PRODUCT MONOGRAPH

Pr *Noxivent™*

nitric oxide for inhalation

100 ppm and
800 ppm

Medical Gas

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ACTIONS AND CLINICAL PHARMACOLOGY

Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the heme 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. Nitric oxide is very rapidly inactivated by binding to hemoglobin. Thus, delivered via inhalation, nitric oxide improves V/Q matching and is a selective pulmonary vasodilation agent.

Inhaled nitric oxide 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.

Effects on Pulmonary Vascular Tone in PPHN: 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. Inhalation of nitric oxide reduces the oxygenation index (OI= mean airway pressure in cm H_2O x fraction of inspired oxygen concentration [FiO_2] x 100 divided by systemic arterial concentration in mm Hg [PaO_2]) and increases PaO_2.

Clinical Studies

The efficacy of nitric oxide has been investigated in term and late pre-term newborns with hypoxic respiratory failure, resulting from a variety of etiologies, who had oxygenation index (OI) measurements of $\geq$ 25 cm H_2O/mm Hg.

In a post-hoc subgroup analysis of data from the NINOS and CINRGI studies, the clinical benefit measured by the receipt of ECMO was greater for the subgroups of patients who did not meet the study ECMO criteria at study entry (NINOS) or whose baseline OI was less than 40 cm H_2O/mm Hg (CINRGI).

NINOS study: The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates ($\geq$ 34 weeks gestational age) with hypoxic respiratory failure and OI values of $\geq$ 25 cm H_2O/mm Hg.

The objective of the study was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO) in a prospectively defined cohort of term or late pre-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants up to 14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mm Hg were initially randomized to receive 100% O2 with (n=114) or without (n=121) 20 ppm nitric oxide for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = > 20 mm Hg, partial = 10-20 mm Hg, no response = <10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm nitric oxide or control gas. The primary results for the intent-to-treat (ITT) population are presented in Table 1.

Table 1
Summary of Clinical Results from NINOS Study
ITT Population

	Control (n=121)	NO (n=114)	P value	Absolute rate reduction (%)	Relative rate reduction (%)
Death or ECMO[a,b]	77 (64%)	52 (46%)	0.006	-18.0	-28.3
Death	20 (17%)	16 (14%)	0.60	Not applicable	Not applicable
ECMO	66 (55%)	44 (39%)	0.014	-15.9	-29.2

[a] Extracorporeal membrane oxygenation
[b] Death or need for ECMO was the study's primary end point

Although the incidence of death by 120 days of age was similar in both groups (NO, 14%; control, 17%), significantly fewer infants in the nitric oxide group required ECMO compared with controls (39% vs. 55%, p = 0.014). The combined incidence of death and/or initiation of ECMO showed a significant advantage for the nitric oxide treated group (46% vs. 64%, p = 0.006).

The primary efficacy endpoint assessed by the actual gas received was evaluated in a post-hoc analysis and is presented in Table 2.

Table 2
Summary of Clinical Results from NINOS Study
Actual-Gas-Received Population

	Control (n=116)	NO (n=119)	P value	Absolute rate reduction (%)	Relative rate reduction (%)
Death or ECMO[a,b]	72 (62%)	57 (48%)	0.036	-14.2	-22.8
Death	18 (16%)	18 (15%)	1.000	Not applicable	Not applicable
ECMO	62 (53%)	48 (40%)	0.050	-13.1	-24.5

[a] Extracorporeal membrane oxygenation
[b] Death or need for ECMO was the study's primary end point

The response rate (full response, partial response, no response) to 20 ppm inhaled nitric oxide for the actual-gas-received population was also determined in a post-hoc analysis and is presented in Table 3.

Table 3
Response Rate to Study Gas
Actual-Gas-Received Population

Response	Placebo (n=112)	NO (n=117)
Full (>20 torr increase in PaO2 30 minutes)	16 (14.3%)	58 (49.6%)
Partial (10-20 torr increase in PaO2 30 minutes)	13 (11.6%)	17 (14.5%)
No (<10 torr increase in PaO2 30 minutes)	83 (74.1%)	42 (35.9%)

Data also showed that only 5.5% of neonates who did not respond, or partially responded to the inhaled nitric oxide therapy at a 20 ppm dose were converted to full response with 80 ppm inhaled nitric oxide, indicating no additional benefit of inhaled nitric oxide at 80 ppm. These findings are consistent with conclusions from the original ITT population.

The rate of death or receipt of ECMO was assessed in a post-hoc analysis of the actual-gas-received population by initial response to 20 ppm inhaled nitric oxide, and is presented in Table 4.

Table 4
ECMO Receipt by Initial Response Status
Actual-Gas-Received Population

Response	Rate of Death or ECMO				
	Placebo (n=112)	**NO (n=117)**	**P Value***	**Absolute rate reduction (%)**	**Relative rate reduction (%)**
Fully responded in the first 30 minutes**	8/16 (50%)	15/58 (25.9%)	0.076	-24.1	-48.2
Partial or no response in the first 30 minutes	63/96 (65.6%)	40/59 (67.8%)	0.862	2.2	3.4

* p-value from Fisher's 2-tailed exact test
** full response was defined as $\geq$ 20 mm Hg increase in PaO_2 after 30 minutes of gas treatment

These results showed that the rate of death or receipt of ECMO between treatment groups differed according to the initial response to 20 ppm inhaled nitric oxide, indicating that patients who initially did not fully respond to inhaled nitric oxide therapy in the first 30 minutes of treatment did not benefit significantly from the therapy.

The nitric oxide group had significantly greater increases in PaO_2 and greater decreases in the OI and the alveolar-arterial oxygen gradient than the control group ($p<0.001$ for all parameters).

No infant had study drug discontinued for toxicity. Inhaled nitric oxide had no detectable effect on mortality. The adverse events collected in the NINOS trial occurred at similar incidence rates in both treatment groups. (See **Adverse Reactions**).

CINRGI study: This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and late pre-term neonates ($\geq$ 34 weeks gestational age) with pulmonary hypertension and hypoxic respiratory failure, with OI values of $\geq$ 25 cm H_2O/mm Hg. The primary objective of the study was to determine whether nitric oxide would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was caused by MAS (35%), idiopathic PPHN (30%), pneumonia/sepsis (24%), or RDS (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean OI of 44 cm H_2O / mm Hg were randomly assigned to receive either 20 ppm nitric oxide (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO_2 >60 mm Hg and a pH < 7.55 were weaned to 5 ppm nitric oxide or placebo. The maximum duration

of nitric oxide therapy was 96 hours. The primary results from the CINRGI study are presented in Table 5.

Table 5
Summary of Clinical Results from CINRGI Study

	Placebo	Nitric Oxide	P value	Absolute rate reduction (%)	Relative rate reduction (%)
ECMO [a,b]	51/89 (57%)	30/97 (31%)	< 0.001	-26.4	-46.0
Death	5/89 (6%)	3/97 (3%)	0.48	Not applicable	Not applicable

[a] Extracorporeal membrane oxygenation
[b] ECMO was the primary end point of this study

Significantly fewer neonates in the nitric oxide group required ECMO compared to the control group (31% vs. 57%, p<0.001). While the number of deaths were similar in both groups (nitric oxide, 3%; placebo, 6%), the combined incidence of death and/or receipt of ECMO was decreased in the nitric oxide group (33% vs. 58%, p<0.001).

In addition, the nitric oxide 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 nitric oxide, 2 (2%) were withdrawn from study drug due to methemoglobin levels > 4%. The frequency and number of adverse events reported were similar in the two study groups (See **Adverse Reactions**).

INDICATION AND CLINICAL USE

Noxivent™, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and late pre-term ($\geq$ 34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

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.

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

An adequate pharmacovigilance study, over a minimum of 5 years, will be carried out to confirm the long-term effects associated with the use of inhaled nitric oxide in neonates.

CONTRAINDICATIONS

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 *Noxivent*™ has the potential to decrease right-to-left blood flow, which, in this condition, is potentially fatal.

WARNINGS

Left to Right Shunting

Treatment with *Noxivent*™ 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. It, therefore, is recommended that prior to the administration of nitric oxide, pulmonary artery catheterization or echocardiographic examination of central hemodynamics be performed.

PRECAUTIONS

General

Initiate any alternative therapies as soon the infant's condition demands, regardless of the response or lack of response to *Noxivent*™.

If it is judged that clinical response is inadequate at 4-6 hours after starting *Noxivent*™, 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 *Noxivent*™*,* the availability of nitric oxide during transport should be assured. Rescue, such as ECMO where available, should be considered based on continued deterioration or failure to improve, defined by local hospital criteria.

Long-term effects, particularly with regard to pulmonary and neurodevelopmental outcomes associated with nitric oxide, have not been established beyond 18-24 months.

The 18-24 months follow-up study of NINOS subjects was based on a relatively small number of patients treated with placebo (n=84) and inhaled nitric oxide (n=88), and the one-year follow-up data of CINRGI subjects was based on 71 patients in the placebo and 74 patients in the inhaled nitric oxide groups. In view of the potential long-term sequelae associated with the underlying condition, persistent pulmonary hypertension of the newborn, and the unknown long-term effects of nitric oxide, it is recommended that these babies be monitored long-term regarding pulmonary, neurodevelopmental, growth and auditory outcomes.

Health professionals at neonatal units that administer *Noxivent*™ should be properly trained (**see Training in Administration**) and familiar with the instructions for use of the nitric oxide delivery system. They should have access to supplier-provided 24 hour/365 days per year technical support on the delivery and administration of *Noxivent*™.

In order to avoid errors in the delivery of *Noxivent*™, health professionals that administer nitric oxide should ensure that the mode and make of mechanical ventilation being utilized are compatible with the *Noxivent*™ delivery system.

Rebound Pulmonary Hypertension following Abrupt Discontinuation
Noxivent™ should not be discontinued abruptly as it may result in rebound pulmonary hypertension (increase in pulmonary artery pressure and worsening of blood oxygenation). If rebound pulmonary hypertension occurs, reinstate therapy immediately.

Rapid rebound reactions have been described and can precipitate cardiopulmonary collapse, even in patients without substantial oxygenation improvement. The patient should be treated with increased FiO_2 and by reinstallment of therapy with *Noxivent*™. When possible, *Noxivent*™ should be continued until the underlying disease has resolved. Weaning from *Noxivent*™ should be performed with caution. See **Dosage and Administration** section**.**

Deterioration in oxygenation and elevation in pulmonary artery pressure may also occur in neonate with no apparent response to *Noxivent*™. Again, weaning from *Noxivent*™ should be performed with caution. See **Dosage and Administration** section.

Methemoglobinemia
Neonates are known to have diminished methemoglobin reductase activity compared to adults and could therefore be at greater risk of developing methemoglobinemia. The concentrations of methemoglobin in the blood should be monitored as *Noxivent*™ is absorbed systemically and the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrate. See **Monitoring Methemoglobin** under **Dosage and Administration**.

Methemoglobinemia increases with the dose of nitric oxide. If methemoglobin levels are > 2.5%, the *Noxivent*™ dose should be decreased and the administration of reducing agent such as methylene blue may be considered. Following discontinuation or reduction of *Noxivent*™*,* methemoglobin levels should return to baseline over a period of hours. If methemoglobin levels do not resolve after discontinuation or reduction of

therapy additional measures may be warranted, see **Symptoms and Treatment of Overdosage** section.

Airway Injury from 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 *Noxivent*™ should be reduced if the concentration of nitrogen dioxide exceeds 0.5 ppm. See **Monitoring Nitrogen Dioxide** under **Dosage and Administration**.

In one study, NO_2 levels were < 0.5 ppm when neonates were treated with placebo, 5 ppm, and 20 ppm nitric oxide over the first 48 hours. The 80 ppm group had a mean peak NO_2 level of 2.6 ppm.

Heart Failure
Patients with left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest). Discontinue *Noxivent*™ while providing symptomatic care.

Bleeding Time
Animal models have shown that nitric oxide may interact with homeostasis, resulting in an increased bleeding time. Data in adult humans are conflicting. Inhaled nitric oxide has been found to approximately double bleeding time in a limited study in rabbits and humans. However, there has been no statistically significant increase in bleeding complications in randomized controlled trials in term and late pre-term neonates with hypoxic respiratory failure.

Adults
Noxivent™ is not indicated for use in the adult population.

Use in Pregnancy
Animal reproduction studies have not been conducted with inhaled nitric oxide. It is not known if nitric oxide can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Passive exposure to nitric oxide during pregnancy and lactation should be avoided. *Noxivent*™ is not intended for adults.

Nursing Mothers
Noxivent™ is not indicated for use in the adult population, including nursing mothers. It is not known whether nitric oxide is excreted in human milk.

Pediatric Use
Nitric oxide for inhalation has been studied in a neonatal population up to 14 days of age who were $\geq$ 34 weeks gestational age. No information about its effectiveness in other age populations is available. Although clinical studies are ongoing, the efficacy and safety of nitric oxide for neonates less than 34 weeks gestational age has not been established. *Noxivent*™ is not indicated for neonates less than 34 weeks gestational age.

Drug Interactions
Experimental studies have suggested that nitric oxide and nitrogen dioxide may react chemically with surfactant and/or surfactant proteins. No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. In particular, although there are no data to evaluate the possibility nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with nitric oxide on the risk of developing methemoglobinemia. Nitric oxide has been administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. *Noxivent*™ should be used with caution in patients receiving NO donor compounds (e.g. nitroprusside, nitroglycerine, and substances known to increase methemoglobin) because of the potential of methemoglobinemia.

Laboratory Tests
Noxivent™ should be administered with monitoring for PaO_2, methemoglobin, and NO_2. Methemoglobin levels should be measured within one hour after initiation of *Noxivent*™ therapy and periodically throughout the treatment period using an analyzer, which can reliably distinguish between fetal hemoglobin and methemoglobin. See **Monitoring Methemoglobin** and **Monitoring Nitrogen Dioxide** under **Dosage and Administration**.

ADVERSE REACTIONS

The NINOS and CINRGI studies were not powered to detect statistically significant differences with regards to adverse events between the placebo and inhaled nitric oxide treatment groups.

In the NINOS trial, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage. The following post-hoc analysis shows the distribution of selected adverse events in the NINOS trial for the actual-drug-received population (n=235).

Selected adverse events in the NINOS trial*
Actual-Gas-Received Population

Adverse Events	Placebo (n=116)	iNO (all doses)** (n=119)
Air Leak	14 (12.1%)	18 (15.1%)
Cerebral or Intracranial Infarct***	21 (18.1%)	21 (17.6%)
Seizures Requiring Treatment	22 (19.0%)	18 (15.1%)
Periventricular leukomalacia (PVL)***	3 (2.6%)	6 (5.0%)
Other CNS Insult	15 (12.9%)	11 (9.2%)
Pulmonary Hemorrhage***	5 (4.3%)	5 (4.2%)
Prolonged Oozing from Heel Stick	9 (7.8%)	8 (6.7%)
GI Bleeding	1 (0.9%)	1 (0.8%)
New Intraventricular hemorrhage (IVH)***	6 (5.2%)	5 (4.2%)

* The NINOS study prospectively planned to collect only adverse events of particular interest; all adverse events were not systematically collected.

**Patients received maximum 20 ppm or 80 ppm inhaled nitric oxide as per the study protocol.

*** In a post-hoc analysis, among patients who did not receive ECMO and considering only the 20 ppm dose, there were numerical increases in the following outcomes: cerebral/intracranial infarct, periventricular leukomalacia, pulmonary hemorrhage, and new intraventricular hemorrhage although there are limitations to such post-hoc analyses.

The table below shows adverse events with an incidence of at least 5% on nitric oxide in the CINRGI study, and that were more common on nitric oxide than on placebo.

Adverse events in the CINRGI trial

Adverse Events	Placebo (n=89)	Inhaled NO (n=97)
Hypotension	9 *(10%)*	13 *(13%)*
Withdrawal	9 *(10%)*	12 *(12%)*
Atelectasis	8 *(9%)*	9 *(9%)*
Hematuria	5 *(6%)*	8 *(8%)*
Hyperglycemia	6 *(7%)*	8 *(8%)*
Sepsis	2 *(2%)*	7 *(7%)*
Infection	3 *(3%)*	6 *(6%)*
Stridor	3 *(3%)*	5 *(5%)*
Cellulitis	0 *(0%)*	5 *(5%)*

Data from a post-hoc analysis among patients in the CINRGI study who did not receive ECMO (not randomized sample) showed that inhaled nitric oxide patients had numerical increases in the following adverse events: tachycardia, hypokalemia, infection, fever, cellulites, coagulation disorder, hemorrhage, deafness, and hematuria.

In the NINOS study, doses of inhaled nitric oxide up to 80 ppm and duration of therapy up to 14 days were permitted. Also the delivery devices used in the NINOS study were not able to provide a consistent dose of inhaled nitric oxide, on the other hand, the standardized delivery devices were used in CINRGI study to provide a consistent dose of inhaled nitric oxide. Consequently, 42.9% of patients in the NINOS study (at maximum dose of 20 ppm) exceeded the proposed 0.5 ppm threshold for NO_2 while only 9.7% of patients exceeded this threshold in the CINRGI study. Similarly, 26.4% patients in the NINOS study and 3.6% in the CINRGI study exceeded the proposed 2.5% threshold for methemoglobin level. These results indicate the importance of using standard delivery devices for the safe administration of inhaled nitric oxide therapy.

Long-term Safety

Follow-up exams were performed at 18-24 months for the infants enrolled in the NINOS study. In the infants with available follow-up, there were no statistically significant differences between the two treatment groups with respect to their mental, motor, audiologic, visual or neurologic evaluations. Seventy-four and one-half percent (74.5%) of infants in inhaled nitric oxide group and 76.1% in placebo group were classified as neurologically normal. Mental development of the infants, as assessed by the Bayley scale of mental developmental index (MDI) was similar between the treatment groups. However, a post-hoc analysis of adverse events for the actual-gas-received population showed some numerical differences between treatment groups (see the table below).

Adverse Events at 18-24 months of follow-up in NINOS subjects
Actual-gas-received population

Adverse Events	Placebo	INO (all doses)*
Gait Disturbance (gait functional, gait device required, and no independent walking)	15/84 (17.9%)	22/88 (25.0%)
Cerebral Palsy Present	8/84 (9.5%)	11/88 (12.5%)
At Least One Seizure Since Discharge	12/85 (14.1%)	5/88 (5.7%)
Sensorineural Loss	6/75 (8.0%)	8/73 (11.0%)
Mean Bayley PDI STD	94.4 ± 17.9	85.0 ± 21.3
PDI < 50	3/76 (3.9%)	11/83 (13.3%)

*Patients received maximum 20 ppm or 80 ppm iNO as per the study protocol.

Long-term effects of nitric oxide, particularly with regard to pulmonary and neurodevelopmental outcomes, have not been established beyond 18-24 months.

Data from the one-year follow-up of CINRGI study subjects (85% follow-up rate) showed that patients in the inhaled nitric oxide group had a higher percentage of hearing loss (4%) than those in the placebo group (0%)[1]. Additionally, patients treated with inhaled nitric oxide had higher percentages of cerebral palsy (4%) than those treated with placebo (1%).

Data from the one-year follow-up of 145 patients of the original 155 infants in the non-pivotal study INO-01/02 showed that 23% of patients in the inhaled nitric oxide group and 14% in placebo group had severe impairment of overall assessment of neurologic status at one year. The patients in this study were treated with three doses of inhaled nitric oxide (5 ppm, 20 ppm and 80 ppm). However, there was no clear dose–response relationship between the adverse event and the inhaled nitric oxide dose.

The overall 5-year follow-up rate of NINOS and CINRGI study subjects was only 25%. The 5-year follow-up data were based on 43 patients in the placebo group and 55 patients in the inhaled nitric oxide group. Patients treated with inhaled nitric oxide had a significantly higher incidence of gait disturbance at 5-year follow-up (16% in inhaled nitric oxide group versus 2% in placebo group, p=0.04). Additionally, the percentage of vision problems, recurrent non-febrile seizures was numerically higher among inhaled nitric oxide patients. Due to the 25% follow-up rate, valid conclusions cannot be made.

Post-marketing Experience
In addition to adverse events reported from clinical trials, the following adverse drug reactions have been identified in neonates (≤ 1 month of age):

Cardiac Disorders: bradychardia following abrupt discontinuation of therapy.

Respiratory, Thoracic and Mediastinal Disorders: hypoxia following abrupt discontinuation of therapy.

Vascular Disorders: hypotension following abrupt discontinuation of therapy.

Accidental Exposure: Chest discomfort, dizziness, dry throat, dyspnea, and headache have been reported in hospital staff after accidental exposure.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with *Noxivent*™ will be manifest by elevations in methemoglobin and NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobinemia reduce the oxygen delivery capacity of the circulation.

Methemoglobinemia 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.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Dosage

The minimum effective dose for the indication has not been optimally identified in randomized clinical trials. The initial dose of *Noxivent*™ 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 *Noxivent*™ at 4-6 hours after starting therapy, further steps should be considered. Between 4-24 hours attempts should be made to decrease the dose as quickly as possible to 5 ppm. Treatment with aggressive attempts to lower the dose to 5 ppm, should be maintained until underlying oxygen saturation has resolved but for no more than 96 hours of therapy at which time the neonate should be weaned from *Noxivent*™ therapy. See **Precautions: General** section.

Efficacy and safety of nitric oxide have not been established beyond 96 hours of use. The duration of therapy is variable, but typically less than four days.

An initial dose of 20 ppm was used in the NINOS and CINRGI trials. In CINRGI, patients whose oxygenation improved with 20 ppm were dose-reduced to 5 ppm as tolerated at the end of 4 hours of treatment. In the NINOS trial, patients whose oxygenation failed to improve on 20 ppm could be increased to 80 ppm, but those patients did not then increase their PaO_2 on the higher dose. The risk of methemoglobinemia and elevated NO_2 levels increases significantly when *Noxivent*™ is administered at doses >20 ppm.

Weaning/Discontinuation

The *Noxivent*™ 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 *Noxivent*™.

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. *Noxivent*™ 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.

When the decision is made to discontinue *Noxivent*™ therapy, the dose should be lowered and steps taken to minimize the frequently encountered transient drop in PaO_2 noted for 10 to 60 minutes after discontinuation of *Noxivent*™. One regimen that accomplished this is to reduce the dose to 1 ppm for 30 to 60 minutes. If there is no change in oxygenation during administration of *Noxivent*™ at 1 ppm, the FiO_2 should be increased by 10%, the *Noxivent*™ is discontinued, and the neonates monitored closely for signs of hypoxemia. If oxygenation falls > 20%, *Noxivent*™ therapy should be resumed at 5 ppm and discontinuation of *Noxivent*™ therapy should be reconsidered after 12 to 24 hours. Infants who cannot be weaned off *Noxivent*™ by 4 days should undergo careful diagnostic work-up for other diseases.

Administration Parameters

Training in Administration
Healthcare professionals involved in the care of patients on *Noxivent*™ therapy need to be trained by the manufacturer of the nitric oxide delivery system or have support from personnel trained by the manufacturer in the following key elements of nitric oxide delivery:

1. theory of device operation
2. delivery system setup including connections to gas cylinders and the breathing circuit
3. pre-use procedures (series of steps and tests to verify that the delivery system is fully functional and ready for safe use)
4. gas sensor calibration
5. setting or changing of therapeutic nitric oxide concentration
6. use of backup nitric oxide delivery mode (independent of the main delivery system) to ensure un-interrupted delivery of nitric oxide for inhalation
7. changing gas cylinders and purging the system
8. checking and adjusting alarm settings
9. troubleshooting procedures
10. delivery system maintenance schedule and procedures according to manufacturer specifications

Administration
Prescription and administration of *Noxivent*™ should be supervised by a physician experienced in neonatal intensive care. Prescription and administration should be limited to those neonatal units that have received adequate training in the use of a nitric

oxide delivery system. *Noxivent*™ should only be delivered according to a neonatologist's prescription.

Noxivent™ is delivered to the patient via mechanical ventilation after dilution with an oxygen/air mixture using an approved nitric oxide delivery system. The delivery system must provide a constant inhaled *Noxivent*™ concentration irrespective of the ventilator. With a continuous flow neonatal ventilator, this may be achieved by infusing a low flow of *Noxivent*™ 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 *Noxivent*™ 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 monitoring equipment. For patient safety, appropriate alerts must be set for *Noxivent*™ (± 2 ppm of the prescribed dose), NO_2 (0.5 ppm), and FiO_2 (± 0.05). The *Noxivent*™ cylinder pressure must be displayed to allow timely cylinder replacement without inadvertent loss of therapy, and backup cylinders must be available to provide timely replacement. *Noxivent*™ 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 availability of these backups will minimize the risk of loss of *Noxivent*™ therapy resulting from failure of the primary nitric oxide administration apparatus. The power supply for the monitoring equipment should be independent of the delivery device function.

In order to minimize the risks of hypoxemia associated with acute interruption of drug therapy and accidental exposure, the device should include provision for attachment of two *Noxivent*™ cylinders which can be used alternately via a manifold, or other means to assure a continuous supply of nitric oxide for normal operation of a primary administration system during replacement of cylinders.

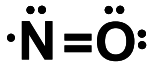
Noxivent™ should be administered with monitoring for PaO_2, methemoglobin, and NO_2.

Monitoring Methemoglobin
Neonates are known to have diminished methemoglobin reductase activity compared to adults. Methemoglobin level should be measured within one hour after initiation of *Noxivent*™ therapy using an analyzer, which can reliably distinguish between fetal hemoglobin and methemoglobin. Although it is unusual for the methemoglobin level to increase significantly if the first level is low, it is prudent to repeat methemoglobin measurements periodically throughout the treatment period. If methemoglobin is > 2.5%, the *Noxivent*™ dose should be decreased and the administration of reducing agents such as methylene blue may be considered.

Monitoring Nitrogen Dioxide
Immediately prior to each patient initiation, proper procedure must be applied to purge the nitric oxide delivery 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 analyzer should be recalibrated, and the *Noxivent*™ and/or FiO_2 should be reduced if possible. If there is an unexpected change in *Noxivent*™ concentration, the delivery system should be assessed for malfunction and the analyzer should be recalibrated.

PHARMACEUTICAL INFORMATION

Drug Substance: Nitric oxide
Proper name: Nitric oxide
Chemical name: Nitric oxide, nitrogen II oxide
Structural formula: NO
Chemical structure: 
Molecular mass: 30.01 grams
Physical form: gas

Composition:
Noxivent™ (nitric oxide) for inhalation is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm; 0.01% and 99.99%, respectively for 100 ppm).

Stability and Storage Recommendations:
The shelf life of *Noxivent*™ is 24 months. Store cylinders at controlled room temperature 15-30 °C.

All regulations concerning handling of pressure vessels must be followed.

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

The installation of a nitric oxide pipeline system with supply station of cylinders, fixed network and terminal units substantially increases the risk of NO_2 formation and delivery to patients and is strongly discouraged.

Transport of cylinders:
The cylinders should be transported with appropriate material in order to protect them from risks of shocks and falls.

Special Instructions:
Used *Noxivent*™ cylinders are returned to Praxair Canada Inc.

Occupational Exposure
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).

Availability of Dosage Forms

Noxivent™ (nitric oxide) for inhalation is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]) and is available in the following sizes:

Size AD portable aluminum cylinders containing 348 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 341 liters).

Size AD portable aluminum cylinders containing 348 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 341 liters).

Size AQ aluminum cylinders containing 2239 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 2197 liters).

Size AQ aluminum cylinders containing 2237 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 2196 liters).

PHARMACOLOGY

Human

Pharmacokinetics

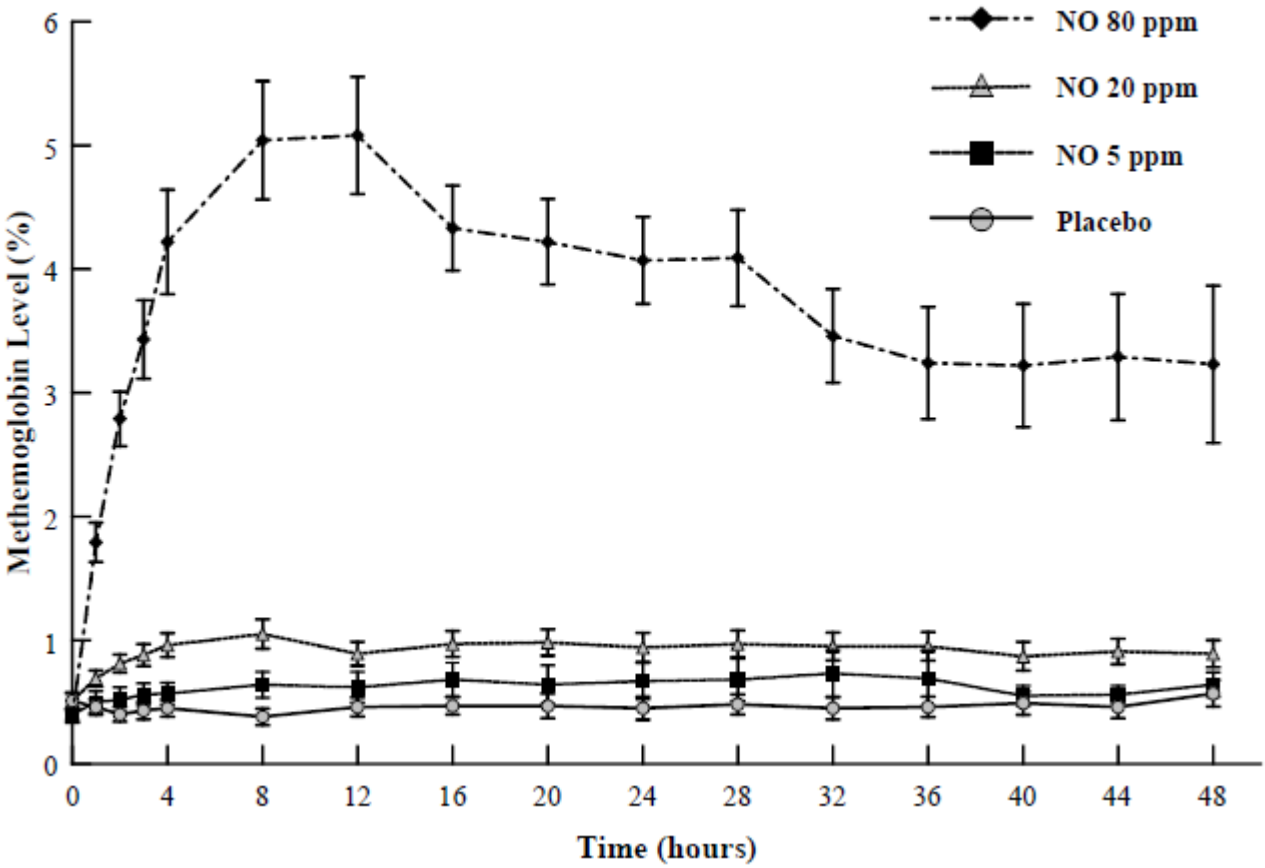
The safety of short-term inhalation of nitric oxide (NO) (40 ppm for 2 hours) in 12 healthy volunteers demonstrated no notable effects on systolic and diastolic blood pressures, heart rate, respiratory rate, or peripheral oxygen saturation. Nor were significant effects on hematologic and chemistry laboratory assessments noted (CTN-NO- 93-006). Normal, healthy adult volunteers studies of inhaled nitric oxide at doses of up to 128 ppm, that is greater than any dose used clinically, demonstrate no clinically significant methemoglobinemia. Maximum levels of methemoglobin are achieved after 3 to 5 hours on NO inhalation and pharmacokinetic modeling was performed on the raw data by Ohmeda (RDR 0076). In both healthy subjects and patients with severe heart failure, the metabolism of NO was found to be dependent on the oxygenation of red cell hemoglobin (CTN-NO-93-008). The data indicate that the inactivation of NO occurred in the red blood cells and suggested that oxyhemoglobin acted as an oxygen donor to the NO molecule in its conversion to nitrate. The fraction of NO inactivated via stoichiometric conversion to nitrate and methemoglobin seemed to be determined by the oxyhemoglobin/hemoglobin ratio in the red blood cells. A study of healthy adult volunteers found that not all of the absorbed NO initially forms methemoglobin, but up to approximately 14% of absorbed NO may be converted directly to nitrogen oxides, which have a volume of distribution equal to about one third of body weight and a clearance similar to the glomerular filtration rate (Young et al [2]). Data for another study in healthy adult men indicated that the conversion of NO into NO_3^- is a major metabolic pathway for inhaled NO in humans and that over 70% of inhaled NO is excreted as NO_3^- in the urine (Westfelt et al [3]).

Pharmacokinetics in Neonates:

Methemoglobin formation is expected during treatment with inhaled nitric oxide in the proposed dose range and should be dose-dependent. Patients not receiving inhaled nitric oxide typically have methemoglobin levels of 0.2 to 1%. The primary problem with elevated methemoglobin is that it reduces the total oxygen-carrying capacity of blood. The acceptable levels for methemoglobin are controversial. Most investigators have used 5 to 10% methemoglobin as the maximum acceptable level.

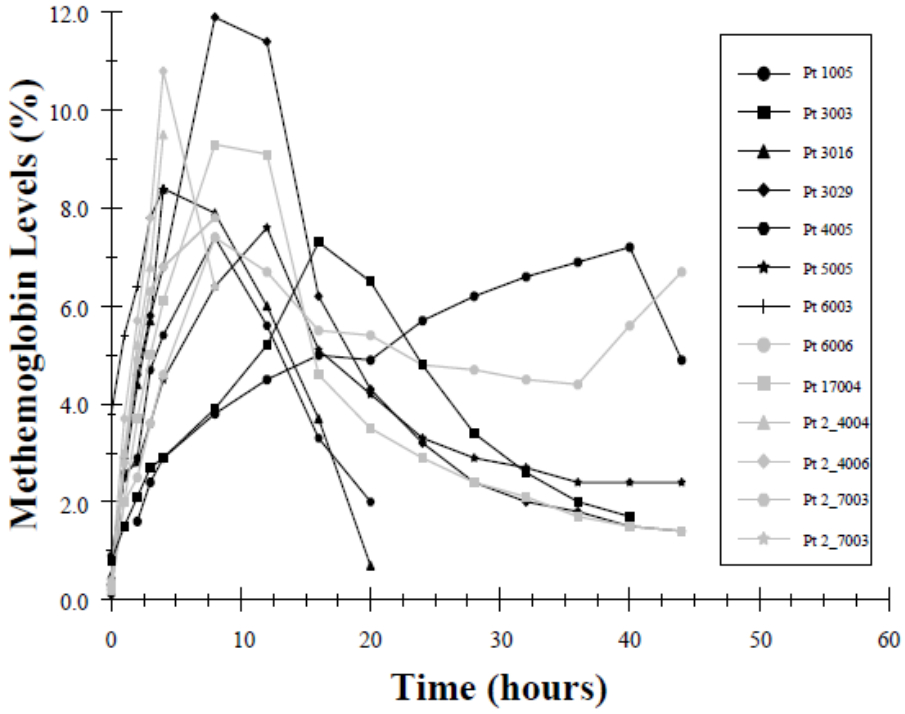
The mean methemoglobin levels for the Ohmeda INO 01/02 trial are shown in Figure 1. As seen, there is a dose-dependent increase in methemoglobin levels with maximal levels of approximately 5% (the predefined level of methemoglobin at which the inhaled nitric oxide dose was to be reduced) in the 80-ppm inhaled nitric oxide dose group. Doses of 20-ppm or less of inhaled nitric oxide, however, had average values for methemoglobin of approximately 1% or less.

FIGURE 1
METHEMOGLOBIN LEVELS- OHMEDA INO 01/02 TRIAL
(MEAN ± STANDARD DEVIATION)



Thirteen of the 37 patients receiving 80-ppm inhaled nitric oxide (35%) in this study developed methemoglobin levels above 7%. The time course for these patients is seen in Figure 2. The mean time to reach their peak level of methemoglobin was 10.5 ± 9.5 hours. Most patients reached this level within the first 18 hours of therapy although one patient did not until 40 hours on inhaled nitric oxide thus emphasizing the need to continue to monitor levels over 48 hours of initiation of therapy. No patient receiving 20-ppm or 5-ppm inhaled nitric oxide in this trial had methemoglobin levels above 7%.

FIGURE 2
METHEMOGLOBIN LEVELS- OHMEDA NO 01/02 TRIAL
PATIENTS WITH METHEMOGLOBINEMIA



Hemostasis Modifying Agents
Endogenous NO is thought to regulate the platelet cGMP and to have antiaggregatory activity (Radomski et al [4]). There is also controversy whether the combination of inhaled NO and other pharmaceutical compounds that have anti-coagulative properties may influence hemostasis synergistically or additively.

In study ICR 013402, randomized volunteers received either placebo inhalation, or 80 ppm inhaled NO, with or without heparin 5000 E given i.v. at the start of inhalation procedure. In no instance did the combination of inhaled NO + heparin cause a prolonged bleeding time, thus ruling out additive/synergistic effects between inhaled NO and an anti-coagulative agent (heparin).

Pharmacodynamics
In patients who are 'responders' to this therapy in terms of improved arterial oxygen tension during mechanical ventilation, the main pharmacodynamic response to inhaled nitric oxide is typically seen within a few minutes from the start of treatment.

The main effect of inhaled nitric oxide is to relax lung vascular smooth muscle, causing dilation of blood vessels and consequently increased blood flow in the region reached by the compound.

Pharmacodynamics in Neonates:
The improvement of arterial oxygen tension in hypoxemic newborns during administration of inhaled nitric oxide is often due to the combined reduction of both extra-pulmonary and intra-pulmonary shunting. The impairment of gas exchange is traditionally estimated by repeated calculations of oxygenation index (OI) in neonates, with OI = 100 x (FiO_2 x MAP)/ PaO_2, with MAP = mean airway pressure, FiO_2 = fraction of inspired oxygen, PaO_2 = postductal arterial oxygen tension. Historical control suggests that OI > 40 is correlated to 80% mortality and is often used as the threshold value for rescue with ECMO.

Any therapy with a clinically meaningful impact on hypoxemic respiratory failure should thus cause a significant reduction of OI, preferably a sustained reduction below 40, which would indicate establishment of acceptable oxygenation requiring less aggressive ventilator settings. The sponsor conducted a dose finding study in neonatal patients (CTN-NO-93-003), which demonstrated a rapid (within 10 minutes) improvement in arterial oxygenation already at dose at or below 10 ppm in a majority of neonates.

Animal
From a study in dogs it can be deduced that the lethal concentration is around 640 ppm nitric oxide for 4 hours, whereas, exposures of 320 ppm nitric oxide are non-lethal. (Study SC940065)

TOXICOLOGY

The preclinical safety profile of nitric oxide was assessed in rats in repeat dose inhalation studies up to 2 years in duration. Age-specific nitric oxide-induced toxicity has not been determined, as juvenile animal toxicity studies were not conducted. There are no reproductive animal studies or human studies to evaluate nitric oxide for effects on fertility or harm to the developing fetus. Nitric oxide has demonstrated genotoxicity in some bacterial strains used in the Salmonella (Ames Test), the mouse lymphoma test, Chinese hamster ovary cell test, in vivo exposure in rats, and human lymphocytes.

Inhalation exposures of F344 rats to 20, 10 or 5 ppm NO for 20 hr/day for up two years were examined. The results of this study indicate that there was no evidence of a toxic effect on the respiratory tract or other organs as determined using clinical and ophthalmoscopic observations, examination of tissues at necropsy, organ and body weight changes, clinical pathology, and histopathologic examination of tissues.

Repeat Dose (Long-Term) Toxicology				
Reports	**Species & Test System**	**Dose/ Concentration**	**Study Type & Duration**	**Comments**
SC940063 Seven-day range-finding study of Nitric Oxide (NO) in the rat via inhalation.	Sprague-Dawley rats	0, 80, 200, 300, 400, 500 ppm NO in air	Nose-only inhalation exposures for 6 hrs/day for up to 7 days	No adverse effects below 200 ppm; dose-related increases in metheme above 200 ppm. Histotoxic anoxia due to metheme leading to lethality above 200 ppm.
RDR-0149 DS Seven-day range-finding study of Nitric Oxide (NO) in the rat via inhalation Supplement Report	Sprague-Dawley rats	0, 200, NO in air, with 2.2 ppm NO_2 in 200 ppm NO group	Report of evaluation of respiratory tract at the level of electronmicroscopy from animals exposed for 1 or 7 days	Moderate increase of interstitial edema after 1 day, Slight increase after 7 days. Findings consistent with NO_2 exposure
SC940064 Twenty-eight day exposure with recovery of nitric oxide (NO) in the rat via inhalation.	Sprague-Dawley rats	0, 40, 80, 160, 200, 250 ppm NO in air with up to 3.5 ppm NO_2 in 250 ppm NO group	Nose-only inhalation exposures for 6 hrs/day for 28 days, with 28 day recovery groups	Exposure-system related elevated dosing excursion (32% on day 14-15); lethality at 200 ppm (n=1) and 250 (n= 17); dose-related increase in metheme from 160 ppm; metheme levels consistent at 7, 14, 21, 28 days; no systemic histopathologic nor hematologic changes
RDR-0150-DS Twenty-eight day exposure with recovery of nitric oxide (NO) in the rat via inhalation. Supplement report:	Sprague-Dawley rats	0, 200, NO in air, with 2.6 ppm NO_2 in 200 ppm NO group	Report of evaluation of respiratory tract at the level of electronmicroscopy from animals exposed for 28 days	Slight ultrastructural changes of ciliated respiratory, type 2 alveolar, and clara cells consistent with NO_2 exposure.

Mutagenicity				
Reports	**Category and Test System**	**Dose/ Concentration**	**Study Type & Duration**	**Comments**
1303/001-1052: Nitric Oxide: Reverse mutation in histidine-requiring strains of Salmonella typhimurium and tryptophan-requiring strains of Escherichia coli.	In vitro/ Salmonella typhimurium (TA 98, TA 100, TA 1535, TA 1537) and E. coli (WP2plcM 101, WP2uvrApKM101); with and without S-9 activation	Up to 5,000 ppm NO under continuous flow; ~1 ppm NO_2	Reverse mutation in bacteria	No toxicity
1303/007-1052 Nitrogen dioxide: Reverse mutation in two histidine-requiring strains of Salmonella typhimurium.	In vitro/ Salmonella typhimurium (TA 100, TA 1535) with and w/out S-9 activation	Up to 40 ppm NO_2	Reverse mutation in bacteria	Mutagenic with and without S-9 activation from 10 ppm NO_2
1303/002-1052 Nitric oxide: Mutation at the thymidine kinase (tk) locus of mouse lymphoma L5178Y cells using the microtitre- fluctuation technique.	In vitro mammalian cell culture (mouse lymphoma-L5178Y cells) using a liquid medium exposure	Up to 2450 ppm NO in nitrogen	Mutation of thymidine kinase locus in cultured mouse cells	Mutagenic above 125 ppm

1303/5-1052 Nitric oxide: Induction of chromosome aberrations in cultured chinese hamster ovary (CHO) cells.	In vitro chromosome aberration in cultured chinese hamster ovary cells (CHO)	Flow thru system with up to 1800 ppm NO in nitrogen	Mitotic inhibition and chromosomal aberration	1650 ppm NO yielded mitotic inhibition of 52 % and increase in structural damage to chromosomes.
1303/4-1052 Nitric oxide: Induction of chromosome aberrations in the peripheral blood lymphocytes of human volunteers after exposure in vivo.	In vivo human exposures	40 ppm NO in 30% O_2 for 2 hrs	Metaphase analysis	No evidence of chromosomal damage
Nguyen et al, 1992. DNA damage and mutation in human cells exposed to nitric oxide in vitro. Proc Natl Acad Sci USA 1992;89:3030-3034.	TK6 human lymphoblasts	0.125, 0.25, 0.375 ml NO gas/ml culture medium for 1 h	Mutation at HPRT and TK locus	Positive mutagenesis and single-strand DNA breaks .

Chronic Toxicity and Carcinogenicity Study				
Reports	**Species & Test System**	**Dose/ Concentration**	**Study Type & Duration**	**Comments**
N005243 Chronic Toxicity and Carcinogenicity Study of Nitric Oxide in Male and Female Rats	F344 Rats	0, 5, 20, and 20 ppm NO in air	Whole-body inhalation exposures for 20 hr/day for up to 2 years	Not carcinogenic

References or Selected Bibliography

[1] Clark R.H., Huckaby J.L., Kueser T.J., et al., Low-dose nitric oxide therapy for persistent pulmonary hypertension: 1-year follow-up. Journal of Perinatology 2003;23:300-303.

[2] Young J.D., Sear J.W., Valvini E.M., Kinetics of methaemoglobin and serum nitrogen oxide production during inhalation of nitric oxide in volunteers, Br J Anaesthesia 1996; 76:652-656.

[3] Westfelt U.N., Benthin G., Lundin S., et al., Conversion of inhaled nitric oxide to nitrate in man, Br J Pharmacol 1995; 114: 1621-1624.

[4] Radomski M.W., Palmer R.M.J., Moncada S., An L-arginine/nitric oxide pathway present in human platelets regulates aggregation, Proc Natl Acad Sci 1990; 87: 5139-5197.

[5] Product Monograph, INOmax® (nitric oxide for inhalation; 100 ppm, 800 ppm), INO Therapeutics, Control No. 167232, Date of Revision: February 12, 2014.

PART III: CONSUMER INFORMATION
***Pr*Noxivent™**
nitric oxide for inhalation
100 ppm and 800 ppm
Medical Gas

This leaflet is part III of a three-part "Product Monograph" published when *Noxivent*™ was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about *Noxivent*™. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

ABOUT THIS MEDICATION

What the medication is used for:
Babies who have been born at term or late pre-term and who have been diagnosed with a condition called hypoxic respiratory failure may be given *Noxivent*™.

A baby with hypoxic respiratory failure has less blood flow through the lungs, and low amounts of oxygen in the blood. Some medical conditions, such as pulmonary hypertension (high blood pressure in the lung), meconium aspiration (fecal material that blocks the lungs) and infection, may cause hypoxic respiratory failure.

Before your baby's doctor prescribes *Noxivent*™, other types of therapy may be given to try to improve your baby's condition. If these other therapies do not improve your baby's condition, *Noxivent*™ may be given.

What it does:
Noxivent™ can improve the flow of blood through the lungs by relaxing the cells in the blood vessels and allowing the blood vessels to widen. This may help to increase the amount of oxygen that reaches your baby's blood.

When it should not be used:
Noxivent™ is not to be given to babies who have an abnormal circulation within the heart.

Some babies may have hypoxic respiratory failure, but may not be helped by *Noxivent*™. If the hypoxic respiratory failure is caused by a condition known as congenital diaphragmatic hernia (when the bowel moves into the lung area), *Noxivent*™ has not been shown to be effective.

Noxivent™ should not be used in pre-mature babies born before 34 weeks from conception.

What the medicinal ingredient is:
nitric oxide

What the nonmedicinal ingredients are:
Nitrogen

What dosage forms it comes in:
Noxivent™ is a drug product that is in the form of a gas and is packaged in gas cylinders in concentrations of 800 and 100 parts per million (ppm).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Your baby's doctor will examine your baby for all side effects, including:
- a decrease in the ability of the blood to carry oxygen
- an increase in the amount of inhaled nitrogen dioxide
- a worsened condition if *Noxivent*™ therapy is stopped too quickly

Noxivent™ is not indicated for use in the adult population. Passive exposure to *Noxivent*™ during pregnancy and breast-feeding should be avoided.

INTERACTIONS WITH THIS MEDICATION

The doctor will decide when to treat your baby with *Noxivent*™ and with other medicines, and will carefully supervise the treatment. *Noxivent*™ could be given with some medicines called "nitric oxide donors" or drugs that themselves can affect the blood's ability to carry oxygen.

PROPER USE OF THIS MEDICATION

Because side effects increase with higher doses of inhaled nitric oxide therapy, your baby will be given a low dose of *Noxivent*™. Since *Noxivent*™ is a gas, the dose is measured in parts per million, or ppm. If for example the nitric oxide dose is 20 ppm, there are 20 parts of nitric oxide in 1 million parts of the inhaled gas mixture.

Your baby's doctor will decide the correct dose of *Noxivent*™ and will administer *Noxivent*™ to your baby's lungs through a system designed for delivering nitric oxide. This system delivers the correct amount of *Noxivent*™ to your baby's lungs by diluting *Noxivent*™ with an oxygen/air mixture immediately before delivery.

For your baby's safety, the delivery systems intended for administration of *Noxivent*™ are fitted with devices that constantly measure the amount of nitric oxide, nitrogen dioxide, and oxygen being delivered to your baby's lungs. In addition, your baby's blood will be tested throughout the treatment period to make sure there is no interference with the ability of the blood to carry oxygen.

Your baby's doctor will decide how long your baby should be treated with *Noxivent*™. Usually a baby is on *Noxivent*™ therapy for 4 days or less.

Noxivent™ treatment should be stopped gradually, so that the circulation in your baby's lungs is able to adjust to oxygen/air without *Noxivent*™. So when your baby's treatment with *Noxivent*™ is almost finished, a gradual reduction in the amount of *Noxivent*™ being administered to your baby will be supervised by your baby's doctor. Low blood pressure has been known to occur if treatment with nitric oxide is stopped suddenly without first lowering the dose.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT DO ABOUT THEM

Like all medicines, nitric oxide can have side effects. Your baby's doctor will examine your baby closely for all side effects. If you notice any side effects not mentioned in this leaflet, even after your baby leaves the hospital, please inform your baby's doctor.

Short-term side effects

When nitric oxide is inhaled it may cause the red blood cells to have less capacity to carry oxygen. It can also be harmful in other ways to your baby's lungs. The doctor should be monitoring the blood for these and other effects.

In some babies with heart failure, inhaled nitric oxide may cause a worsening of the blood circulation in the heart and lungs.

If your baby has these side effects, the long-term clinical outcomes are unknown.

When your baby is receiving *Noxivent*™ therapy the *Noxivent*™ cannot be stopped too quickly. The dose of *Noxivent*™ will be gradually reduced because oxygen levels in your child's blood may get worse when *Noxivent*™ is stopped too quickly.

Other side effects of inhaled nitric oxide may include: low blood pressure, blood in urine, high blood sugar, blood poisoning, infection, and skin infection.

Nitric oxide gas may in some cases cause blood not to clot as well and cause bleeding in the brain or lungs.

Long-term side effects

Studies of inhaled nitric oxide in newborn babies have not followed the babies' condition for more than 2 years, so long-term side effect information is not definitely known. There are possibly long-term side effects that could affect the development of the lungs, brain and walking ability.

If your baby receives *Noxivent*™ therapy, it is recommended that you have your baby checked by a doctor periodically and monitored for normal developmental signs, including: growth, hearing, physical development, lung development, and learning development.

In order to find out more information about the long-term effects of nitric oxide therapy given to newborn babies, the company that manufactures nitric oxide has committed to Health Canada to collect additional safety information. This safety information will be collected on children at several stages in their development and will continue until they are at least 5-years old.

Controlling side effects

Your baby's doctor will give the lowest *Noxivent*™ dose possible to try to avoid any side effects. Your baby's doctor will check for any side effects of the *Noxivent*™ therapy and will decrease the *Noxivent*™ dose or stop the *Noxivent*™ therapy completely if necessary.

This is not a complete list of side effects. For any unexpected effects while taking Noxivent™, contact your doctor.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Storage

Noxivent™ cylinders are stored at controlled room temperature 15-30 °C.

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Praxair Canada Inc., at:
1-800-PRAXAIR (800-772-9247)

This leaflet was prepared by Praxair Canada Inc.
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