

---

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20845**

**FINAL PRINTED LABELING**

**INOMax™ (nitric oxide) for inhalation****100 and 800ppm (parts per million)****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 (0.8%) and nitrogen (99.2%). 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:

**CLINICAL PHARMACOLOGY**

Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide produces pulmonary vasodilation.

INOMax appears to increase the partial pressure of arterial oxygen (PaO<sub>2</sub>) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

**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 PaO<sub>2</sub>).

**PHARMACOKINETICS**

The pharmacokinetics of nitric oxide has been studied in adults.

**Uptake and Distribution:** Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhemoglobin to transiently form nitrosylhemoglobin, which is converted to nitrogen oxides and methemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrate.

**Metabolism:** Methemoglobin disposition has been investigated as a function of time and nitric oxide exposure 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.

**Methemoglobin Concentration- Time Profiles  
Neonates Inhaling 0, 5, 20 or 80 ppm INOMax**



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  $10 \pm 9$  (SD) hours (median, 8 hours) in these 13 patients; but one patient did not exceed 7% until 40 hours.

**Elimination:** Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

#### CLINICAL TRIALS

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 oxygenation index (OI = mean airway pressure in cm H<sub>2</sub>O x fraction of inspired oxygen concentration [F<sub>i</sub>O<sub>2</sub>] x 100 divided by systemic arterial concentration in mm Hg [PaO<sub>2</sub>]) and increases PaO<sub>2</sub> (See **CLINICAL PHARMACOLOGY**.)

(i) **NINOS study:** The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted 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 caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants  $\leq 14$  days of age (mean, 1.7 days) with a mean PaO<sub>2</sub> of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H<sub>2</sub>O / mm Hg were initially randomized to receive 100% O<sub>2</sub> 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 PaO<sub>2</sub> 30 minutes after starting treatment (full response =  $\geq 20$  mm Hg, partial = 10-20 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 NINOS study are presented in Table 1.

Table 1

## Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO <sup>a,b</sup>	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

<sup>a</sup> Extra-corporeal membrane oxygenation

<sup>b</sup> Death or need for 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 greater increases in PaO<sub>2</sub> and greater decreases in the OI and the 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 a lack of additional benefit for the higher dose of nitric oxide. 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. (See **ADVERSE REACTIONS**.) Follow-up exams were performed at 18-24 months for the infants enrolled in this trial. In the infants with available follow-up, the two treatment groups were similar with respect to their mental, motor, audiological, or neurologic evaluations.

(ii) **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 caused by MAS (35%), idiopathic PPHN (30%), pneumonia/sepsis (24%), or RDS (8%). Patients with a mean PaO<sub>2</sub> of 54 mm Hg and a mean (OI) of 44 cm H<sub>2</sub>O / mm Hg were randomly assigned to receive either 20 ppm INOmax (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO<sub>2</sub> >60 mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax or placebo. The primary results from the CINRGI study are presented in Table 2.

Table 2

## Summary of Clinical Results from CINRGI Study

	Placebo	INOmax	P value
ECMO <sup>a,b</sup>	51/89 (57%)	30/97 (31%)	< 0.001
Death	5/89 (6%)	3/97 (3%)	0.48

<sup>a</sup> Extra-corporeal membrane oxygenation

<sup>b</sup> 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 PaO<sub>2</sub>, OI, and alveolar-arterial gradient ( $p < 0.001$  for all parameters). Of the 97 patients treated with INOmax, 2 (2%) were withdrawn from study drug due to methemoglobin levels  $> 4\%$ . The frequency and number of adverse events reported were similar in the two study groups. (See ADVERSE REACTIONS.)

#### INDICATIONS

INOmax, 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.

#### CONTRAINDICATIONS

INOmax should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

#### PRECAUTIONS

##### Rebound

Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure.

##### Methemoglobinemia

Methemoglobinemia increases with the dose of nitric oxide. In the clinical trials, maximum methemoglobin levels usually were reached approximately 8 hours after initiation of inhalation, although methemoglobin levels have peaked as late as 40 hours following initiation of INOmax therapy. In one study, 13 of 37 (35%) of neonates treated with INOmax 80 ppm had methemoglobin levels exceeding 7%. Following discontinuation or reduction of nitric oxide the methemoglobin levels returned to baseline over a period of hours.

##### Elevated NO<sub>2</sub> Levels

In one study, NO<sub>2</sub> levels were  $< 0.5$  ppm when neonates were treated with placebo, 5 ppm, and 20 ppm nitric oxide over the first 48 hours. The 80 ppm group had a mean peak NO<sub>2</sub> level of 2.6 ppm.

##### 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. In particular, although there are no 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. INOmax has been administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation.

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

No long-term studies in animals to evaluate the carcinogenic potential of nitric oxide have been performed. 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 or harm to the developing fetus.

Pregnancy: Category C

# 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.