

**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) for inhalation**  
**Initial U.S. Approval: 1999**

**RECENT MAJOR CHANGES**

Dosage and Administration (2.2) 3/2013

**INDICATIONS AND USAGE**

INOmax is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks gestation) 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 (1.1).

Monitor for PaO<sub>2</sub>, methemoglobin, and inspired NO<sub>2</sub> during INOmax administration (1.1).

Utilize additional therapies to maximize oxygen delivery (1.1).

**DOSAGE AND ADMINISTRATION**

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

Administration:

- Use only with an INOmax DS<sub>IR</sub><sup>®</sup>, INOmax<sup>®</sup> DS, or INOvent<sup>®</sup> operated by trained personnel (2.2)
- Wean from INOmax gradually (2.2).

**DOSAGE FORMS AND STRENGTHS**

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

**CONTRAINDICATIONS**

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

**WARNINGS AND PRECAUTIONS**

Rebound: Abrupt discontinuation of INOmax 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 NO<sub>2</sub> Levels: Monitor NO<sub>2</sub> levels continuously with a suitable Nitric Oxide Delivery System (5.3).

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

**ADVERSE REACTIONS**

Methemoglobinemia and NO<sub>2</sub> levels are dose dependent. The most common adverse reaction is hypotension (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](http://www.fda.gov/medwatch).

**DRUG INTERACTIONS**

**Nitric oxide donor agents:** Nitric oxide donor compounds, such as prilocaine, sodium nitroprusside, and nitroglycerin, when administered as oral, parenteral, or topical formulations, may have an additive effect with INOmax on the risk of developing methemoglobinemia (7).

Revised: 3/2013

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Treatment of Hypoxic Respiratory Failure

INOMax<sup>®</sup> is a vasodilator, which, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>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.

Utilize additional therapies to maximize oxygen delivery with validated ventilation systems [*see Dosage and Administration (2.2)*]. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of INOMax have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies [*see Clinical Studies (14)*].

Monitor for PaO<sub>2</sub>, methemoglobin, and inspired NO<sub>2</sub> during INOMax administration.

### 2 DOSAGE AND ADMINISTRATION

To ensure safe and effective administration of INOMax to avoid adverse events associated with nitric oxide or NO<sub>2</sub>, administration of INOMax should only be performed by a health care professional who has completed and maintained training on the safe and effective use of a Nitric Oxide Delivery System provided by the manufacturer of the delivery system and the drug.

#### 2.1 Dosage

##### **Term and near-term neonates with hypoxic respiratory failure**

The recommended dose of INOMax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOMax therapy.

As the risk of methemoglobinemia and elevated NO<sub>2</sub> levels increases significantly when INOMax is administered at doses >20 ppm; doses above this level are not recommended.

#### 2.2 Administration

Methemoglobin should be measured within 4-8 hours after initiation of treatment with INOMax and periodically throughout treatment [*see Warnings and Precautions (5.2)*].

##### **Nitric Oxide Delivery Systems**

INOMax must be administered using the INOMax DS<sub>IR</sub><sup>®</sup>, INOMax<sup>®</sup> DS, or INOvent<sup>®</sup> Nitric Oxide Delivery Systems, which deliver operator-determined concentrations of nitric oxide in conjunction with a ventilator or breathing gas administration system after dilution with an oxygen/air mixture. A Nitric Oxide Delivery System includes a nitric oxide administration apparatus, a nitric oxide gas analyzer and a nitrogen dioxide gas analyzer. Failure to calibrate the Nitric Oxide Delivery System could result in under- or over- dosing of nitric oxide.

To address potential power failure, keep available a backup battery power supply. To address potential system failure, keep available an independent reserve nitric oxide delivery system. Failure to transition to a reserve nitric oxide delivery system can result in abrupt or prolonged discontinuation of nitric oxide [*see Warnings and Precautions (5.1)*].

### **Training in Administration**

The user of INOMax and Nitric Oxide Delivery Systems must complete a comprehensive 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 INOMax at 1-877-566-9466.

### **Weaning and Discontinuation**

Abrupt discontinuation of INOMax may lead to increasing pulmonary artery pressure (PAP) and worsening oxygenation even in neonates with no apparent response to nitric oxide for inhalation. To wean INOMax, downtitrate in several steps, pausing several hours at each step to monitor for hypoxemia.

## **3 DOSAGE FORMS AND STRENGTHS**

INOMax (nitric oxide) for inhalation is a gas available in 100 ppm and 800 ppm concentrations.

## **4 CONTRAINDICATIONS**

INOMax is contraindicated in the treatment of neonates known to be 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 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)*].

### **5.3 Airway Injury from Nitrogen Dioxide**

Nitrogen dioxide (NO<sub>2</sub>) forms in gas mixtures containing NO and O<sub>2</sub>. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If the concentration of NO<sub>2</sub> in the breathing circuit exceeds 0.5 ppm, decrease the dose of INOmax.

If there is an unexpected change in NO<sub>2</sub> concentration, 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 NO<sub>2</sub> analyzer should be recalibrated. The dose of INOmax and/or FiO<sub>2</sub> should be adjusted as appropriate.

### **5.4 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, bradycardia and cardiac arrest. Discontinue INOmax while providing symptomatic care.

## **6 ADVERSE REACTIONS**

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.

### **6.1 Clinical Trials Experience**

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

## **6.2 Post-Marketing Experience**

### **Accidental Exposure**

Based upon post-marketing experience, 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**

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. INOmax has been administered with dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOmax on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

Pregnancy Category C

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

### **8.2 Labor and Delivery**

The effect of INOmax on labor and delivery in humans is unknown.

### **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

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