INOMAX® (nitric oxide) gas, for inhalation

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Initial U.S. Approval: 1999

INDICATIONS AND USAGE
INOMAX® 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.

DOSE 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:
- Avoid abrupt discontinuation (2.2, 5.1).

DOSE FORMS AND STRENGTHS
INOMAX (nitric oxide) gas is a gas available in 800 and 4,880 ppm concentrations (3).

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

2.2 Administration
Nitric Oxide Delivery Systems
INOmax must be administered using a calibrated, FDA-cleared Nitric Oxide Delivery System (NODS). There are various FDA-cleared NODS; refer to the NODS labeling to identify which NODS to use with this drug product and for approximating rates.

When utilizing a nitric oxide delivery system specifically cleared for use in the MRI suite (e.g., the INOmax DSIR® Plus MRI) only use INOmax MR conditional cylinders at 100 gauss or less [see How Supplied/Storage and Handling (16)].

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 INOmax and periodically throughout treatment [see Warnings and Precautions (5.2)].

Monitor for PaO2 and inspired NO2 during INOmax administration [see Warnings and Precautions (5.2)].

Weaning and Discontinuation
Avoid abrupt discontinuation of INOmax [see Warnings and Precautions (5.1)]. To wean INOmax, discontinue in several steps, pausing several hours at each step to monitor for hypoxemia.

3 DOSE FORMS AND STRENGTHS
INOmax (nitric oxide) gas is available in 800 and 4,880 ppm concentrations.

4 CONTRAINDICATIONS
INOmax is contraindicated in neonates dependent on right-to-left shunting of blood.

5 WARNINGS AND PRECAUTIONS
5.1 Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation
Wean from INOmax [see Dosage and Administration (2.2)]. Abrupt discontinuation of INOmax 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 INOmax therapy immediately.

5.2 Hypoxemia from Methemoglobinemia
Nitric oxide donor compounds may increase the risk of developing methemoglobinemia (7).

5.3 Airway Injury from Nitrogen Dioxide
Nitrogen dioxide may cause airway inflammation and damage to lung tissues.

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If there is an unexpected change in NO2 concentration, or if the NO2 concentration reaches 3 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System O&M Manual troubleshooting section, and the NO2 analyzer should be recalibrated. The dose of INOmax and/or IF2 should be adjusted as appropriate.

5.4 Worsening Heart Failure
Patients with pre-existing left ventricular dysfunction, INOmax may increase pulmonary capillary wedge pressure leading to pulmonary edema (5.4).

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Adverse Reactions
The most common adverse reaction is hypoxemia. (6).

To report SUSPECTED ADVERSE REACTIONS, contact INO Therapeutics at 1-877-566-9466 and http://www.inomax.com/ or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

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USE IN SPECIFIC POPULATIONS
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8 USE IN SPECIFIC POPULATIONS
8.4 Pediatric Use
8.5 Geriatric Use

11 DESCRIPTION
INOmax (nitric oxide gas) is a gas administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax 800 ppm is a gaseous blend of nitric oxide (0.88%) and nitrogen (99.92%). INOmax 4,880 ppm is a gaseous blend of nitric oxide (0.488%) and nitrogen (99.51%). INOmax 800 ppm is supplied in aluminum cylinders as a compressed gas under high pressure (2,000 pounds per square inch (psig)); INOmax 4,880 ppm is supplied in aluminum cylinders as a compressed gas under high pressure (3,000 psig).

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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))

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

In both the NINOS and CINIRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax 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 CINIRGI, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypoxemia (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
8.4 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
Overdose with INOmax is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO2. Elevated NO2 may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of INOmax and/or INOmax therapy.

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
INOmax (nitric oxide gas) is a gas administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator.
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 INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygen index (OI: mean airway pressure in cm H2O x fraction of inspired oxygen concentration [FIo2]) by increasing the alveolar-arterial oxygen concentration in mm Hg (PAO2) and increases PAO2 (see Clinical Pharmacology 12.1).

INOmax INOmax 20 ppm (n = 36)
INOmax 5 ppm (n = 41)
Control (n = 121)
NO (n = 114)
P value
Death or ECMO* 1 1
77 (64%) 70 (61%) 0.006
Death
20 (17%) 16 (14%) 0.60
ECMO
66 (55%) 44 (39%) 0.014
* Extracorporeal membrane oxygenation

Table 1: Summary of Clinical Results from NINOS Study

Figure 1: Methemoglobin Concentration-Time Profiles Neonates Inhaling 0.5, 20, or 80 ppm INOmax are shown in Figure 1.

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 INOmax groups but reached approximately 5% in the 80 ppm INOmax 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
Nitric oxide is cleared from the body by the kidneys so that 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 hours/day for up to two years. Higher exposures have not been investigated.

13.2 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, INOmax improves oxygenation (as indicated by significant increases in PAO2).

13.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults. Inhalation and absorption of nitric oxide is almost complete. The plasma half-life is 2-4 minutes. Nitric oxide is distributed throughout the body and enters the systemic circulation are predominantly methemoglobin and nitrate. Nitrite, respectively, which interact with oxyhemoglobin to produce nitrosylhemoglobin, which is converted to nitric oxide and methemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitric oxide and nitrite, respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrite. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrite.

Metabolism

Methemoglobin disposition has been investigated as a function of time and nitric oxide 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 INOmax are shown in Figure 1.

Figure 1: Methemoglobin Concentration-Time Profiles Neonates Inhaling 0.5, 20, or 80 ppm INOmax

Nitric oxide is available in the following sizes:

16 HOW SUPPLIED/STORAGE AND HANDLING

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

- Size D Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01)
- Size BB Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-002-02)
- 0.4 liter Portable aluminum cylinders containing 78 liters at STP of nitric oxide gas in 4,880 ppm concentration in nitrogen (delivered volume 70 liters) (NDC 64693-002-03)

All regulations concerning handling of pressure vessels must be followed. Protect the cylinders from shocks, falls, oxidizing and flammable material, moisture, and sources of heat or ignition. Methemoglobin MR conditional labeled cylinders (i.e., size 88 aluminum cylinder) may be used at 100 gauze or less. Use of any other cylinders (e.g., size D or 0.4 liter aluminum cylinder) may create a projectile hazard.

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

The safety and efficacy of INOmax for the prevention of chronic lung disease (bronchopulmonary dysplasia, BPD) in neonates ≤ 34 weeks gestation requiring invasive respiratory support has been studied in four large, multi-center, double-blind, placebo-controlled clinical trials in a total of 2,600 preterm infants. Of these, 1,290 received placebo, and 1,310 received INOmax 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 INOmax for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not recommended.

16.1 INOmax (nitric oxide) is available in the following sizes:

<table>
<thead>
<tr>
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Ocupational Exposure

The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO, the limit is 5 ppm.

For a list of patients: see https://www.mallinckrodt.com/patients/distributed/INOmax/Teradex/INOmax/INOmaxTherapeuticsLLC

Bridgewater, NJ 08807, USA

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