INOMAX- nitric oxide gas
INO Therapeutics

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

INOMAX (nitric oxide) gas, for inhalation
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. (1)

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:
• Avoid abrupt discontinuation (2.2, 5.1).

------ DOSE FORMS AND STRENGTHS ------
INOmax (nitric oxide) gas is available in a 800 ppm concentration (3).

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Dosage
2.2 Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation
5.2 Hypoxemia from Methemoglobinemia
5.3 Airway Injury from Nitrogen Dioxide
5.4 Worsening Heart Failure
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Post-Marketing Experience
7 DRUG INTERACTIONS
7.1 Nitric Oxide Donor Agents

---Warnings and Precautions 5.3---
Neonates dependent on right-to-left shunting of blood (4).

------ CONTRAINDICATIONS ------
Rebound: Abrupt discontinuation of INOMAX may lead to worsening oxygenation and increasing pulmonary artery pressure (5.3).

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, INOMAX may increase pulmonary capillary wedge pressure leading to pulmonary edema.

------ ADVERSE REACTIONS ------
The most common adverse reaction is hypoxia. (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.

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

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

---Warnings and Discontinuation---
Avoid abrupt discontinuation of INOMAX (see Warnings and Precautions (5.1)). To wean INOMAX, downtitrte in several steps, passing several hours at each step to monitor for hypoxemia.

---DOSAGE FORMS AND STRENGTHS---
INOmax (nitric oxide) gas is available in a 800 ppm concentration.

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

---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, bradyarrhythmia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate INOMAX 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 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.

If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOMAX, additional therapy may be warranted to treat methemoglobinemia (see Overdosage (10.1)).

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 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 NO2 should be adjusted as appropriate.

5.4 Worsening Heart Failure
Patients with left ventricular dysfunction treated with INOMAX may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradyarrhythmia and cardiac arrest. Discontinue INOMAX 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 INOMAX doses of 5 to 80 ppm and 251 patients on placebo. The 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 CNRIS 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 CNRIS 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 were not observed.

In CNRIS, the only adverse reaction (~2% higher incidence on INOMAX 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
8.4 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, or discontinuing, INOMAX.

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 drug administered by inhalation. Nitric oxide, the active substance in INOMAX, is a pulmonary vasodilator. INOMAX is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm). INOMAX is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).
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 neonates with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (O2: mean airway pressure in cm H2O x fraction of inspired oxygen concentration [FiO2], x 100 divided by systemic arterial concentration in mm Hg [PaO2]) and increases PaO2 [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 defined by PaO2/PaCO2 < 100/60, and/or initiation of ECMO by hemoglobin (Hb) < 6 g/dL, no response = <10 mm Hg). Neonates with a less than full response were randomized to receive 80 ppm nitric oxide or control gas. The primary results from the NINOS study are presented in Table 1.

<table>
<thead>
<tr>
<th>Control</th>
<th>NO</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=121)</td>
<td>(n=114)</td>
<td></td>
</tr>
<tr>
<td>Death or ECMO**</td>
<td>77 (64%)</td>
<td>52 (46%)</td>
</tr>
<tr>
<td>Death</td>
<td>20 (17%)</td>
<td>16 (14%)</td>
</tr>
<tr>
<td>ECMO</td>
<td>66 (55%)</td>
<td>44 (39%)</td>
</tr>
</tbody>
</table>

** Extracorporeal membrane oxygenation
* Death or 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 lower PaO2/PCO2 ratios in the 3rd and 4th 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 the risk of additional benefit for the higher dose regimen.

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. The follow-up exams were performed from 18–24 months for the infants enrolled in this trial. These 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 INOmax would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was causally linked to MAS (32%), idiopathic PPHN (17%), or respiratory distress syndrome (RDS; 11%). Infants ≤ 14 days of age (mean, 7.7 days) with a mean PaO2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H2O/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 PaO2 in 30 minutes after starting treatment (full response: >40 mm Hg, partial = 20–40 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 CINRGI study are presented in Table 2.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>INOmax</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=69)</td>
<td>(n=97)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5 (7%)</td>
<td>9 (6%)</td>
</tr>
</tbody>
</table>

** Extracorporeal membrane oxygenation
* ECMO was the primary end point of this study

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

In addition, the INOmax group had significantly improved oxygenation as measured by PaO2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 79 patients treated with INOmax, 2 (2%) were withdrawn from the study due to a combination of high methemoglobin levels (>4%). The frequency and number of adverse events reported were similar in the two study groups. In a post hoc analysis, the INOmax group had a higher incidence of death. In a clinical trial, 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)
A randomized, double-blind, placebo-controlled 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 PaO2/FiO2 < 200 mm Hg despite optimal oxygenation and ventilation, received placebo (n=193) or INOmax (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 INOmax 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). INOmax is not indicated for use in ARDS.

14.3 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)
The safety and efficacy of INOmax for the prevention of chronic lung disease (bronchopulmonary dysplasia, BPD) in neonates ≤ 34 weeks gestational age requiring respiratory support has been studied in four large, multicenter, double-blind, placebo-controlled clinical trials in a total of 2,600 preterm infants. Of these, 1,290 received placebo, and 1,310 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 prevention of BPD. Overall, efficacy for the prevention of bronchopulmonary dysplasia in preterm infants was demonstrated with the use of inhaled nitric oxide in pregnancy. The use of INOmax for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not recommended.

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 1998 liters) (NDC 64693-002-02)

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.

INOmax MR conditioned labeled cylinders (i.e., size 88 aluminum cylinder) may be used at 100 gauss or less. Use of any other cylinder (e.g., size D aluminum cylinder) may create a projectile hazard.

Occupational Exposure
The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO2, the limit is 5 ppm. Distributed by INO Therapeutics LLC, Bedminster, NJ 07921 USA. © 2021 Mallinckrodt.

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