

## 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

#### RECENT MAJOR CHANGES

Dosage and Administration (2.2) 10/2015

#### 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.

#### 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 an INOMax DS<sub>IR</sub><sup>®</sup> operated by trained personnel (2.2)
- Avoid abrupt discontinuation (2.2, 5.1).

#### DOSAGE FORMS AND STRENGTHS

INOMax (nitric oxide) is a gas available in an 800 ppm concentration (3).

#### CONTRAINDICATIONS

Neonates 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 (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

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

Revised: 10/2015

## 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 Compounds

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

#### 8.3 Nursing Mothers

#### 8.4 Pediatric Use

#### 8.5 Geriatric Use

### 10 OVERDOSAGE

### 11 DESCRIPTION

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

#### 12.2 Pharmacodynamics

#### 12.3 Pharmacokinetics

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

### 14 CLINICAL STUDIES

#### 14.1 Treatment of Hypoxic Respiratory Failure (HRF)

#### 14.2 Ineffective in Adult Respiratory Distress Syndrome (ARDS)

#### 14.3 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)

### 16 HOW SUPPLIED/STORAGE AND HANDLING

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

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

INOmax<sup>®</sup> 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 INOmax 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 INOmax therapy.

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

#### 2.2 Administration

##### Training in Administration

The user of INOmax 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 INOmax at 1-877-566-9466.

##### Nitric Oxide Delivery Systems

INOmax must be administered using a calibrated INOmax DS<sub>IR</sub><sup>®</sup> Nitric Oxide Delivery System. Only validated ventilator systems should be used in conjunction with INOmax. Consult the Nitric Oxide Delivery System label or call 877.566.9466/visit inoamax.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 INOmax and periodically throughout treatment [*see Warnings and Precautions (5.2)*].

Monitor for PaO<sub>2</sub> and inspired NO<sub>2</sub> during INOmax administration [*see Warnings and Precautions 5.3*].

##### Weaning and Discontinuation

Avoid abrupt discontinuation of INOmax [see *Warnings and Precautions (5.1)*]. 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) gas is available in an 800 ppm concentration.

### **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 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 there is an unexpected change in NO<sub>2</sub> concentration, or if the NO<sub>2</sub> 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 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 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, bradycardia 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. 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

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

#### 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 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 INOmax is manifest by elevations in methemoglobin and pulmonary toxicities associated with inspired NO<sub>2</sub>. Elevated NO<sub>2</sub> may cause acute lung injury. Elevations in methemoglobin reduce the oxygen delivery capacity of the circulation. In clinical studies, NO<sub>2</sub> 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]).

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

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.