HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NOXIVENT™ safely and effectively. See full prescribing information for NOXIVENT™.

NOXIVENT™ (nitric oxide) gas, for inhalation Initial U.S. Approval: 1999

----------RECENT MAJOR CHANGES----------

Dosage and Administration (2.2) 10/2015

---------- INDICATIONS AND USAGE----------

Noxivent™ is a vasodilator indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

----------DOSAGE AND ADMINISTRATION ----------

The recommended dose is 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved (2.1).

Doses greater than 20 ppm are not recommended (2.1, 5.2) Administration:

- Use only with a NOxBOXi® operated by trained personnel (2.2)
- Avoid abrupt discontinuation (2.2, 5.1).

---------- DOSAGE FORMS AND STRENGTHS----------

Noxivent™ (nitric oxide) is a gas available in 100 ppm and 800 ppm concentrations (3).

---------- CONTRAINDICATIONS ----------

Neonates dependent on right-to-left shunting of blood (4).

---------- WARNINGS AND PRECAUTIONS ----------

Rebound: Abrupt discontinuation of NoxiventTM may lead to worsening oxygenation and increasing pulmonary artery pressure (5.1).

Methemoglobinemia: Methemoglobin increases with the dose of nitric oxide; following discontinuation or reduction of nitric oxide, methemoglobin levels return to baseline over a period of hours (5.2).

Elevated NO2 Levels: Monitor NO2 levels (5.3).

Heart Failure: In patients with pre-existing left ventricular dysfunction, NoxiventTM may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

---------- ADVERSE REACTIONS ----------

The most common adverse reaction is hypotension. (6).

To report SUSPECTED ADVERSE REACTIONS, contact Praxair, Inc. at 1-800-772-9247 and http://www.praxair.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS----------

Nitric oxide donor compounds may increase the risk of developing methemoglobinemia (7).

FULL PRESCRIBING INFORMATION: CONTENTS *

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Noxivent™ is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

2. DOSAGE AND ADMINISTRATION

2.1 Dosage

Term and near-term neonates with hypoxic respiratory failure

The recommended dose of Noxivent™ is 20 ppm. Maintain treatment up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from Noxivent™ therapy.

Doses greater than 20 ppm are not recommended *[see Warnings and Precautions (5.2)]*.

2.2 Administration

Training in Administration

The user of Noxivent™ and Nitric Oxide Delivery Systems must satisfactorily complete a comprehensive periodic training program for health care professionals provided by the delivery system and drug manufacturers. Health professional staff that administers nitric oxide therapy have access to supplier-provided 24 hour/365 days per year technical support on the delivery and administration of Noxivent™ at 1-833-669-8368.

Nitric Oxide Delivery Systems

Noxivent™ must be administered using a calibrated NOxBOXi®. Only validated ventilator systems should be used in conjunction with Noxivent™. Consult the Nitric Oxide Delivery System label or call 1-833-669-8368 / visit praxair.com for a current list of validated systems.

Keep available a backup battery power supply and an independent reserve nitric oxide delivery system to address power and system failures.

Monitoring

Measure methemoglobin within 4-8 hours after initiation of treatment with Noxivent™ and periodically throughout treatment *[see Warnings and Precautions (5.2)]*.

Monitor for PaO_2 and inspired NO_2 during Noxivent™ administration *[see Warnings and Precautions 5.3)]*.

Weaning and Discontinuation

Avoid abrupt discontinuation of Noxivent™ *[see Warnings and Precautions (5.1)]*. To wean Noxivent™, downtitrate in several steps, pausing several hours at each step to monitor for hypoxemia.

3. DOSAGE FORMS AND STRENGTHS

Noxivent™ (nitric oxide) gas is available in 100 ppm and 800 ppm concentrations.

4. CONTRAINDICATIONS

Noxivent™ is contraindicated in neonates dependent on right-to-left shunting of blood.

5. WARNINGS AND PRECAUTIONS

5.1 Rebound Pulmonary Hypertension Syndrome following AbruptDiscontinuation

Wean from Noxivent™ *[see Dosage and Administration (2.2)]*. Abrupt discontinuation of Noxivent™ may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate Noxivent™ therapy immediately.

5.2 Hypoxemia from Methemoglobinemia

Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of Noxivent™; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of Noxivent™ to optimize oxygenation.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of Noxivent™, additional therapy may be warranted to treat methemoglobinemia *[see Overdosage (10)]*.

5.3 Airway Injury from Nitrogen Dioxide

Nitrogen dioxide (NO_2) forms in gas mixtures containing NO and O_2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO_2 concentration, or if the NO_2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the NOxBOXi and NOxMixer Technical Guide troubleshooting section, and the NO_2 analyzer should be recalibrated. The dose of Noxivent™ and/or FiO_2 should be adjusted as appropriate.

5.4 Worsening Heart Failure

Patients with left ventricular dysfunction treated with Noxivent™ may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue Noxivent™ while providing symptomatic care.

6. ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the label:

Hypoxemia *[see Warnings and Precautions (5.2)]*
Worsening Heart Failure *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from the clinical studies does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

Controlled studies have included 325 patients on nitric oxide doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on nitric oxide, a result adequate to exclude nitric oxide mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in nitric oxide and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received nitric oxide and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, 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.

In CINRGI, the only adverse reaction (>2% higher incidence on nitric oxide than on placebo) was hypotension (14% vs. 11%).

6.2 Post-Marketing Experience

Post marketing reports of accidental exposure to nitric oxide for inhalation in hospital staff has been associated with chest discomfort, dizziness, dry throat, dyspnea, and headache.

7. DRUG INTERACTIONS

7.1 Nitric Oxide Donor Agents

Nitric oxide donor agents such as prilocaine, sodium nitroprusside and nitroglycerine may increase the risk of developing methemoglobinemia.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Animal reproduction studies have not been conducted with Noxivent™. It is not known if Noxivent™ can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Noxivent™ is not indicated for use in adults.

8.3 Nursing Mothers

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

8.4 Pediatric Use

The safety and efficacy of nitric oxide for inhalation has been demonstrated in term and near- term neonates with hypoxic respiratory failure associated with evidence of pulmonary hypertension *[see Clinical Studies (14.1)]*. Additional studies conducted in premature neonates for the prevention of bronchopulmonary dysplasia have not demonstrated substantial evidence of efficacy *[see Clinical Studies (14.3)]*. No information about its effectiveness in other age populations is available.

8.5 Geriatric Use

Nitric oxide is not indicated for use in the adult population.

10. OVERDOSAGE

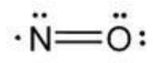
Overdosage with Noxivent™ is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, nitric oxide.

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.

11. DESCRIPTION

Noxivent™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in Noxivent™, is a pulmonary vasodilator. Noxivent™ 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). Noxivent™ is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).

The structural formula of nitric oxide (NO) is shown below:



12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nitric oxide 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 selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature.

Noxivent™ 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.

12.2 Pharmacodynamics

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. In neonates with PPHN, Noxivent™ improves oxygenation (as indicated by significant increases in PaO_2).

12.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults.

Absorption and Distribution

Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhemoglobin to transiently form nitrosylhemoglobin, which is converted to nitrogen oxides and methemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrate.

Metabolism

Methemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. The methemoglobin (MetHb) concentration-time profiles during the first 12 hours of exposure to 0, 5, 20, and 80 ppm nitric oxide are shown in Figure 1.

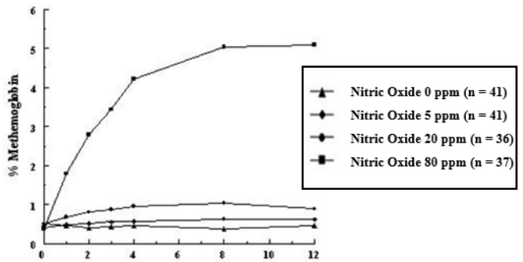


Figure 1: Methemoglobin Concentration-Time Profiles Neonates Inhaling 0, 5, 20, or 80 ppm Nitric Oxide

Methemoglobin concentrations increased during the first 8 hours of nitric oxide exposure. The mean methemoglobin level remained below 1% in the placebo group and in the 5 ppm and 20 ppm nitric oxide groups but reached approximately 5% in the 80-ppm nitric oxide group.

Methemoglobin levels >7% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients, but one patient did not exceed 7% until 40 hours.

Elimination

Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 20 hr/day for up to two years. Higher exposures have not been investigated.

Nitric oxide has demonstrated genotoxicity in Salmonella (Ames Test), human lymphocytes, and after *in vivo* exposure in rats. There are no animal or human studies to evaluate nitric oxide for effects on fertility.

14. CLINICAL STUDIES

14.1 Treatment of Hypoxic Respiratory Failure (HRF)

The efficacy of nitric oxide has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of nitric oxide reduces the oxygenation index (OI= mean airway pressure in cm H_2O × fraction of inspired oxygen concentration [FiO_2]× 100 divided by systemic arterial concentration in mm Hg [PaO_2]) and increases PaO_2 *[see Clinical Pharmacology (12.1)]*.

NINOS Study: The Neonatal Inhaled Nitric Oxide Study (NINOS) was a double-blind, randomized, placebo- controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. 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 near-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 ≤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% O_2 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 from the NINOS study are presented in Table 1.

Table 1
Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO [*,†]	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

[*] Extracorporeal membrane oxygenation

[†] 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 nitric oxide group also 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). Significantly more patients had at least a partial response to the initial administration of study drug in the nitric oxide group (66%) than the control group (26%, p<0.001). Of the 125 infants who did not respond to 20 ppm nitric oxide or control, similar percentages of NO-treated (18%) and control (20%) patients had at least a partial response to 80 ppm nitric oxide for inhalation or control drug, suggesting a lack of additional benefit for the higher dose of nitric oxide. 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 (6.1)]*.

Follow-up exams were performed at 18–24 months for the infants enrolled in this trial. In the infants with available follow-up, the two treatment groups were similar with respect to their mental, motor, audiologic, or neurologic evaluations.

CINRGI Study: This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. 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 primary results from the CINRGI study are presented in Table 2.

Table 2
Summary of Clinical Results from CINRGI Study

	Placebo	Nitric Oxide	P value
ECMO [*,†]	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

[*] Extracorporeal membrane oxygenation

[†] 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 PaO_2, 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 (6.1)]*.

In clinical trials, reduction in the need for ECMO has not been demonstrated with the use of inhaled nitric oxide in neonates with congenital diaphragmatic hernia (CDH).

14.2 Ineffective in Adult Respiratory Distress Syndrome (ARDS)

In a randomized, double-blind, parallel, multicenter study, 385 patients with adult respiratory distress syndrome (ARDS) associated with pneumonia (46%), surgery (33%), multiple trauma (26%), aspiration (23%), pulmonary contusion (18%), and other causes, with PaO_2/FiO_2 <250 mm Hg despite optimal oxygenation and ventilation, received placebo (n=193) or nitric oxide (n=192), 5 ppm, for 4 hours to 28 days or until weaned because of improvements in oxygenation.

Despite acute improvements in oxygenation, there was no effect of nitric oxide on the primary endpoint of days alive and off ventilator support. These results were consistent with outcome data from a smaller dose ranging study of nitric oxide (1.25 to 80 ppm). Noxivent™ is not indicated for use in ARDS.

14.3 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)

The safety and efficacy of nitric oxide for the prevention of chronic lung disease [bronchopulmonary dysplasia, (BPD)] in neonates ≤ 34 weeks gestational age requiring respiratory support has been studied in three large, multi-center, double-blind, placebo-controlled clinical trials in a total of 2,149 preterm infants. Of these, 1,068 received placebo, and 1,081 received inhaled nitric oxide at doses ranging from 5-20 ppm, for treatment periods of 7-24 days duration. The primary endpoint for these studies was alive and without BPD at 36 weeks postmenstrual age (PMA). The need for supplemental oxygen at 36 weeks PMA served as a surrogate endpoint for the presence of BPD. Overall, efficacy for the prevention of bronchopulmonary dysplasia in preterm infants was not established. There were no meaningful differences between treatment groups with regard to overall deaths, methemoglobin levels, or adverse events commonly observed in premature infants, including intraventricular hemorrhage, patent ductus arteriosus, pulmonary hemorrhage, and retinopathy of prematurity.

The use of nitric oxide for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not recommended.

Additional information regarding another clinical study in which efficacy was not demonstrated is approved for Mallinckrodt Hospital Products IP Limited's INOmax® (nitric oxide) gas for Inhalation. However, due to Mallinckrodt Hospital Products IP Limited's marketing exclusivity rights, this drug product is not labeled with that pediatric information.

16. HOW SUPPLIED/STORAGE AND HANDLING

Noxivent™ (nitric oxide) is available in the following sizes:

Size AD Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 59579-102-02)

Size AQ Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 2082 liters) (NDC 59579-102-01)

Size AD Portable aluminum cylinders containing 362 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 59579-101-02)

Size AQ Aluminum cylinders containing 2154 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 2082 liters) (NDC 59579-101-01)

Store at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F) [see USP Controlled Room Temperature].

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.

Occupational Exposure

The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO_2 the limit is 5 ppm.

Distributed by

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