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) neonates with hypoxic respiratory failure. 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) 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.

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

Wean from INOmax gradually. If methemoglobin levels do not return to baseline over several hours at each step to monitor for hypoxemia.

Dosage and Administration
INOmax is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

ADVERSE REACTIONS
INOmax and Nitrogen Dioxide levels are dose dependent. The most common adverse reaction is hypoxemia.

INOMAX nitric oxide gas INO Therapeutics

INOMAX (nitric oxide) for inhalation
See full prescribing information for INOmax.

These highlights do not include all the information needed to use INOmax safely and effectively. See full prescribing information for INOmax.

CONTRAINDICATIONS
Neonates known to be dependent on right-to-left shunting of blood.

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 clinical use, a 60% reduction in the concentration of nitric oxide, methemoglobin levels return to baseline over 100 ppm

Elevated NO Levels: Monitor NO 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 NO2 levels are dose dependent. The most common adverse reaction is hypoxemia.

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 agents: Nitric oxide donor agents, such as prilocaine, sodium nitroprusside, and nitroglycerin, when administered as oral, parenteral, or topical forms, may have additive effect with NO2 on the risk of developing methemoglobinemia (7).

Revised: 03/2013

Full prescribing information is available at www.inomax.com.

INOmax DS®; INOmax®, or INOvent® operated by trained personnel.

INOmax is contraindicated in the treatment of neonates known to be dependent on right-to-left shunting of blood.

Dosage: The recommended dose of INOmax is 20 ppm, maintained on the safe and effective use of a Nitric Oxide Delivery System provided by the manufacturer of the delivery system and the drug.

Wean from INOmax gradually. If methemoglobin levels do not resolve with decrease in dose or discontinuation of INOmax, additional therapy may be warranted to treat methemoglobinemia (7).

INOmax mortality being more than 40% worse than placebo.

Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude the null hypothesis.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo groups (90 days). INOmax mortality being more than 40% worse than placebo.

INOmax mortality being more than 40% worse than placebo.

INOmax mortality being more than 40% worse than placebo.

INOmax mortality being more than 40% worse than placebo.

INOmax mortality being more than 40% worse than placebo.

INOmax mortality being more than 40% worse than placebo.

INOmax mortality being more than 40% worse than placebo.

INOmax mortality being more than 40% worse than placebo.
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Nitric oxide is a gaseous molecule produced by many cells of the body. It relaxes vascular smooth muscle by binding to constitutively expressed guanylate cyclase, and subsequently increases the intracellular levels of cyclic guanosine 5′-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide competes for the enzyme responsible for producing nitrite, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic vasculature.

INOmax appears to increase the partial pressure of arterial oxygen (PaO2) by dilating pulmonary vessels in infants with PPHN, resulting in an improvement in the oxygen delivery capacity of the circulation. In initial clinical studies, PaO2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

12.2 Pharmacodynamics
Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with methylene blue, an intravenous methemoglobin reductase, or blue, transfusion based on the clinical situation.

12.3 Pharmacokinetics
Methemoglobin concentrations increased during the first 8 hours of nitric oxide exposure. The intravenous inhaled nitric oxide mediated the decrease in methemoglobin levels, and the administration of an inhaled nitric oxide solution had a greater effect on the methemoglobin levels compared to the intravenous administration.

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 daily maximum occupational exposure limits. Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, and is an excreted form of nitric oxide. The safety and efficacy of INOmax for the prevention of chronic lung disease [bronchopulmonary dysplasia, bronchopulmonary fibrosis] in neonates has not been established.

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 in a double-blind, randomized, placebo-controlled, multicenter trial in 125 neonates with hypoxic respiratory failure. The objective of the study was to determine whether inhaling nitric oxide to a mean arterial pressure (MAP) of 25 mm Hg for 48 hours significantly increases in PaO2 and foramen ovale. In neonates with PPHN, INOmax improves oxygenation (as indicated by significant increases in PaO2).

14.2 Ineffective in Adult Respiratory Distress Syndrome (ARDS)
INOmax is not indicated for use in the adult population, including nursing mothers. It is not known whether nitric oxide is excreted in human milk.

14.3 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)
INOmax for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not indicated.

14.4 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)
INOmax for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not indicated.

14.5 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)
INOmax for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not indicated.

14.6 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)
INOmax for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not indicated.

15.1 Ineffective in Prevention of Bronchopulmonary Dysplasia (BPD)
INOmax for prevention of BPD in preterm neonates ≤ 34 weeks gestational age is not indicated.

16 HOW SUPPLIED/STORAGE AND HANDLING
INOmax (nitric oxide) is available in the following sizes:

Size 88
Portable aluminum cylinders containing 353 liters at STP of nitric oxide (NDC 64693-001-02)

Size 122
Portable aluminum cylinders containing 150 liters at STP of nitric oxide (NDC 64693-002-01)

Size 353
Portable aluminum cylinders containing 353 liters at STP of nitric oxide in gas form (NDC 64693-003-01)

Size 444
Portable aluminum cylinders containing 444 liters at STP of nitric oxide in gas form (NDC 64693-004-01)

Size 888
Portable aluminum cylinders containing 888 liters at STP of nitric oxide in gas form (NDC 64693-005-01)