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: (2.2) Dosage and Administration

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. See WARNINGS AND PRECAUTIONS (5.2).

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 NOBOX®-operated by trained personnel (2.2).
- Avoid abrupt discontinuation (2.2, 5.5).

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

Neonates dependent on right-to-left shunting of blood (6).

WARNINGS AND PRECAUTIONS

- Abrupt discontinuation of NoxiventTM may lead to worsening oxygenation and increasing pulmonary artery pressure (5.2).

- 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 1-800-772-0047 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).

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7.1 Nitric Oxide Donor Agents

Noxivent® is contraindicated in neonates dependent on right-to-left shunting of blood. See WARNINGS AND PRECAUTIONS (5.2).

Monitoring
Measure methioninogen within 4-6 hours after initiation of treatment with Noxivent® and periodically thereafter (see warnings and precautions (5.3)).

Monitor for PaO2 and inspired NO2 during Noxivent® administration (see Warnings and Precautions (5.3)).

Wandering and Discontinuation
Avoid abrupt discontinuation of Noxivent® (see Warnings and Precautions (5.5)). To wean Noxivent®, maintain treatment in the neonates in steps, paving several hours each step to monitor for hypoxemia.

DOSAGE AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

5.1 Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation

Wear from Noxivent® (see Dosage and Administration (2.1)). 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 hypertension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, initiate 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 decrease 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).

5.3 Airway Injury from Nitrogen Dioxide

Nitrogen dioxide (NO2) forms in gas mixtures containing NO and O2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

If there is an unexpected change in NO concentration, or if the NO concentration reaches 5 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the NOBOX® and NOXIVENT® Technical Guide troubleshooting section, and the NO analyzer should be recalibrated. The dose of Noxivent® and/or NO2 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 hypertension, 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. To estimate the adverse reaction information from the clinical trials data, 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 doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the placebo group was 11% on placebo and 9% on nitric oxide. The patients appeared to exclude nitric oxide mortality being more than 4% 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 272 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 in nitric oxide than on placebo) was hypertension (74% 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 prilozain, sodium nitroprusside and nitriniglycerine 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 Trials (14.1)). Additional studies conducted in premature neonates for the prevention of bronchopulmonary dysplasia have not demonstrated substantial evidence of efficacy (see Clinical Trials (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. Elevated NO may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical experience, NO concentrations ≥1 ppm or methemoglobin levels ≥17% 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 on 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 pressurized carbon dioxide container of nitric oxide and nitrogen (0.26% and 98.66%, 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.

N O
Elimination

Metabolism

Absorption and Distribution

the kidney at rates approaching the rate of glomerular filtration.

Nitrate has been identified as a cause of methemoglobinemia. At low oxygen saturation, nitric oxide relaxes vascular smooth muscle by binding to the heme moiety of cytosolic nitric oxide synthase, realizing a decrease in the partial pressure of arterial oxygen (PaO₂) and increases PaO₂ (see Pharmacology/17.1).

Mechanism of Action

The efficacy of nitric oxide has been investigated in neonatal and newborn animals with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of nitric oxide reduces the oxygenation index (O₂-increase in arterial oxygen pressure/inspired oxygen concentration {[PaO₂ × 100 divided by systemic arterial concentration in mm Hg]} and increases PaO₂ (see Table 2). The mechanism of action of nitric oxide has been extensively studied and results in the relaxation of the pulmonary vasculature, and because of efficient delivery of oxygen to the alveoli, improvement in oxygenation (PaO₂).

Pharmacokinetics

Noxivent™ (nitric oxide) appears to increase the partial pressure of arterial oxygen (PaO₂) and increases PaO₂ (see Pharmacology/17.1).

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity, mutagenicity, or teratogenicity has been observed in the nonclinical studies evaluated for nitric oxide for efficacy on nitric oxide for efficacy on nitric oxide.

14. CLINICAL STUDIES

14.1 Use of Inhaled Hypoxic Respiratory Failure (HRP)

The efficacy of nitric oxide has been investigated in neonatal and newborn animals with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of nitric oxide reduces the oxygenation index (O₂-increase in arterial oxygen pressure/inspired oxygen concentration {[PaO₂ × 100 divided by systemic arterial concentration in mm Hg]} and increases PaO₂ (see Table 2).

MNOS Study: The Neonatal Inhaled Nitric Oxide Study (MNOS) was a double-blind, randomized, placebos-controlled, multicenter trial in 256 neonates with hypoxic respiratory failure. The objective of the study was to determine whether 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 (21%), idiopathic pulmonary hypertension (the neonate was born alive; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤14 days of age (mean ± 1.7 days) with a mean PaO₂ of 46 mm Hg and a mean oxygen index (O₂-index of 43 ± 19.7 mm Hg) were randomized to receive 0% (n=114) or without (n=141) 20 ppm nitric oxide for up to 14 days. Response to study drug was defined as a change from baseline in PaO₂ 30 minutes after treatment (full response = > 20 mm Hg, partial = 10-20 mg, no response = ≤ 10 mg Hg). Neatliness with a less than full response were evaluated for a secondary endpoint. The primary endpoint of the MNOS study is presented in Table 1.

Table 1

<table>
<thead>
<tr>
<th>Study</th>
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<th>No. of patients</th>
<th>P value</th>
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<td>Death</td>
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<td>16/161 (31%)</td>
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In the MNOS study, nitric oxide appeared to reduce the occurrence of death and/or initiation of ECMO in the cohort of neonates with 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 (55%), idiopathic APHNN (32%), pneumonia (34%), or RDS (8%) in 5 ppm. Patients with a mean PAO₂ of 54 mm Hg and a mean O₂ index of 44 mm Hg were randomly assigned to receive either 20 ppm nitric oxide (n=74) or oxygen gas placebo (n=89) in addition to their ventilatory support. Patients who exhibited a PAO₂ >60 mm Hg and a PaO₂ > 75 were randomized to 5 ppm nitric oxide or placebo. The primary results from the MNOS study are presented in Table 2.

Table 2

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ECMO = Extracorporeal membrane oxygenation

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How Supplied/Storage and Handling

Nitric oxide (nitric oxide) is available in the following sizes:

- Size 10 aluminum cylinders containing 362 liters at STP of nitric oxide gas in 50 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 55979-102-02)
- Size 10 aluminum cylinders containing 362 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 323 liters) (NDC 55979-101-10)
- Size 10 aluminum cylinders containing 214 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 202 liters) (NDC 55979-101-02)