**Table 1: Summary of Clinical Results from NINOS Study**

<table>
<thead>
<tr>
<th>Control (n=121)</th>
<th>NO (n=114)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or ECMO&lt;sup&gt;1&lt;/sup&gt;</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>

<sup>1</sup> Extracorporeal membrane oxygenation

<sup>2</sup> ECMO was the primary end point of this study

In clinical trials, 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)

In a randomized, double-blind, parallel, multicenter study, 365 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 PaO<sub>2</sub>/FiO<sub>2</sub> <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 from INOmax therapy.

The results were consistent with outcome data from a large, multi-center, double-blind, placebo-controlled clinical trial in a total of 2,600 preterm infants. Of these, 1,290 received placebo, and 1,310 received INOMAX at doses ranging from 5-20 ppm, for treatment periods of 7-24 days or until the underlying oxygen desaturation has resolved.

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

The use of INOMAX for the prevention of chronic lung disease [bronchopulmonary dysplasia, (BPD)] in neonates ≤ 34 weeks gestational age has not 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 INOMAX at doses ranging from 5-20 ppm, for treatment periods of 7-24 days or until the underlying oxygen desaturation has resolved.

### 14.4 Ineffective in Prevention of Neonatal Necrotizing Enterocolitis (NEC)

The use of INOMAX for the prevention of NEC in neonates ≤ 34 weeks gestational age has not 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 INOMAX at doses ranging from 5-20 ppm, for treatment periods of 7-24 days or until the underlying oxygen desaturation has resolved.

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### 14.8 Ineffective in Prevention of Neonatal Necrotizing Enterocolitis (NEC)

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### 14.9 Ineffective in Prevention of Neonatal Necrotizing Enterocolitis (NEC)

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### 14.11 Ineffective in Prevention of Neonatal Necrotizing Enterocolitis (NEC)

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### 14.12 Ineffective in Prevention of Neonatal Necrotizing Enterocolitis (NEC)

The use of INOMAX for the prevention of NEC in neonates ≤ 34 weeks gestational age has not 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 INOMAX at doses ranging from 5-20 ppm, for treatment periods of 7-24 days or until the underlying oxygen desaturation has resolved.
Nitrogen dioxide (NO₂)

5.3 Airway Injury from Nitrogen Dioxide

If methemoglobin levels do not resolve with decrease in dose more before steady-state methemoglobin levels are attained. In the NINOS, the only adverse reaction (>2% higher incidence on INOmax than on placebo) was hypotension (14% vs. 11%).

6.2 Post-Marketing Experience

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

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 manifested by elevations in methemoglobin and pulmonary toxicities associated with inspired NO₂. Elevated NO₂ may cause acute lung injury. Elevations in methemoglobin range from 0.08% to 99.92% of hemoglobin, which does not transport oxygen. Methemoglobin, which is a pigmented red protein, is produced when oxygen and water to produce nitrogen dioxide and nitrite, scavenging by hemoglobin, has minimal effect on the systemic circulation.

INOmax appears to increase the partial pressure of arterial oxygen (PaO₂) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from regions of low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

12.2 Pharmacodynamics

Effects on Pulmonary Vascular Tone in PPHN

Persistent pulmonary hypertension of the newborn (PPHN) and as a primordial 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 PaO₂).

12.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Nitric oxide has demonstrated genotoxicity in Salmonella typhimurium, human lymphocytes, and in vitro exposure in rats. There are no animal or human studies to evaluate nitric oxide donor agents in fertility.

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 resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (DrO₂= mean airway pressure in cm H₂O × fraction of inspired oxygen concentration [FiO₂]×100 divided by systemic arterial concentration in mm Hg [PaO₂]) and improves survival [see Clinical Pharmacology (12.1)].

INOmax is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm). Nitric oxide 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: \[ \text{NO} \]

INOmax 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 80 ppm INOmax group. Methemoglobin levels did not decrease unless ventilation was attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methemoglobin concentration was 10 to 18 hours (median, 8 hours) in 13 patients, but one patient did not exceed 7% until 40 hours.

Nitrate has been identified as the predominant nitric oxide metabolite, amounting to >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

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Nitrate has been identified as the predominant nitric oxide metabolite, amounting to >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.
Nitrogen dioxide (NO) is warranted to treat methemoglobinemia or discontinuation of INOmax, additional therapy may be required. If methemoglobin levels do not resolve with a decrease in dose of INOmax, monitor methemoglobin and adjust the dose of INOmax to achieve more before steady-state methemoglobin levels are attained.

5.2 Hypoxemia from Methemoglobinemia

Elevations in methemoglobin reduce the oxygen delivery capacity to tissues. 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 risk analysis excluded 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 is 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, gastrointestinal 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

Nitric oxide donor agents such as prilocaine, sodium nitropusside 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.

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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.

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The safety and efficacy of nitric oxide for inhalation has been demonstrated in term and premature 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.

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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. Elevated NO may cause acute lung injury. Elevations in methemoglobin and pulmonary toxicities associated with the oxygen delivery capacity of the circulation. In clinical studies, NO levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobin 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). NO gas 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:

\[ \text{N} = \text{O} \]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Nitric oxide 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 selectively dilates the pulmonary vasculature, and because of efficient scavenging by hemoglobin, has minimal effect on the systemic circulation.

INOmax appears to increase the partial pressure of arterial oxygen (PaO2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

12.2 Pharmacodynamics

Effects on Pulmonary Vascular Tone in PPHN

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical and 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 (PDA) and foramen ovale. In neonates with PPHN, INOmax improves oxygenation (as indicated by significant increases in PaO2).

12.3 Pharmacokinetics

The pharmacokinetics of nitric oxide has been studied in adults.

Absorption and Distribution

Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhemoglobin to transiently form nitrosyhemoglobin, 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.

Figure 1: Methemoglobin Concentration-Time Profiles

Neonates Infusing 0, 5, 20 or 80 ppm INOmax

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% at 80 ppm INOmax. Methemoglobin levels >5% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methemoglobin was 10 ± 3.9 hours (median, 8 hours) for 13 patients, but one patient did not exceed 7% until 40 hours.

Elimination

Nitrate has been identified as the predominant nitric oxide metabolite, with nitrite 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.

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 dose (20 ppm), in rats for 20 hr/day for up to two years. Higher exposures have not been investigated.

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 mutagenicity in vitro.

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 resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygen index (OEF= mean airway pressure in cm H2O× fraction of inspired oxygen concentration [FiO2]×100 divided by systemic arterial concentration in mm Hg [PaO2]) and improves survival [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 the need for rehospitalization for hypoxic respiratory failure 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 congenital heart disease, pulmonary aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants were born at a gestational age (mean, 1.7 days) with a mean PaO2 of 46 mm Hg and a mean oxygen saturation index (Oxi) 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, 30 minutes after starting treatment (full response = >20 mm Hg, partial = 10–20 mm Hg, no response = <10 mm Hg). Neonates with a less than full
In clinical trials, 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)

In a randomized, double-blind, parallel, multicenter study, 357 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 with INOmax on the primary endpoint of days alive and off ventilator support, these results were consistent with outcome data from a larger 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 was a surrogate endpoint for the presence of BPD. Overall, efficacy for the prevention of bronchopulmonary dysplasia in preterm infants was not established. There were no meaningful differences between treatment groups with regard to overall death, bronchopulmonary dysplasia level, or adverse events commonly observed in premature infants, including intraventricular hemorrhage, patent ductus arteriosus, pulmonary hemorrhage, and necrotizing enterocolitis. 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 333 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01)

Size 88
Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 4247 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.

Occupational Exposure

The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO, the limit is 5 ppm (OSHA PEL, 1981). Mallinckrodt, the "M" brand mark, the Mallinckrodt Pharmaceuticals logo and other brands are trademarks of a Mallinckrodt company.

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SFC-LBL-03933MI

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 DSIR® operated by trained personnel (2.2)
• Avoid discontinuation (2.2, 5.1)

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16 HOW SUPPLIED/STORAGE AND HANDLING

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

2.2 Administration

Training in Ad Equipment Administration

The use of INOmax and Nitric Oxide Delivery System must satisfy complete a comprehensive periodic training program for health care professionals provided by the delivery system manufacturer. Health professionals that administrators 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.

INOmax® (nitric oxide) gas is a available in a 800 ppm concentration (3).

Nitric Oxide Delivery Systems

INOmax® must be administered using a calibrated INOmax DSIR® Nitric Oxide Delivery System. Only validated ventilator systems should be used in conjunction with INOmax. Consult the Nitric Oxide Delivery System label or call 1-877-566-9466/visit inomax.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.

INOMAX (nitric oxide) gas, for inhalation

Dosage and Administration

Possible 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%). Neonates who died or received ECMO at birth 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 PaO2 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 drug, suggesting a lack of additional benefit for the higher dose of nitric oxide. No infant had study drug discontinued for toxicity.

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