



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all plans administered by CIGNA Companies including plans administered by Great-West Healthcare, which is now a part of CIGNA.

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## Subject Inhaled Nitric Oxide (INO)

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### Hyperlink to Related Coverage Policies

Measurement of Exhaled Nitric Oxide and Exhaled Breath Condensate in the Management of Respiratory Disorders Ventricular Assist Devices (VADs)

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans as well as benefit plans formerly administered by Great-West Healthcare. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA

## Coverage Policy

CIGNA covers inhaled nitric oxide as medically necessary for **ANY** of the following indications:

- treatment of hypoxic respiratory failure in neonates with a gestational age of at least 34 weeks in the absence of a congenital diaphragmatic hernia when there is failure, contraindication or intolerance to conventional therapy
- the postoperative management of pulmonary hypertension following repair of congenital heart disease
- for pulmonary hypertension during heart catheterization to determine pulmonary vasoreactivity

**CIGNA does not cover inhaled nitric oxide for any other indication, including but not limited to acute respiratory distress syndrome, because it is considered experimental, investigational or unproven.**

## General Background

Nitric oxide (NO) is a lipophilic, endogenous compound, naturally produced in numerous cells in the body and synthesized by an enzyme called NO synthase (NOS). NO is involved in numerous physiologic functions and aids in pulmonary vasodilatation, inhibition of platelet aggregation, renal perfusion, erection, fertilization, peristalsis and neurotransmission. It is found in neurons, macrophages and in the endothelial cells in the lining of the lumen of blood vessels. With each systole, the endothelial cells within the blood vessels release NO, causing the vessels to relax and dilate, enhancing blood flow through the vessels. During metabolism, NO binds

to hemoglobin and is converted to nitrites and nitrates, which are then excreted in the urine (Mosby's, 2006; Kimball, 2006; FDA, 2004; Klinger, 2002).

NO is commercially available as a colorless, nonflammable, almost odorless gas used for therapeutic administration by inhalation (i.e., inhaled nitric oxide). Inhaled nitric oxide (INO), a pulmonary vasodilator, has been proposed for the treatment of conditions associated with reversible vasoconstriction and pulmonary hypertension. Absorbed systemically after inhalation, NO combines with hemoglobin and enters circulation as methemoglobin and nitrate. The administration of INO is a minimally invasive treatment involving the inhalation of NO in conjunction with ventilatory support. INO vasodilates only those areas that are ventilated which results in improvement of perfusion and oxygenation. Nitric oxide, unstable in air, undergoes spontaneous oxidation to nitrogen dioxide (NO<sub>2</sub>). NO<sub>2</sub> is known to be directly toxic to the respiratory tract. Due to this instability and potential toxicity, continuous, in-line monitoring of the administration of INO is the standard of care during therapeutic administration (Ryan and Tobias, 2007; Mosby's, 2006; Hayes; Sep 2005; Griffiths and Evans, 2005; U.S. Food and Drug Administration [FDA], 2004; Weinberger, et al., 2001).

### **U.S. Food and Drug Administration (FDA)**

A complete nitric oxide delivery system is comprised of three medical devices: a nitric oxide administration apparatus, a nitric oxide gas analyzer, and a nitrogen dioxide gas analyzer. The FDA has regulated and approved the use of INO and its administration since 1999. In 2000, the FDA published a "Guidance Document for Premarket Notification Submissions for Nitric Oxide Delivery Apparatus, Nitric Oxide Analyzer and Nitrogen Dioxide Analyzer."

INOMax<sup>®</sup> (INO Therapeutics Inc., Clinton, NJ) is the only commercial brand of INO and was initially approved by the FDA in 1999. INOMax, in conjunction with ventilatory support and other appropriate agents (e.g., surfactant), is approved by the FDA "for the treatment of term and near-term (i.e., > 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." INOMax is a gaseous blend of NO and nitrogen, supplied under pressure in cylinders as a compressed gas (FDA, 1999).

The apparatuses for administration of INO are regulated by the FDA as Class II devices and are approved by the FDA 510(k) process. Examples of the delivery devices include the ViaNOx delivery system (Pulmonox Medical, Inc., Alberta, CA) and the INOvent delivery system (Ohmeda Medical, Laurel, MD).

### **Hypoxic Respiratory Failure**

The primary clinical indication for the use of INO, in conjunction with ventilatory support and other treatment modalities (e.g., surfactant and high-frequency ventilation), is hypoxic respiratory failure secondary to pulmonary hypertension in the neonate greater than 34 weeks' gestation (FDA, 2004). Persistent pulmonary hypertension (PPHN) may occur as a primary developmental defect or as a condition secondary to morbidities such as respiratory distress syndrome (i.e., hyaline membrane disease), meconium aspiration syndrome, pneumonia, sepsis, congenital diaphragmatic hernia, cardiac malformations and pulmonary hypoplasia. Signs of PPHN include tachypnea, tachycardia, respiratory distress and cyanosis. In addition to the presence of clinical signs, PPHN is diagnosed with the aid of laboratory studies (e.g., arterial blood gas, especially pre- and post-ductal gases greater than 10 millimeters [mm] of mercury [Hg]), pulse oximetry, lumbar puncture, chest x-ray, and echocardiogram. Complications of PPHN may include: shock, heart failure, brain hemorrhage, seizures, renal failure, organ damage and death. PPHN is one of the most serious conditions in the neonatal period (Hayes, Sep 2005; FDA, 2004; Weinberger, et al., 2001; American Academy of Pediatrics [AAP] 2000; Hintz, et al., 2000; Oliveira, et al., 2000).

The goal of therapy for PPHN is to maximize the amount of oxygen transported by the lungs and, in turn, available to systemic circulation. Conventional therapies include high concentrations of oxygen, hyperventilation, high-frequency ventilation, induction of alkalosis, neuromuscular blockade, and sedation. When conventional therapies fail, INO may be indicated. INO improves oxygenation, decreases the need for extracorporeal membrane oxygenation (ECMO) and decreases mortality. In addition to pulmonary vasodilatation and a reduction in extrapulmonary right-to-left shunting, INO also improves ventilation/perfusion matching, decreases lung inflammation, and enhances growth in the immature lung (Kinsella, 2006 ; AAP, 2000; Walsh-Sukys, et al., 2000).

Studies have also demonstrated that INO was ineffective or had minimal effect in newborns with congenital diaphragmatic hernia, even when INO treatment was combined with surfactant. Response is low due to the possible combination of lung hypoplasia and immaturity and PPHN aggravated by left ventricular underdevelopment. INO has not been proven to be beneficial in the treatment of hypoxic respiratory failure in the infant less than 34 weeks' gestation or in the treatment of other conditions, such as acute respiratory distress syndrome, in the premature infant or in the adult (Kinsella, 2006; Kinsella and Abman, 2005; Finer and Barrington, 2001; Weinberger, et al., 2001; Clark, et al., 2000; Neonatal Inhaled Nitric Oxide Study Group (NINOS), 1997).

**Literature Review:** INO is a well-established treatment modality for infants with a gestational age of 34 weeks and older who are poor candidates for conventional therapy or are nonresponsive or intolerant to conventional therapy. Several randomized controlled trials including infants with respiratory failure secondary to PPHN, respiratory distress syndrome, perinatal aspiration syndrome, pneumonia, sepsis, or pulmonary hypoplasia have compared the outcomes of ventilator-supported infants who were treated with INO (n=29–150) to infants who did not receive INO (n=28–149). Collectively, the outcomes demonstrated that INO improved systematic oxygenation and that fewer infants required ECMO and/or developed chronic lung disease. Some studies reported a higher survival rate following INO therapy (Field, et al., 2007; Konduri, et al., 2004; Clark, et al., 2000; Roberts, et al., 1997; Neonatal Inhaled Nitric Oxide Study Group, 1997; Wessel, et al., 1997).

One randomized controlled trial assessed the effects of INO on neurodevelopment. In the 234 infants available for 18–24 months follow-up, outcomes demonstrated that early INO therapy did not increase neurodevelopmental abnormalities or hearing loss (Konduri, et al. 2007). A Cochrane review (Finer and Barrington, 2006) which included 14 randomized controlled trials and a meta-analysis (Oleira, et al., 2000) including seven randomized control trials (n=548) also concluded that INO decreased the need for ECMO and improved systemic oxygenation in infants without congenital diaphragmatic hernia (CDH).

The studies consistently demonstrated the ineffectiveness of INO when used in the treatment of infants with congenital diaphragmatic hernia (CDH).

#### **Postoperative Management of Pulmonary Hypertension with Congenital Heart Disease (CHD)**

Depending upon the severity of the disease, CHD can increase pulmonary blood flow or cause pulmonary venous obstruction, leading to pulmonary artery smooth muscle hypertrophy, vasoconstriction, vascular obliteration and pulmonary hypertension. At this point, surgical intervention is indicated to reverse the condition and ward off impending death. Following surgical intervention, infants and children can experience life-threatening reactive or persistent elevated pulmonary arterial pressure, or pulmonary hypertension. Due to its specificity for the pulmonary vascular bed, INO acts directly on pulmonary vascular smooth muscle. It is inactivated when exposed to hemoglobin, therefore avoiding side effects of systemic vasodilation that may be encountered with the use of other available vasodilators. Alternatives to the use of INO include ECMO and ventricular assist devices. Because of INO's ability to decrease PVR and intrapulmonary shunting, and increase oxygenation, INO has become a standard of care for the treatment of pulmonary hypertension following surgical repair of congenital heart disease (Kliegman, et al., 2007; Ichinose, et al., 2004; Kawakami and Ichinose, 2004; Carroll, et al., 2003; Hermon, et al., 2003).

**Literature Review:** Studies evaluating the use of INO for the post-operative treatment of pulmonary hypertension include small, heterogeneous patient populations and short-term follow-ups. Hermon et al. (2003) conducted a retrospective study to evaluate the cumulative effect of INO on methemoglobin formation in children (n=38) who had undergone surgery for congenital heart disease and had pulmonary hypertension despite treatment with hyperventilation and inspired oxygen levels of 100%. INO was administered to the study group for 2–29 days at a dosage of 5–40 ppm. The level of methemoglobin was measured prior to the initiation of INO (T0), and following the administration of INO at 24 hours (T1), at half-time therapy (T2), at the end of therapy (T3) and 24 hours following the cessation of therapy (T4). Methemoglobin levels increased significantly following the administration of INO (T0 vs. T1 p<0.05; T0 vs. T2 p<0.001; T1 vs. T3 p<0.05; T1 vs. T4 p<0.001; T2 vs. T3 and T4 p<0.001). The highest measured level of methemoglobin was 3.9%. None of the levels were considered toxic. No significant correlation was found between the duration of INO treatment and the methemoglobin levels. Five of the children died and six required ECMO. Neurologically, three children were considered moderately handicapped and ten were severely handicapped. None of these adverse outcomes were attributed to INO therapy or methemoglobin levels.

Schulze-Neick et al. (2003) conducted a study to compare the effects of INO to intravenous sildenafil in the treatment of 12 children with CHD who had increased mean pulmonary arterial pressure and 12 children who had undergone congenital heart surgery who had increased PVR. Outcomes were assessed during heart catheterization or within two hours following surgery, respectively. The effects of INO were compared before and after the infusion of sildenafil. For the medical children treated in the laboratory, sildenafil resulted in a decreased mean pulmonary artery pressure ( $p=0.004$ ) and PVR ( $p=0.010$ ) compared to no significant change with INO. A higher pulmonary vasodilating capability was seen with sildenafil compared to INO ( $p<0.005$ ). For those children treated postoperatively, sildenafil caused a reduction in mean systemic blood pressure ( $p<0.01$ ) and lowered pulmonary artery pressure more than INO ( $p=0.09$ ). However, sildenafil resulted in increased intrapulmonary shunting postoperatively ( $p=0.04$ ). Sildenafil was more effective than INO in the nonoperative children, but there was no overall significant differences were recorded in the postoperative group.

Rimensberger et al. (2001) conducted a study to compare the pulmonary vascular capacity of INO to aerosolized iloprost in children ( $n=15$ ) with pulmonary hypertension and CHD. During normoventilation with inspired oxygen, all children received INO 20 ppm for ten minutes; returned to baseline, received 25 nanograms (ng) of aerosolized iloprost for ten minutes, and were then given both drugs simultaneously for ten minutes. Using arterial blood samples, outcomes were measured by the levels of cyclic guanosine monophosphate (cGMP), the INO indicator and cyclic adenosine monophosphate (cAMP), the iloprost indicator. Both INO and iloprost resulted in a significant reduction in the pulmonary-to-systemic vascular resistance ratio ( $R_p/R_s$ ) in 14 patients ( $p<0.001$ ;  $p<0.05$ , respectively). Used in combination, the drugs did not add any significant decrease. The level of cGMP increased by 97% with the use of INO ( $p<0.01$ ) and also when combined with iloprost ( $p<0.001$ ). The cAMP level increased by 20% following administration of iloprost ( $p<0.05$ ), as well as in combination with INO ( $p<0.05$ ). No changes in systemic arterial pressure or vascular resistance were noted following the administration of iloprost. An author-noted limitations of the study involved the fact that iloprost was always given after INO because iloprost has a longer half-life and it cannot be ruled out that there was an interaction from the INO effects and the iloprost vasodilator capacities on the endothelial cell.

Sharma et al. (2001) conducted a study to evaluate the effect of INO on 24 children, ages 15 days to 14 months who had residual pulmonary hypertension following congenital heart surgery. Patients were treated with intermittent intravenous pancuronium and fentanyl for at least 48 hours following surgery. INO was initiated 0–72 hours following surgery in patients with a mean PAP/systemic artery pressure (SAP) ratio greater than 0.5. Duration of therapy ranged from 1–10 days. Twenty-two patients experienced a significant drop in mean PAP ( $p<0.001$ ) and ten patients developed a stable PAP/SAP ratio less than 0.5. Six patients maintained a PAP/SAP less than 0.3. Seven patients without PAP monitoring demonstrated a drop in the PAP on echocardiogram. Patients who did not respond to INO or were intolerant or dependent on INO ( $n=9$ ) did not survive. Five additional patients died from pulmonary hypertension alone with one neurological death and one reoperation.

Day et al. (2000) conducted a randomized controlled trial to compare the outcomes of patients ( $n=38$ ), ages 1 day to 20 years, with CHD who underwent biventricular repair and were at risk for developing pulmonary hypertension. Patients were randomized to either INO 20 ppm ( $n=19$ ) or conventional therapy ( $n=19$ ). The occurrence of pulmonary hypertensive crisis was the primary outcome. Three INO-treated patients and four control group patients experienced pulmonary hypertensive crisis. An acute  $\geq 10$ -20% decrease in systolic pulmonary and arterial pressures was experienced by 8 control and 13 INO-treated patients. There were no significant differences in the baseline and 1-hour measurements of heart rate, systolic pulmonary pressure, systolic systemic pressure, right and left atrial pressure, pH, partial pressure of carbon dioxide ( $PaCO_2$ ) and  $PaO_2/FIO_2$  between the two groups. However the change in the ratio of systolic pulmonary and systemic arterial pressures approached statistical significance ( $p=0.066$ ).

Miller et al. (2000) conducted a randomized controlled trial to evaluate the outcomes of 124 infants with high pulmonary flow and/or pressure who underwent cardiac surgery for congenital heart disease. Patients were randomized to either 10 ppm INO ( $n=63$ ) or to nitrogen placebo ( $n=61$ ). Outcomes included the number of hypertension crisis, duration of treatment, and hours in intensive care. The study was conducted from the initiation of the gas until weaning. Infants treated with INO had fewer pulmonary hypertension crisis ( $p<0.001$ ), a shorter median time to eligibility for extubation ( $p=0.019$ ), a shorter duration on study gas ( $p=0.023$ ), a lower PVR index ( $p<0.001$ ) and a longer weaning time than the placebo group. Twenty-two infants were weaned on the seventh study day, while 102 were weaned prior to day seven. There were no significant differences in the number of extubation delays, methemoglobin or nitrogen dioxide levels (which were considered nontoxic), time to discharge from intensive care, or number of deaths. No deaths were contributed to the use of INO.

Morris, et al. (2000) conducted a randomized cross-over controlled trial in which 12 children were treated with INO compared to hyperventilation for postoperative pulmonary hypertension following biventricular repair for CHD. The objective was to “compare the hemodynamic effects of mild alkalosis (pH 7.5), induced by HV, with iNO.” Each subject was treated with both interventions with a 30 minute wash-out period between therapies, and thereafter treatments were administered simultaneously. INO was delivered at an initial 5 ppm dose for 15 minutes then followed by 40 ppm for an additional 15 minutes. Hyperventilation resulted in a decrease in the PaCO<sub>2</sub> (43.7 ± 5.3 mm Hg to 32.3 ± 5.4 mm Hg); increased arterial pH (7.40 ± 0.04 to 7.50 ± 0.03); significant changes in systemic and pulmonary hemodynamics including an increase in systemic vascular resistance index (SVRI); and a decrease in pulmonary artery pressure (PAP), PVR index, central venous pressure, and cardiac index; and an increase in oxygen extraction (p<0.05). INO resulted in selective pulmonary vasodilatation with no change in the SVRI or cardiac index. No differences were seen with a change in INO dosage between five and 40 ppm. The combined use of INO and HV increased the SVRI and caused a further reduction in the pulmonary artery pressure.

### **Diagnostic Testing for Pulmonary Hypertension**

The initial evaluation for the diagnosis of pulmonary hypertension may include conventional therapies, such as chest radiography, electrocardiogram, echocardiogram, doppler echocardiography, pulmonary function studies and arterial blood gases. If the pulmonary hypertension cannot be confirmed by these conventional diagnostic studies, a right-heart catheterization using a pulmonary vasodilator may be indicated. INO is well-established in the management of pulmonary hypertension as a vasodilator used to assess pulmonary vasoreactivity. A positive response to a vasodilating agent is indicative of favorable long-term clinical outcomes. A decrease in pulmonary artery pressure or PVR in response to INO predicts a subsequent beneficial response to oral vasodilators such as nifedipine and identifies candidates who will benefit from long-term calcium channel blockers. INO testing can also help to determine if a patient is a good surgical candidate. Intravenous prostacyclin, adenosine and channel blockers may also be used to assess pulmonary vasoreactivity. Proponents of INO state that due to the potent, short-acting vasodilatory effect of INO and the potential of severe hypotension, increased intrapulmonary right-to-left shunting and death in response to other agents, INO is considered a safer alternative (Barst, 2007; Bloch, et al., 2007; Minai and Budev, 2007; Krishnaswamy, et al., 2006; Channic and Lewis, 2005; Ichinose, et al., 2004; Balzer, et al., 2002).

Review articles discussing the management of pulmonary arterial hypertension state that INO is a vasodilator used to confirm the diagnosis of pulmonary arterial hypertension and the degree of vasoreactivity by measuring the change in PVR (Minai and Budev, 2007; Gildea, et al., 2003). Textbooks also list INO as a vasodilating agent used during right heart catheterization in the diagnosis of pulmonary hypertension (Park, 2008; Barst, 2007, Krishnaswamy, et al., 2006; Channic and Lewis, 2005) and in determining operability in adults with congenital heart disease with elevated PVR (Fraser and Carberru, 2008).

**Literature Review:** Cannon et al. (2005) conducted a preoperative case series to “characterize responses in PVR to oxygen and increasing doses of NO during cardiac catheterization and to determine if any related factors affect the response of the pulmonary vascular bed to NO.” INO testing was performed on 42 patients, age range two months to 27 years, with CHD and elevated PVR. Outcomes were measured at baseline, 100% oxygen and 100% oxygen plus 20, 40 and 80 ppm of INO. Thirty-three patients responded to oxygen/INO but not to oxygen alone, and 30 patients responded to both oxygen alone and oxygen/INO. Compared to baseline, there was a significant decrease in mean PVR (p<0.02) with 100% oxygen. There was an even greater significant decrease when 100% oxygen was administered in combination with 20 ppm INO (p<0.01). Increasing the INO to 40 and 80 ppm did not improve the outcomes. With 100% oxygen alone, the PVR/SVR decreased 27% (p<0.01) compared to a 38% decrease with the addition of 20 ppm of INO. The decrease in PVR was not as significant in patients with chromosomal abnormalities and trisomy 21.

Leuchte et al. (2004) conducted a study to compare the use of INO, iloprost aerosol and oral sildenafil to “test acute hemodynamic response during right-heart catheterization” in ten patients, ages 33–59 years, with primary pulmonary hypertension. Values were established initially and following the administration of each vasodilator. INO (40 ppm for five minutes), aerosolized iloprost (fifty micrograms in 4.5 milliliters of saline) and sildenafil (50 mg followed by 50 mg in 30 minutes with measurements 30 minutes following each dose) were administered in sequential order in all patients. The administration of INO resulted in a decline in the mean PAP (p<0.05), an increase in cardiac output (CO) (p>0.05), and a reduction in PVR (p<0.01). Four patients were responders with a ≥ 20% PVR reduction and three patients with a ≥ 20% mean PAP response. Iloprost resulted in a reduced mean PAP (p<0.01), increased CO (p>0.05), and an overall PVR reduction (p<0.01). Seven patients were

responders with a  $\geq 20\%$  PVR reduction and five patients with a  $\geq 20\%$  mean PAP response. Following the cumulative dose of 100 mg of oral sildenafil, the mean PAP declined ( $p < 0.01$ ), CO increased ( $p > 0.05$ ) and the PVR dropped ( $p < 0.01$ ). Four patients were responders with a  $\geq 20\%$  PVR reduction and three patients with a  $\geq 20\%$  mean PAP response. Two patients experienced a paradoxical increase in mean PAP and PVR following INO dosage compared to none with sildenafil. INO and sildenafil resulted in a comparable overall reduction in mean PAP and PVR, and both INO and sildenafil caused a significant PVR reduction of  $\geq 20\%$  in 40% of the patients. Positive INO responders were also positive sildenafil responders. A more pronounced fall in mean PAP and increase CO were seen with sildenafil and iloprost, but they were not statistically significant. Comparing INO to iloprost, a greater response was seen in reductions of PVR ( $p < 0.05$ ) and mean PAP ( $p < 0.01$ ) with iloprost. The PVR response was 30% higher with iloprost compared to sildenafil. Fifty-seven percent of iloprost responders were also INO and sildenafil responders. A significant increase was seen in arterial oxygen pressure with iloprost and not with INO and sildenafil. No significant effects were recorded on pulmonary capillary wedge pressure, mean systemic arterial pressure, or systemic vascular resistance by any vasodilator. Two INO patients demonstrated an increase in mean PAP and PVR. Limitations of the study include the small patient population and the lack of randomization of the use of the vasodilators.

Balzer et al. (2002) also conducted a preoperative study to determine if hemodynamic evaluation with oxygen with INO would provide a more accurate diagnosis than oxygen alone. Surgical candidates ( $n=124$ ), age range 1–569 months, with congenital or acquired heart disease without heart defects from ten institutions were included in the study. Following testing, 78 patients were considered operative candidates, and 7 of those were lost to postoperative follow-up. When oxygen alone was compared with oxygen/INO administration, sensitivity (64% vs. 97%, respectively) and accuracy (68% vs. 90%, respectively) were increased when the systemic vascular resistance index:systemic vascular resistance index ( $R_p:R_s < 0.33$ ) was used as the criterion for operability. When a 20% decrease in  $R_p:R_s$  from baseline was used as the criterion for operability, specificity was 8%. Patients were more accurately selected for surgery when tested with oxygen/INO combination. The authors noted that the study was limited by the small patient population and “a lack of objective measures in the clinical diagnosis of right heart failure.” They noted that “the most appropriate values of  $R_p$  and  $R_p:R_s$  to use for patient selection, and the optimal combination of assisted ventilation, supplemental oxygen, inhaled nitric oxide and other pulmonary vasodilators that will narrow the range of  $R_p:R_s$  values for which the outcome of corrective surgery and transplantation remains uncertain.” Other limitations of the study include the lack of a control group and the loss to follow-up.

Atz et al. (1999) compared the outcomes of the use of oxygen ( $O_2$ ) alone, INO alone and a combination of oxygen and INO in 46 patients with pulmonary hypertension. The testing was conducted to determine “suitability for corrective surgery, transplantation and assessment of long-term prognosis.” Group 1 ( $n=25$ ) was tested at room air, following 15 minutes of 100%  $O_2$ , 15 minutes of room air and 15 min of 80 ppm of INO in 23%  $O_2$ . Group 2 ( $n=25$ ) was studied at room air, 15 minutes of 100%  $O_2$  and 15 minutes of 80 ppm INO in 91%  $O_2$ . In group 1, one oxygen administration resulted in a decreased PVR ( $p < 0.05$ ), as did INO ( $p < 0.05$ ). Group 2 also experienced a decreased PVR ( $p < 0.05$ ) and an even greater decrease with INO ( $14.3 \pm 6.1$  U.m<sup>2</sup> vs.  $10.5 \pm 1.7$  U.m<sup>2</sup>). In 22 of 25 patients treated with INO/ $O_2$  a  $\geq 20\%$  response was seen compared to 16 of 25 patients in  $O_2$  alone. No evidence of toxicity was noted. Limitations of the study include the heterogeneous, small patient population and lack of randomization.

### **Other Proposed Indications**

Due to INO's success in treating PPHN in term and near-term neonates, it is hypothesized that its pulmonary vasodilatation characteristic may be effective as a treatment modality in other conditions, including:

- respiratory distress in preterm infants less than 34 weeks' gestation
- chronic lung disease in preterm infants
- acute respiratory failure in older children and adults
- sickle cell disease
- lung transplant
- cardiopulmonary disorders
- pain from coronary artery disease

**Respiratory Distress in Preterm Infants less than 34 Weeks' Gestation:** Studies for the administration of INO in premature infants less than 32 weeks' gestation with respiratory distress of various etiologies have

shown promise, but are ongoing and inconclusive. Barrington and Finer (2007) conducted a systematic review to evaluate the efficacy and toxicities of INO in infants less than 35 weeks' gestation "to determine whether, for preterm newborn infants with respiratory disease, inhaled nitric oxide reduced the rates of death, bronchopulmonary dysplasia (BPD), intracranial hemorrhage, or neurodevelopmental disability." Eleven randomized controlled trials were included. The infants had received treatment with surfactant prior to inclusion in the studies. Due to the differences in the inclusion criteria, pooling of the results was considered "not appropriate" and the 11 trials were subdivided for analysis. The first group of studies (n=7), considered "early rescue treatment," included acutely ill infants, undergoing ventilation who were enrolled within the first three days of life. The second group included infants three days of age who were at risk for developing BPD (n=2 studies). The third group was comprised of two studies in which infants were less than age three days and were intubated but had no criteria regarding severity of illness. In these two studies INO was considered "early routine use." The authors concluded that for the early rescue treatment group INO did not improve survival rates, survival with BPD or survival without brain injury, and there was some evidence that INO contributed to intracranial hemorrhage and/or periventricular leukomalacia. The authors also noted that the use of INO to treat preterm infants on ventilation who were not severely ill, but were at risk for BPD and brain damage showed promise and suggested that additional studies are needed to validate findings.

Di Fiore et al. (2007) conducted a study to determine if INO improved airway resistance and compliance in ventilated infants (n=71) with evolving BPD. The infants, gestational age 24.3–26.7 weeks, weight 574–930 g, ages 11.5–19.6, days, were randomized to either INO (n=34) or placebo gas (n=37). Pulmonary function was assessed prior to initiation of the study, one hour and 24 hours following the initiation of therapy, and weekly thereafter until the infant was extubated or switched to high-frequency ventilation. Pulmonary function measurements included expiratory resistance (R<sub>exp</sub>) and compliance normalized by weight (C<sub>kg</sub>). There were no significant differences in the two groups in the one hour R<sub>exp</sub> and C<sub>kg</sub> values (p=0.66, p=0.40, respectively) nor at the end of week one (p=0.63, p=0.29, respectively). During week one, eight placebo-treated infants were switched to high frequency ventilation and one infant expired compared to seven INO-treated infants who were switched to high frequency ventilation. At the end of two weeks, 16 placebo-treated infants and ten INO-treated infants were available for assessment. Values at the end of week two were constant from week one. Limitations of the study include the small patient population and the number of infants lost to follow-up.

Hintz et al. (2007) conducted a multicenter randomized controlled trial to evaluate the effects of INO on neurodevelopmental impairment (NDI) and mortality in infants (n=418), gestational age less than 34 weeks, weight 401–1500 g, with severe respiratory failure. NDI was defined as moderate to severe cerebral palsy (CP), bilateral blindness, or deafness, and a score less than 70 on Bayley Scales of Infant Development [BSID] II, Mental Developmental Index [MDI] or Psychomotor Developmental Index [PDI]. Follow-up occurred at 18 to 22 months of age corrected for prematurity. The infants were randomized to receive either INO (n=210) or placebo (n=208) based upon birth weight (i.e., 401–750 g; 751–1000 g; 1001–1500 g). Of the available infants at follow-up, 91 of 101 (90%) INO-treated infants and 102 of 112 (91%) placebo-treated infants survived. There were no significant differences in the death rate or NDI of the INO group compared to the placebo group (78% vs. 73%, respectively). Compared to the placebo group, a slightly increased risk of moderate to severe CP or death was reported in INO-treated infants with a birth rate less than 1000 g (p=0.01). Limitations of the study include the number of infants lost to follow-up and the short-term follow-up.

Tanaka et al. (2007) conducted a retrospective review of preterm infants, less than 34 weeks gestation, with PPHN who were treated with INO (n=16) or 100% oxygen (n=15). In the three-year follow-up period, 26 infants died and four were lost to follow-up. There was no significant difference in the mortality rate of INO-treated infants compared to infants treated with 100% oxygen (p=0.791). Comparing INO-treated infants to 100% oxygen-treated infants, the incidence of outcomes included "8.8% vs. 29.6% for patent ductus arteriosus, 17.6% vs. 25.9% for intraventricular hemorrhage (grade 3 or 4), 8.8% vs. 0% for necrotizing enterocolitis, and 11.8% vs. 16.0% for pulmonary hemorrhage." INO-treated infants experienced a lower incidence of CP (p=0.54). One hour following initiation of INO, the oxygenation index was lower for INO-treated infants compared to the 100% oxygen-treated patients (p=0.13). Limitations of the study include the small patient population, infants lost to follow-up and the short-term follow-up.

Van Meurs et al. (2007) conducted a pilot randomized controlled trial to determine if the use of INO would reduce the incidence of death and BPD. Infants requiring mechanical ventilation for severe respiratory failure, less than 34 weeks gestation, weight greater than 1500 g, were randomized to either INO (n=14) or placebo (n=15). Five INO-treated infants and four control group infants died before discharge. There were no significant differences between the two groups in death, BPD, death and/or BPD or NDI outcomes. The trial was

terminated due to the high incidence of grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia in the INO-treated infants. Author noted limitations of the study include the small patient population and the short duration of INO administration (i.e., maximum 14 days).

A randomized controlled trial (n=29) by Meurs et al. (2007) evaluated the use of INO in infants less than 34 weeks and greater than 1500 grams (g) to determine if INO would reduce the risk of death and BPD. The trial was terminated due to the significantly high incidence of intraventricular hemorrhage and periventricular leukomalacia in infants receiving INO. The outcomes of the enrolled subjects demonstrated that INO was also not effective in reducing BPD. A Kinsella 2006 review of INO therapy in premature newborns with hypoxemic respiratory failure and PPHN summarized the results of nine randomized controlled studies. He reported that the studies “yielded conflicting results and the role of INO in this population remains controversial.”

Ballard et al. (2006) conducted a randomized controlled trial including 582 infants from 21 centers. The infants, gestational age 26 weeks, had a birth weight of 1250 g or less, were on mechanical ventilators, at high risk for BPD, and between ages seven and 21 days. Infants were randomly assigned to INO (n=294) and non-INO (n=288) and stratified according to weight (i.e., 500–799 g and 800–1250 g). INO was initially administered at 20 ppm, and the dosage was decreased at weekly intervals until a minimal of 24 days of treatment had been administered. The goal was survival without BPD. In the study group, 43.9% survived without BPD compared to 36.8% in the control group. INO infants received supplemental oxygen for a shorter period of time and were discharged sooner. Survival without BPD was similar in both birth-weight strata. Infants treated with INO required less supplemental oxygen and were discharged sooner. INO administered between 7 and 21 days of age improved pulmonary outcomes in preterm infants at risk for BPD. The authors pointed out that this trial differed in design from other studies in that INO was not started until the seventh day, and INO was administered for a longer period of time (i.e., 24 days versus 76 hours to 14 days). They also stated that definitive recommendations for the use of INO in this population were contingent upon long-term neurodevelopmental outcomes.

Kinsella et al. (2006) also conducted a multicenter randomized controlled trial (n=793) to evaluate the effectiveness of INO in the treatment of newborns, 34 weeks or less gestational age, requiring mechanical ventilation. Infants were randomized to the INO group (n=398) or to the control-placebo group (n=395). The groups were further stratified by weight (i.e., 500–749 g, 750–999 g, 1000–1250 g). The study group received 5 ppm INO, within 48 hours of birth, for a median of 14 days (range 0–24). Primary outcome was death or BPD at 36 weeks of postmenstrual age. Overall, there were no significant differences in the outcomes between the INO group (71.6% experienced death or BPD) and the control group (75.3% experienced death or BPD). In the 1000–1250 g birth-weight group, INO reduced BPD compared to the control group, 29.8% and 59.6%, respectively. For all the subjects, the occurrence of intracranial hemorrhage, periventricular leukomalacia, ventriculomegaly, and periventricular leukomalacia alone was reduced. INO infants had a lower incidence of periventricular leukomalacia than the control group infants. The largest reduction of periventricular leukomalacia or intracranial hemorrhage was seen in the INO 750–999 g subgroup and, overall, the INO group experienced fewer incidences of ventriculomegaly (5.2% compared to 8.9%). In the overall population, INO reduced the risk of brain injury, but it did not reduce the risk of BPD in 500–1250 g infants.

In a single-site, randomized controlled trial (Dani, et al., 2006) infants less than 30 weeks' gestation, age 0 to 7 days, with severe respiratory distress were randomized to an INO group (n=20) or to a control group (n=20). INO was administered at 10 ppm for four hours and was then decreased to 6 ppm until the infant was weaned completely by gradual decrease of the INO dosage. Death or BPD was experienced in 50% of the INO group compared to 90% of the control group. INO was less effective in infants with a birth weight lower than 750 g. INO did not decrease the need for respiratory support. The authors noted that INO therapy decreased the cumulative incidence of BPD, and death and birth weight may affect the success of INO therapy. Due to the small patient population, the authors stated that future studies were needed to confirm these findings.

A meta-analysis by Hoehn et al. (2006) of INO in the treatment of severe hypoxemic respiratory failure in preterm infants was conducted. The analysis incorporated five randomized controlled trials, which included 808 infants age less than 34 weeks' gestation. As a result of their study, the authors concluded that there was no significant difference in the rate of major intracranial hemorrhage and mortality rate in infants treated with INO. It was also noted that INO significantly reduced the incidence of chronic lung disease (CLD) and mortality of infants with CLD. However, the authors stated that the data from these studies was preliminary and should be regarded cautiously.

Van Meurs (2005) reviewed the results of five randomized clinical trials of preterm infants with respiratory distress syndrome who were treated with INO. One trial demonstrated improvement with the use of INO (Schreiber, et al., 2003), but the other studies showed no improvement. Other authors have noted discrepancies among outcomes and stated that they may be attributed to variations in the severity of illness, underlying conditions, composition of the study population, and single-center versus multicenter (Martin and Walsh, 2005).

Mestan et al. (2005) conducted a prospective longitudinal follow-up study on 138 preterm infants to investigate neurodevelopmental outcomes on two year-olds who had received INO or placebo. These infants were a subset of the Schreiber et al. (2003) study mentioned above which demonstrated a positive outcome with the use of INO in preterm infants. In Mestan's study, the subjects were assessed using neurologic examinations, neurodevelopmental assessment and anthropometric measurements. In the INO group (n=70), 17 children had either a disability (i.e., cerebral palsy, bilateral blindness, or bilateral hearing loss) or a delay as defined by a score on the Mental or Psychomotor Development Index of the Bayley Scales of Infant Development II. In the placebo group, 68 children exhibited either a disability or a delay. The study supported the hypothesis that administration of INO improved neurodevelopmental outcomes at two years of age.

Van Meurs et al. (2005) conducted a randomized clinical trial on the use of INO in premature infants with severe respiratory distress. The study included 420 neonates < 34 weeks' gestation with respiratory distress who had received one dose of surfactant at least four hours prior to meeting inclusion criteria. Subjects were randomly assigned to the simulated gas flow control group (n=21) or to the INO group (n=21). The authors reported that there was no difference in the outcomes between the two groups. INO did not reduce the incidence of death or of bronchopulmonary dysplasia. Another randomized study was conducted by Hamon et al. (2005) "to assess the oxidative balance in premature infants who were exposed to low dose INO and the relationship with their clinical outcome on day 28 of life." The study involved 274 infants, < 32 weeks' gestation, randomly assigned to receive 5 ppm INO. The results of the study group were compared to a nonhypoxemic infant group as a reference. They reported that INO seemed to be clinically beneficial for up to 28 days of life.

**Chronic Lung Disease (CLD):** CLD affects approximately 12,000 infants in the United States each year. CLD is defined as the "continuing need in preterm infants for supplemental inspired oxygen at 36 weeks" postconceptional age (Clark, et al., 2000). Causes of CLD include low birth weight, inflammation, mechanical distortion of the lung, and oxidative injury. INO is proposed as a treatment option due to its anti-inflammatory effect and its ability to reduce neutrophil accumulation, improve ventilation-perfusion matching, and reduce pulmonary hypertension (Truog, 2005; Clark, et al., 2000).

A review by Truog (2005) summarized the results of "definitive, interventional randomized clinical trials designed to reduce the incidence of, or the severity of, CLD of prematurity." Truog reviewed three trials, including over 700 infants, that had been conducted to study the effect of INO on CLD and two trials that were in process. He stated that there was a "discouraging paucity" of proven safety and efficacy. A disparity that he noted was that other therapies were administered during some of the trials. Clark et al. (2002) studied 33 neonates, 10–20 days in age, with CLD requiring mechanical ventilation, to determine if INO would improve oxygenation in this population. The duration of the therapy was seven days. INO acutely improved pulmonary oxygenation uptake in most infants with CLD. The authors noted that this study did not sufficiently support the widespread use of INO for the treatment of CLD infants on assisted ventilation. Long-term studies are needed to establish the safety and efficacy of INO in this population.

**Acute Respiratory Distress Syndrome (ARDS):** ARDS, or respiratory distress syndrome (RDS), is the acute onset of pulmonary edema in the absence of volume overload or depressed left ventricular function. ARDS, found in children and adults, occurs as a result of an insult or injury involving damage to the alveolar epithelium and vascular endothelium. The injury results in an accumulation of fluid, disrupts the production and function of pulmonary surfactant, and results in poor gas exchange. ARDS may occur as a result of pulmonary contusion, sepsis, pneumonia, transfusion, overdose, drowning or smoke inhalation. Treatment may include 100% oxygen administration, high levels of positive end-expiratory pressure (PEEP), high inspiratory flow rates and pharmacological therapy. It has been proposed that INO may be a treatment modality for ARDS in cases unresponsive to conventional therapy for its pulmonary vasodilator effect. ARDS is often accompanied by multisystem organ failure and patients typically, do not die of primary lung injury. Outcomes of clinical trials have not demonstrated that INO has a significant effect on mortality, and it is speculated that the administration of INO may increase the risk of mortality.

Adhikari et al. (2007) conducted a systematic review and meta-analysis of 12 randomized trials including 1237 subjects, adults and children, in which patients were treated with INO for acute lung injury and ARDS compared to infants treated with placebo or usual treatment. Outcomes included “mortality, duration of ventilation, oxygenation, pulmonary arterial pressure and adverse events.” Although INO increased the ratio of partial pressure of oxygen to a fraction of inspired oxygen and decreased the oxygen index on day one, and in some cases, up to day four, there was no effect on mean pulmonary arterial pressure. There was no significant effect on the outcomes, and some patients exhibited an increased risk of developing renal dysfunction.

Angus et al. (2006) conducted a randomized controlled trial to evaluate the effects of INO on survival and quality of life in adults with ARDS. The study also included a cost-effective analysis. Patients with an onset of ARDS within the preceding 72 hours were eligible for the study. Subjects were randomly assigned to the study group, treated with 5 ppm of INO (n=184) or to the placebo group, treated with nitrogen (n=184). Treatment was administered until oxygenation was adequate, or for up to 28 days, or if death occurred. Because the study included subjects from multiple centers across the country, survival and quality of life data were collected via telephone interviews six months and one year following treatment. Interview tools included the Quality of Well-Being scale and interview questions. There was no significant difference in survival between the two groups at 28 days. Activities of daily living (ADL) decreased during the first 28 days (i.e., 40% below baseline), improved by the end of year one, but did not return to baseline levels. There were no significant differences in the ADL between the study group and the control group. Quality of Well-Being scores between the two groups were not statistically significant. The one-year survival rate for the study group was 67.3% compared to 68.3% for the control group (p=0.71). Limitations of the study as recognized by the authors included: possible selection bias, self-reported telephone interviews; and one-year follow-up.

An observational study by Fioretto et al. (2004), conducted in a pediatric intensive care setting, compared children (i.e., one month–12 years of age) treated with INO (n=18) to children historically treated with conventional therapy (CTG) (n=12) for acute respiratory distress syndrome. The groups were observed during different time spans. The partial pressure of oxygen in arterial blood (PaO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>) ratio was lower in the INO group (p<0.0001) and the oxygen index was higher (p<0.0001). There was also a significant difference in the mortality rate in the INO group (3 of 18 infants) compared to the CTG (10 of 21 infants) (p<0.001). No difference was seen in the length of stay in the intensive care or in the duration of mechanical ventilation (p>0.05 for each). Two infants experienced severe pulmonary vasoconstriction (i.e., rebound) during the weaning process.

Taylor et al. (2004) conducted a study to evaluate the effectiveness of INO at 5 ppm for the treatment of patients with acute lung injury not due to sepsis and without evidence of nonpulmonary organ system dysfunction. This multicenter, randomized, placebo-controlled study included 385 patients from 46 hospitals. The patients, ≥ 18 years old, had sustained a moderately severe, acute lung injury from multiple causes, and met the criteria for definition of ARDS. Patients were randomly assigned to the INO group (n=192) or to the nitrogen oxide placebo group (n=193). INO was administered for up to 28 days, or until the assisted device was discontinued, or the patient died. Utilizing intent-to-treat analyses, INO did not improve the number of days alive and off assisted ventilation (p=0.97). There was no significant difference in mortality (p=0.54), days alive following a 2-hour unassisted ventilation trial (p=0.54), days alive without assisted breathing by day 28 (p=0.40), or days alive and meeting extubation criteria (p=0.89). A statistically significant increase in PaO<sub>2</sub> occurred during the initial 24 hours, but was resolved by 48 hours. There were no significant differences in the complications.

Sokol et al. (2003) conducted a Cochrane meta-analysis of five randomized controlled trials which analyzed 535 patients with acute hypoxemic respiratory failure (AHRF). Participants were adults and children, older than age one month, who were treated in an intensive care setting. The analysis revealed that INO had some immediate benefit on oxygenation (i.e., within the first four days), but did not demonstrate any statistically significant effect on mortality. Methemoglobinemia occurred with the administration of 40 ppm or more of INO, otherwise there were no reports of significant side effects. The authors stated that data were lacking, clinical indicators for effectiveness were inconsistent, and future trials were indicated.

**Other Conditions:** Al Hajeri et al. (2008) conducted a systematic review of the literature to identify randomized or quasi-randomized trials that addressed the use of INO in the treatment acute chest syndrome in patients with sickle cell disease. No studies met inclusion criteria. In a randomized controlled trial, Botha et al. (2007) evaluated the ability of INO to reduce neutrophil infiltration and primary graft dysfunction when administered

from the onset of ventilation following lung transplantation. The outcomes demonstrated no significant effect from INO therapy. Perrin et al. (2006) conducted a randomized controlled trial to determine if INO would be effective in the treatment of pulmonary edema following lung transplantation (n=30) and concluded that INO had no effect on this population. A randomized controlled trial by Fattouch et al. (2006) assessed the effectiveness of INO and inhaled prostacyclin (iPGI2) compared to intravenous vasodilators in patients with pulmonary hypertension undergoing cardiac surgery (n=58). INO and iPGI2 reduced and maintained the mean pulmonary artery pressure and PVR compared to baseline. These findings were not demonstrated by the control group. Although INO was effective, the authors stated that iPGI2 has a “number of advantages over INO.” In addition to conducting a cost analysis, George et al. (2006) reported on a prospective review of 376 patients who received INO to treat patients with pulmonary and right ventricular failure who were undergoing orthotopic heart transplantation (OHT), orthotopic lung transplantation (OLT), cardiac surgery, ventricular assist device placement, and patients who experienced hypoxemia in other surgery and some medical patients. The overall mortality was highest among medical patients (n=59) and lowest after OHT (n=67) and OLT (n=45).

### **Professional Societies/Organizations**

The 2007 “Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease” stated that the administration of INO in patients with stable COPD can worsen the gas exchange because of “altered hypoxic regulation of ventilation-perfusion balance” and is, therefore, contraindicated (Global Initiative for Chronic Obstructive Lung Disease [GOLD], 2007).

In their evidence-based practice guidelines for the treatment of pulmonary arterial hypertension, the American College of Chest Physicians (ACCP) states that patients with idiopathic pulmonary hypertension “should undergo acute vasoreactivity testing using a short-acting agent such as IV epoprostenol, adenosine or inhaled nitric oxide.” In the assessment of symptomatic pulmonary arterial hypertension, they state that “a positive acute vasodilator response is defined as a fall in mean PAP  $\geq$  10 mm Hg to  $\leq$  40 mm Hg, with an unchanged or increased cardiac output when challenged with inhaled nitric oxide, IV epoprostenol, or IV adenosine” (Badesch, et al., 2007).

The European expert recommendations from the European Society of Intensive Care Medicine and the European Association of Cardiothoracic Anaesthesiologists identifies conditions in which it is reasonable to use INO as a “rescue treatment in patients with severe acute pulmonary arterial hypertension and/or severe refractory arterial hypoxaemia” They also state that INO is useful for testing for “pulmonary vasoreactivity in patients undergoing heart transplantation or in patients with pulmonary arterial hypertension.” According to their recommendations, benefits of INO therapy include the following: 1) in relation to heart failure, “response to iNO treatment may identify patients still suitable for heart or heart/lung transplantation or to help to identify patients with congenital heart disease” and “iNO testing is useful to demonstrate the remaining reactivity of the precapillary component or postcapillary pulmonary hypertension;” 2) in pulmonary arterial hypertension, INO may be useful in revealing the extent of reversibility in selected patients, but there is insufficient data to recommend long-term INO therapy; 3) for perioperative pulmonary hypertension in adult cardiac surgery, “clinical experience suggests that in patients with confirmed acute right ventricular dysfunction and elevated PVR use of iNO may result in hemodynamic improvement when used during or after cardiac surgery;” 4) for left ventricular assist devices (VAD), the panel recommended that INO therapy “is effective in providing favorable pulmonary hemodynamics leading to improved right ventricular and left-sided VAD assisted cardiac output in patients with pulmonary hypertension and inadequate left-sided VAD flow refractory to conventional maneuvers. On the basis of these improved critical physiological variables the expert panel recommends that it is reasonable to consider the use of iNO in this clinical situation among other vasodilator therapies;” 5) regarding ARDS, INO improves oxygenation and hemodynamics acutely, but no benefit is seen beyond 24–72 hours, but it is reasonable to use INO as a “rescue treatment in patients with severe refractory hypoxaemia.”

The European recommendations state that there is insufficient evidence to support the routine use of INO in the management of thromboembolic disease, pulmonary arterial hypertension, sickle cell disease, COPD, one-lung ventilation, and ischemia-reperfusion injury (Germann, et al., 2005).

The consensus guidelines for the use of INO in neonates and children from the European Society of Paediatric and Neonatal Intensive Care, the European Society of Paediatric Research and the European Society of Neonatology state that INO “appears to improve outcomes in hypoxemic term and near-term infants” with the exception of infants with congenital heart disease, and state that sufficient data is lacking to recommend the routine use of INO in preterm infants. They also state that INO may be “justified as rescue therapy in life

threatening hypoxaemia after lung recruitment has been optimized.” As it relates to cardiac disease, they concluded that “there is insufficient evidence to recommend the routine use of prophylactic postoperative iNO in congenital heart patients at risk of pulmonary hypertension.” They further stated there is sufficient evidence “to support a trial of 20 ppm iNO for 10 minutes, increasing to 40 ppm if no response to the lower dose, in patients with clinically significant pulmonary hypertension complicating their perioperative course. In this setting it is recommended that iNO should only be continued if there is documented evidence of important haemodynamic improvement. After a 30-minute trial of iNO at 20 ppm, increasing to 40 ppm, consideration should be given to the discontinuing the drug if no clinically significant response has occurred” (Macrae, et al., 2004).

In their guidelines on the management of pulmonary arterial hypertension, the European Society of Cardiology states that acute vasodilator testing including intravenous prostacyclin or adenosine and inhaled nitric oxide should be used at the time of initial right heart catheterization. They state that it is “generally accepted” that acute vasodilator challenge can identify those individuals who may benefit from long-term calcium channel blockers (Galie, et al., 2004).

The “Clinical Practice Parameters for the Hemodynamic Support of Pediatric and Neonatal Patients in Septic Shock” developed by the American College of Critical Care Medicine, stated that treatment of PPHN in the newborn should include “hyperoxygenate initially with 100% oxygen, and institute metabolic alkalization (up to pH 7.50) with sodium bicarbonate (NaHCO<sub>3</sub>) or tromethamine. Mild hyperventilation can also be instituted until 100% oxygen saturation and < 5% difference in preductal and postductal saturations are obtained. Therapeutic narcosis with fentanyl and paralysis with neuromuscular blockers should be considered to reduce pulmonary blood pressures in ventilated patients without response to the PPHN therapy outlined above. Inhaled nitric oxide should be administered when available.” This guideline is rated as reasonably justified by the scientific evidence and strongly supported by expert critical care opinion (Carcillo, et al., 2002).

The American Academy of Pediatrics (AAP, 2000) Committee on Fetus and Newborn issued a statement which addressed the conditions under which iNO should be administered to infants with hypoxic respiratory failure. Their recommendations were as follows:

- Infants with progressive hypoxic respiratory failure should be cared for in centers with the expertise and experience to provide multiple modes of ventilatory support and rescue therapies or be transferred in a timely manner to such an institution.
- iNO therapy should be given using the indications, dosing, administration, and monitoring guidelines outlined on the product label. An echocardiogram to rule out congenital heart disease is recommended. Center-specific criteria for treatment failure should be developed to facilitate timely consideration of alternative therapies.
- iNO therapy should be directed by physicians qualified by education and experience in its use and offered only at centers that are qualified to provide multisystem support, generally including on-site ECMO capability.
- Generally, iNO should be initiated in centers with ECMO capability. If iNO is offered by a center without ECMO capability, for geographic or other compelling reasons, mutually acceptable treatment failure criteria and mechanisms for timely transfer of infants to a collaborating ECMO center should be established prospectively. Transfer must be accomplished without interruption of iNO therapy.
- Centers that provide iNO therapy should provide comprehensive long-term medical and neurodevelopmental follow-up.
- Centers that provide iNO therapy should establish prospective data collection for treatment time course, toxic effects, treatment failure, use of alternative therapies, and outcomes.
- Administration of iNO for indications other than those approved by the FDA or in other neonatal populations, including compassionate use, remains experimental. As such, iNO should be administered according to a formal protocol that has been approved by the FDA and the institutional review board and with informed parental consent.

## Summary

Inhaled nitric oxide (iNO) is a commercially available gas (e.g., INOmax<sup>®</sup>) approved for the treatment of term and preterm infants who are at least 34 weeks' gestation, are experiencing hypoxic respiratory failure associated with persistent pulmonary hypertension (PPHN), and have not responded to, or are not expected to

respond to, conventional therapy. Evidence in the peer-reviewed scientific literature and the American Academy of Pediatrics support the indications for INO for the treatment of this population.

Although there are a limited number of studies addressing the use of INO for other indications, there is some evidence in clinical trials, and support from textbooks and professional societies and organizations for the use of INO in the postoperative treatment of congenital heart disease in patients with pulmonary hypertension. INO may also be administered as a vasodilating agent during heart catheterization to assess pulmonary vasoreactivity and aid in the diagnosis of pulmonary hypertension.

The evidence in the peer-reviewed literature does not support the safety and efficacy of INO for the treatment of hypoxic respiratory failure in neonates  $\leq$  34 weeks' gestation, nor in the treatment of infants, children and adults with other conditions such as chronic lung disease, sickle cell anemia pain, and respiratory distress in infants, children and adults.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary:**

CPT <sup>®*</sup> Codes	Description
94002	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, initial day
94003	Ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, each subsequent day

HCPCS Codes	Description
	No specific codes

ICD-9-CM Diagnosis Codes	Description
416.0	Primary pulmonary hypertension
765.28	35-36 completed weeks of gestation
765.29	37 or more completed weeks of gestation
768.5	Severe birth asphyxia
768.6	Mild or moderate birth asphyxia
768.9	Unspecified birth asphyxia in liveborn infant
770.88	Hypoxemia of newborn

**Experimental/Investigational/Unproven/Not Covered:**

ICD-9-CM Diagnosis Codes	Description
518.82 <sup>†</sup>	Acute respiratory distress syndrome
	Multiple/varied

<sup>†</sup>**Note:** Diagnosis is Experimental/Investigational/Unproven/Not covered when used in association with the administration of Inhaled Nitrous Oxide.

\*Current Procedural Terminology (CPT<sup>®</sup>) ©2007 American Medical Association: Chicago, IL.

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	06/15/2008	0453	Inhaled Nitric Oxide (INO)

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Connecticut General Life Insurance Company has acquired the business of Great-West Healthcare from Great-West Life & Annuity Insurance Company (GWLA). Certain products continue to be provided by GWLA (Life, Accident and Disability, and Excess Loss). GWLA is not licensed to do business in New York. In New York, these products are sold by GWLA’s subsidiary, First Great-West Life & Annuity Insurance Company, White Plains, N.Y.