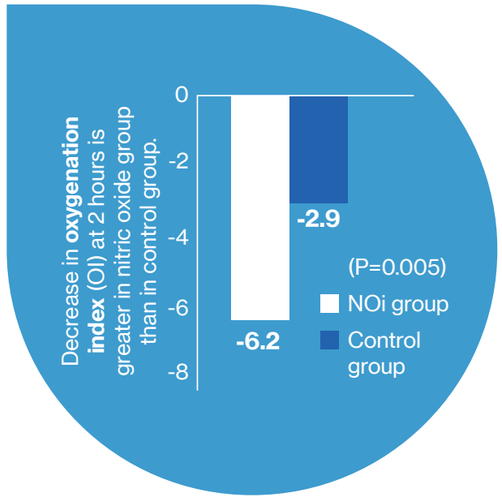
- A rapid and reversible action[1]
- A selective vasodilator which redistributes pulmonary blood flow[1]
- Reduces the oxygenation index (OI) and increases PaO_2[1]
- Absence of systemic effect[2]
- Reduction in the shunt effect (V/Q) by acting only on ventilated alveoli[2]



KINOX™ 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[1]

In persistent pulmonary hypertension of the newborn, inhaled nitric oxide has been proven to:

- Improve arterial oxygenation and shorten duration of mechanical ventilation and stay in ICU (Franco-Belgium collaborative NO Trial)[3]



Mercier: prospective, randomized, controlled, multicenter study of inhaled Nitric Oxide in preterm (<33 weeks) and near-term (>33 weeks) neonates with respiratory failures and an oxygenation index (OI) from 12.5 to 30.0 and 15 to 40, who required assisted ventilation. Patient received eitheir inhaled nitric oxide 10 ppm (n=105) or control ventilation therapy (n=99). The primary endpoint was the oxygenation index at 2 hours.

- Reduce the incidence of the initiation of extracorporeal membrane oxygenation (ECMO)[4,5] without increasing the incidence of adverse outcomes at 1 year of age[6]

Summary of the large, multicenter, randomized trials of iNO in term newborns with hypoxemic respiratory failure or PPHN, showing the effect of iN0 on ECMO use, mortality, and neuro-developmental impairment.

Study	N	Initial oxygenation Index	% ECMO		% Mortality	
			Control	**iNO**	Control	iNO
Neonatal Inhaled Nitric Oxide Study Group[8]	235	44	**55**	**39***	17	14
Clark et al[9]	248	39	**64**	**38***	8	7

* $p < 0.05$; significant reduction

NINOS: A prospective randomized, double blind, placebo-controlled, multicenter study of inhaled nitric oxide in term and near-term (≥34 weeks gestation and ≤14 days old) infants with HRF and oxygenation index (OI) ≥25 who required assisted ventilation. Patients received the most aggressive forms of therapy before randomization. Patients received either nitric oxide 20 PPM (n=114) or 100% oxygen (n=121) for a maximum of 14 days. The primary endpoint was use of ECMO and/or death by day 120.

Clark: A randomized, physician-blinded, placebo-controlled, multicenter study of low dose of Nitric oxide in near-term newborns (≥34 weeks' gestation and ≤4 days old) with PPHN and an OI ≥25 who required assisted ventilation. Inhaled NO (n=126) was dosed as 20 ppm for up to 24 hours, followed by 5ppm up to 96 hours. Patients rendomized to placebo received N2 gas (n=122). The primary endpoint was oxygenation index at 2 hours.

KINOX™ inhaled NO

KINOX™ is indicated, in conjunction with ventilator support and other appropriate agents, for the treatment of[1]

- 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

KINOX™ is available in 800 PPM concentration, in 2 cylinder sizes[1]

- Dosage form: 800 PPM
- 2 sizes: 362 L cylinder (sz MD15) and 2138 L cylinder (sz NO88)

Air Liquide Healthcare labelling clearly identifies the drug, its concentration and expiry date

KINOX™ posology

Initial dose of inhaled NO should be 20 PPM, but the principle of the lowest effective dose must remain a rule to limit the toxicity[1]

The initial dose of nitric oxide should be as low as possible and in no cases higher than 20 PPM for no more than 4 hours.

In cases of failure to respond to nitric oxide at 4-6 hours after starting therapy, further steps should be considered to ensure adequate ventilation and recruitment. Between 4-24 hours, attempts should be made to decrease the dose as quickly as possible to 5 PPM[1]

Method of administration

KINOX™ is to be introduced in the respiratory circuits with an air/oxygen mixture and this device must provide:

- Reliable and precise sequential administration[2]
- Constant concentration proportional to ventilatory flow
- Ability to administer dosage as low as 0.1 PPM

The device must also contain a pneumatic back-up system to assure uninterrupted treatment in any situation

Monitoring of treatment[2,1]

The inspired NO, NO_2 and FiO_2 concentrations must be measured continuously in the inspiratory limb of the respiratory circuit near the patient. The device must include monitoring of values and comprehensive alarms

Weaning[1]

KINOX™ treatment must not be stopped abruptly to avoid risk of increasing pulmonary arterial pressure and/or inducing rebound hypertension. Weaning from inhaled nitric oxide must be progressive and carried out with precaution as per the drug monograph

SoKINOX™

evolving to inspire better care

SoKINOX™ brings inhaled NO therapy to the next level

Delivering excellence

- SoKINOX™ delivers an innovative and intuitive inhaled Nitric Oxide therapy dosing and monitoring device with a simplified business model. Providing reliability, accuracy, and ease of use for clinicians in a constantly changing healthcare environment.

Continuous improvement

- SoKINOX™ has been designed and developed incorporating important human factor principles and testing. The development team is continuously improving the device and its user interface to exceed the evolving clinical and patient acuity requirements.

24/7 clinical support

- Our knowledgeable in-house clinical affairs team is dedicated to Canadian healthcare professionals, supporting the delivery of NO using SoKINOX™ with clinical application expertise and training.

SoKINOX™ technology

KINOX™ and its user-friendly device SoKINOX™ inspire breath into life

Universal

- SoKINOX™ functions with various ventilation modes, for all types of patients, thanks to its reliable and disposable flow sensor

Intuitive controls

- The large tactile colour screen provides clear and organized information with numeric dosing features, making the device very intuitive and user friendly

Compact

- Its compact design includes a pneumatic hand-bagging KINOX™ administration system in case of emergency, transport, or the need for alveolar recruitment

The easy-to-use interface features a quick pre-use check with integrated setup instructions to facilitate a rapid and error-free response in emergencies

SO SAFE, SO INNOVATIVE – SoKINOX™

Key safety features:

- **Automatic Cylinder Switch** – SoKinox™ uniquely detects when the level of a cylinder is low, and switches automatically to the other cylinder - ensuring treatment continuity, while minimizing user manipulations
- **Automatic Emergency Dosing** – SoKinox™ allows continuation of therapy in certain critical situations
- Back-up system with a manual mode which is independent of the main system
- Automatic purging of device and cylinders
- User configurable default parameters and alarm level

Key innovative features:

- **Gas Supply Calculator** – allows the clinician to validate precisely how long a cylinder will last, based on ventilatory parameters and the set NO dose
- **AUTOSENSE and CONSTANT RATE Settings** – allows the clinician to select flow feedback from injector module for precise dosing
- **Flow and Trend Waveforms Display** – clear and simple format to visualize pertinent patient information
- **Two Flow Sensors available** – allowing a wide range of flows from 0.25-120 LPM
- **High Range Sensor Calibration** – required every 3 months or as needed

SoKINOX™ allows for information to be downloaded to a USB, as well as electronic charting compatibility (through RS232 port)

KINOX™ + services

KINOX™ + is our a comprehensive support solution including implementation, ongoing clinical resources, troubleshooting and service support

Implementation

- **Complete training program** provided to Respiratory Therapists and medical staff, which includes device and clinical application training
- Delivery of a **complete start-up kit** for each department

Ongoing clinical education

- Training and quick reference tools for the clinicians
- Comprehensive in-service training video, which guides you through various procedures on the use of SoKINOX™
- Ongoing education as needed

24/hour support & preventative maintenance

- KINOX™ + also includes a preventative maintenance program and SoKINOX™ troubleshooting through our 24/hour support line **(1-833-SOKINOX)**

KINOX™ safety information

The safety and effectiveness of nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation[1]

- In clinical trials, no efficacy has been demonstrated with the use of inhaled nitric oxide in patients with congenital diaphragmatic hernia[1]
- In patients with the rare cardiovascular defect in which the systemic oxygenation is wholly dependent on extra-pulmonary right-to-left shunting, the use of inhaled nitric oxide has the potential to decrease right-to-left blood flow, which, in this condition, is potentially fatal[1]
- Methemoglobinemia is a dose-dependent side effect of inhaled nitric oxide therapy Therefore, methemoglobin levels should be monitored during KINOX™ administration. Methemoglobinemia increases with the dose of nitric oxide. If methemoglobin levels are >2.5%, the nitric oxide dose should be decreased. Caution should be used when administering KINOX™ with other drugs that may cause methemoglobinemia regardless of their route of administration[1]
- Nitrogen dioxide (NO_2) forms rapidly in gas mixtures containing nitric oxide and oxygen. NO_2 formed in this way may cause airway inflammation and damage. The dose of nitric oxide should be reduced if the concentration of nitrogen dioxide exceeds 0.5 PPM[1]
- Abrupt discontinuation of KINOX™ therapy may lead to worsening of PaO_2 and increasing pulmonary artery pressure (PAP). Deterioration in oxygenation and elevation in PAP may also occur in patients with no apparent response to KINOX™[1]

REFERENCES

1. KINOX™ Product Monograph, Air Liquide Healthcare America Corporation, 2016
2. Fumito Ichinose: A selective Pulmonary Vasodilator: Current uses and therapeutic potential. Circulation 2004:109:3106-3111.
3. The Franco-Belgium Collaborative NO Trial Group. Early compared to delayed inhaled nitric oxide in moderately hypoxemic neonates with respiratory failure: a randomized controlled trial. Lancet 1999:354:1066-1071
4. The Neonatal inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. N Eng J Med 1997: 336: 597-604.
5. Clark. R.H et al. Low dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. NEJM volume 342, number 7
6. Clark. R.H et al. Low dose nitric oxide therapy for persistent pulmonary hypertension: 1 year follow-up. J Perinatol 2003:23:300-303

KINOX™

KINOX™, its user-friendly device SoKINOX™ and reliable services KINOX + inspire breath into life

- **KINOX™**
  inhaled nitric oxide is a selective pulmonary vasodilator developed by Air Liquide Healthcare
- **SoKINOX™**
  brings easy-to-use inhaled NO to the next level: universal, intuitive, controlled and compact
- **KINOX™ +,**
  a range of clinical, training and maintenance support services to assist you at any time

Contact

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Changing care. With you.

Air Liquide HEALTHCARE

Air Liquide Healthcare is a world leader in medical gases, home healthcare, hygiene products and healthcare specialty ingredients. It aims to provide customers in the continuum of care from hospital to home with medical products, specialty ingredients and services that contribute to protecting vulnerable lives.

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