



CIGNA MEDICAL COVERAGE POLICY

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Subject Inhaled Nitric Oxide (INO)

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Coverage Policy

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

- hypoxic respiratory failure in a neonate with a gestational age at birth of at least 34 weeks in the absence of a congenital diaphragmatic hernia when there is failure, contraindication or intolerance to conventional therapy
- postoperative management of pulmonary hypertension following repair of congenital heart disease
- 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 and heart and/or lung transplantation, 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, 2005; 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 (NO₂). NO₂ 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; Griffiths and Evans, 2005).

U.S. Food and Drug Administration (FDA)

A complete nitric oxide delivery system is comprised of a nitric oxide administration apparatus, a nitric oxide gas analyzer, and a nitrogen dioxide gas analyzer. INOmax[®] (INO Therapeutics Inc., Clinton, NJ) is the only commercially available brand of INO and was initially approved by the FDA in 1999. INOmax, a gaseous blend of nitric oxide (0.8%) and nitrogen (99.2%), is supplied in aluminum cylinders as a compressed gas under high pressure. 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."

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

In 2009, the FDA updated the INOmax safety labeling stating that "in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema. Patients who had pre-existing left ventricular dysfunction treated with inhaled nitric oxide, even for short durations, experienced serious adverse events (e.g., pulmonary edema)".

Hypoxic Respiratory Failure

The primary clinical indication for INO, in conjunction with ventilatory support and other treatment modalities (e.g., surfactant), is hypoxic respiratory failure secondary to pulmonary hypertension in the neonate birth age 34 weeks gestation or greater. 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 (American Academy of Pediatrics [AAP] 2010; Weinberger, et al., 2001; 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 (AAP, 2010; Kinsella, 2006; Walsh-Sukys, et al., 2000).

The recommended initial dose of INO is 20 parts per million (ppm). Studies have included treatment with 5–80 ppm of INO. Toxicity is typically seen in doses \geq 80 ppm; however, the occurrence of toxicity has also been seen at lower doses. The duration of therapy is normally less than five days, but may be maintained for up to 14 days, or until the underlying oxygen desaturation has been resolved. To avoid rebound vasospasm, the infant should be slowly weaned off of INO. Abrupt withdrawal of INO may lead to worsening oxygenation and increased pulmonary artery pressure. According to AAP, INO is indicated when ventilatory therapy has failed, and ECMO is usually initiated only after INO fails due to the significant morbidity and mortality rates associated

with ECMO. Because hypoxic respiratory failure often progresses rapidly, it is suggested that ECMO be available at facilities that have INO. If the infant must be transferred for ECMO, INO should not be discontinued (AAP, 2010; Stoll and Kliegman, 2004; Hintz, et al., 2000; Walsh-Sukys, et al., 2000).

Studies have 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 birth age 34 weeks gestation or in the treatment of other conditions, such as acute respiratory distress syndrome (Kinsella, 2006; Kinsella and Abman, 2005; Finer and Barrington, 2001; Weinberger, et al., 2001; Clark, et al., 2000).

Literature Review: Systematic reviews, meta-analysis, and randomized controlled trials have reported that INO improved systematic oxygenation and that fewer infants birth age greater than 34 weeks gestation required ECMO and/or developed chronic lung disease. Some studies reported a higher survival rate following INO therapy. The studies consistently demonstrated the ineffectiveness of INO when used in the treatment of infants with congenital diaphragmatic hernia (CDH) (Hoskote, et al., 2008; Field, et al., 2007; Konduri, et al., 2004; Clark, et al., 2000; Oleira, et al., 2000).

In a follow-up study, Berti et al. (2010) reported on the neurodevelopmental outcomes of neonates (n=31) who had been treated with INO for hypoxic respiratory failure with PPHN at gestational birth age 27–36 weeks. Five infants were born at less than 34 weeks. The ages of the children at the time of neurological examination ranged from 12–70 months (mean 41 months). Evaluations included a complete physical examination, measurement of growth parameters, and parental interviews. Based on the age of the child at the time of the follow-up, Bayley Scales of Infant Development and Wechsler Preschool and Primary Scale of Intelligence were used for neurodevelopmental examinations. Five of 25 (20%) children had a mental/verbal pathologic score < 70 which was considered an “extremely low” score. Eight percent of the children had a performance/motor score < 70, six children had linguistic deficits (22%), and seven children (26%) showed “minor” behavioral problems. Electrophysiological tests (n=17) showed no significant abnormalities. Cerebral ultrasounds were negative in 22 cases, mild persistent flare was seen in seven cases and two children had a grade II or IV intraventricular hemorrhage, one with cerebral palsy and one who died on discharge. The mortality rate was 6.4% (2/31).

Rosenberg et al. (2010) conducted a follow-up study to report the outcomes of a cohort of school-age children (n=109), mean age 7.1 years (range 5.1–10.6 Years), treated with INO for PPHN. A total of 77 were treated with INO, of which 12 also received extracorporeal membrane oxygenation (ECMO) and 32 received conventional management (e.g., high-frequency or conventional ventilation) without INO. Follow-ups included physical examinations, parental interviews, audiological exams, growth measurements, room air oxygen saturations, chest x-rays and echocardiograms. Psychomotor evaluations were conducted using the Wechsler Scales, Vineland Adaptive Behavior Scales, Kaufman Test of Educational Achievement, Children’s Category Test, Wisconsin Card Sorting Test and Achenbach Child Behavior Checklist. Outcomes were evaluated and compared in three groups (i.e., children not treated with INO, children treated with INO, and children treated with INO who advanced to ECMO). There were no statistically significant differences in the outcomes between the three groups.

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

Depending on 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 may be indicated to reverse the condition and ward off impending death. Following surgical intervention, children and adults 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 its ability to decrease pulmonary vascular resistance (PVR) and intrapulmonary shunting, and increase oxygenation, INO is an established treatment option for pulmonary hypertension following surgical repair of congenital heart disease (Kliegman, et al., 2007; Carroll, et al., 2005; Ichinose, et al., 2004; Kawakami and Ichinose, 2004; Hermon, et al., 2003).

Literature Review: Randomized controlled trials, non-randomized comparative studies and case series reported that INO effectively lowered pulmonary vascular resistance and pulmonary artery pressure in children and adults with pulmonary hypertension after open heart surgery. However, it did not appear to increase the survival rate in those with severe pulmonary hypertension (Sharma, et al., 2001; Miller, et al., 2000; Morris, et al., 2000; Day, et al., 2000).

Diagnostic Testing for Pulmonary Hypertension

The initial evaluation for the diagnosis of pulmonary hypertension in adults and children 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 may be administered as a vasodilator to assess pulmonary vasoreactivity in the management of pulmonary hypertension. A positive response to a vasodilating agent is indicative of favorable long-term clinical outcomes. A decrease in pulmonary artery pressure or pulmonary vascular resistance (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. INO is an established vasodilator for diagnostic testing for pulmonary hypertension (Fraser and Carberru; 2008; Park, 2008; 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).

Literature Review: Randomized controlled trials, case series and nonrandomized comparative studies reported a significant decrease in systemic and pulmonary vascular resistance and mean pulmonary artery pressure, as well as an increase in cardiac output following INO therapy. The administration of INO with oxygen compared to oxygen alone resulted in more accurate selection of surgical candidates. When oxygen alone was compared to oxygen/INO administration, accuracy (68% vs. 90%, respectively) and sensitivity (64% vs. 97%, respectively) were increased with INO administration when the systemic vascular resistance index:systemic vascular resistance index (Rp:Rs) < 0.33 was used as the criterion for operability (Barst, et al., 2010; Cannon, et al., 2005; Leuchte, et al., 2004; Balzer, et al., 2002; Atz, et al., 1999).

Other Proposed Indications

Due to INO's success in treating PPHN in term and near-term neonates and the postoperative management of pulmonary hypertension following repair of congenital heart disease, INO has been proposed for the treatment of other conditions, including: respiratory distress in preterm infants less than birth age 34 weeks gestation; chronic lung disease or bronchopulmonary dysplasia in preterm infants; acute respiratory failure in older children and adults; heart and lung transplantation; chronic obstructive pulmonary disease in adults; pulmonary vascular resistance following ventricular assist device insertion; sickle cell disease; chronic pulmonary hypertension; cardiogenic shock; pain associated with coronary artery disease; and other conditions associated with pulmonary hypertension. There is insufficient evidence in the published peer-reviewed scientific literature to support the safety and efficacy of INO for all other indications. Selection criteria for patients who will benefit from INO, dosage and duration of therapy, beneficial clinical outcomes, and long-term outcomes have not been established (Arul and Konduri, 2009; Ichinose, et al., 2009).

Respiratory Distress in Preterm Infants less than Birth Age 34 Weeks Gestation: Studies for the administration of INO in premature infants less than birth age 34 weeks gestation with respiratory distress of various etiologies including bronchopulmonary dysplasia (BPD) are ongoing and inconclusive. Collectively, the results of the studies indicated that INO has not been proven beneficial for the treatment of this subpopulation. The long-term pulmonary and extrapulmonary effects (e.g., pulmonary cell proliferation and differentiation, alveolar and microvascular development) of INO have not been reported.

Huddy et al. (2008) reported 4–5 year outcomes of 108 infants, age less than 34 weeks gestation, who had severe respiratory failure, required ventilatory support, and were age less than 28 days when INO was administered. Infants were randomized to ventilation with INO (n=55) or ventilation without INO (n=53). "A satisfactory response was defined as an increase in post-ductal arterial oxygen tension (PaO₂) of more than 3 kPa [kilopascal] (22.5 millimeters of mercury) after the first 15 minutes of giving INO." Dosage began at 5 ppm,

was doubled to 10 ppm and maximized at 40 ppm if no satisfactory response was achieved. No evidence of dose-response relationship was reported. Overall assessments included the following outcomes: eight children were classified as normal across all domains at the age of 4–5 years (five INO vs. three no INO); five (three INO vs. two no INO) had impairment only; ten were classified as having mild disability (six INO vs. four no INO); nine had moderate disability (five INO vs. four no INO); six children were severely disabled (three in each group); 34 of 55 INO (62%) died or were severely disabled at the last follow-up compared to 37 of 53 (70%) of the no INO group. Of the four children unable to participate in cognitive assessment due to the severity of disability, three were in the INO group. Of the 19 INO and 15 no INO children able to participate in cognitive assessment, there were no significant differences between the two groups in mean general conceptual ability score, verbal ability scores, pictorial reasoning, spatial abilities, or non-verbal composite. There were no significant differences in neuromotor, sensory, communication, and behavior outcomes. Based on the results of this study, there were no benefits or harms to the use of INO in preterm infants.

Barrington and Finer (2010) 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.” Fourteen 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=9), 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=3 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 INO did not appear to improve the chances of the babies having improved outcomes and may cause excessive bleeding.

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 grams (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_{exp}) and compliance normalized by weight (C_{kg}). There were no significant differences in the two groups in the one hour R_{exp} and C_{kg} 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.

Van Meurs et al. (2007) conducted a randomized controlled trial to determine if 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 included the small patient population and the short duration of INO administration (i.e., maximum 14 days).

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 (Nitric Oxide for Chronic Lung Disease [No CLD] trial). 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.

Three follow-up studies have been conducted on the Ballard et al. (2006) study discussed above. Because of the known role of INO in oxidative damage and the concern that INO could potentially increase formation of reactive oxygen and nitrogen species, Ballard et al. (2008) prospectively collected blood samples from a subset of 100 infants to determine the effect of INO on plasma biomarkers of oxidative stress for premature infants. Birth weights ranged from 502–1105 g and gestational age ranged from 22.7–30.0 weeks. Infants were entered into the study between days 7 and 21. At each of the three time points (1–10 days) during exposure to study gas, there were no significant differences between control and treated infants for concentrations of plasma protein, 3-nitrotyrosine, and carbonylation. The authors noted that the blood samples were collected over a period of four years and stored for prolonged periods. Hibbs et al. (2008) reported one-year outcomes to determine if INO decreased indicators of long-term pulmonary morbidities in this study group. There were 230 INO-treated infants and 225 control group infants available for follow-up. Following discharge from neonatal intensive care, the INO infants received significantly less bronchodilators, inhaled steroids, systemic steroids, diuretics, and supplemental oxygen. There were no significant differences in wheezing, whistling or rehospitalizations. Walsh et al. (2010) prospectively reported the two-year neurodevelopmental and growth outcomes of this study group. There were 243 surviving INO study patients and 234 non-INO patients available for evaluation at two years. There were no significant differences in the growth variable or the neurodevelopment impairments (i.e., moderate or severe cerebral palsy, bilateral blindness, bilateral hearing loss, or score <70 on the Bayley Scales II) in the INO group compared to the placebo group (p=0.39).

Kinsella et al. (2006) 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 were 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, 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. 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 included 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.

In a technology assessment, the Agency for Healthcare Research and Quality (AHRQ) (2010) conducted a systematic review and meta-analysis of the evidence on INO for the treatment of preterm infants born at or before 34 weeks gestation age who received respiratory support. The review included 14 randomized controlled trials and eight observational studies. There were no significant differences in the mortality rate, incidence of cerebral palsy, neurodevelopment impairment, cognitive impairment or bronchopulmonary dysplasia (BPD) at 36 weeks. Meta-analysis showed no difference in the risk of brain injury. There was a seven percent reduction in the risk of the composite outcome of death or BPD at 36 weeks postmenstrual age, but no reduction in death or BPD alone. AHRQ concluded that "there is currently no evidence to support the use of INO in preterm infants with respiratory failure outside the context of rigorously conducted randomized clinical trials."

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. Treatment includes 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 for its pulmonary vasodilation effect in cases

unresponsive to conventional therapy. 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.

Afshari et al. (2010) conducted a systematic review of randomized controlled trials (n=14 studies; 1303 patients) that compared INO with no intervention or placebo for the treatment of ARDS in adults and children. A transient statistically significant improvement in oxygenation in the first 24 hours, expressed as the ratio of partial pressure of oxygen to fraction of inspired oxygen and the oxygenation index, was seen. However, there was no statistically significant difference in overall mortality in the INO groups compared to the control groups (40.2% vs. 38.6%). Available data indicated a statistically insignificant effect of INO on duration of ventilation, ventilator free days, and length of stay in the intensive care unit and hospital. INO appeared to increase the risk of renal impairment among adults but not the risk of bleeding or the formation of methaemoglobin or nitrogen dioxide. Based on their analysis, the authors concluded that INO could not be recommended for the treatment of ARDS because its use did not reduce mortality and it may be harmful.

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 (n=378) 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. The 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 (PaO₂)/fraction of inspired oxygen (FiO₂) 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 randomized controlled trial (n=385) 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 study included patients from 46 hospitals. The patients, age ≥ 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 were no significant differences 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_2 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.

Cardiac Surgery: INO has been proposed for use during cardiac surgery to reduce pulmonary hypertension. However, data from randomized controlled trials have not shown that INO improves health outcomes. In a randomized controlled trial, Winterhalter et al. (2008) compared the efficacy of inhaled iloprost ($n=23$) to inhaled nitric oxide ($n=23$) in reducing pulmonary hypertension immediately following weaning from cardiopulmonary bypass during cardiac surgery. Although both drugs resulted in a significant increase in cardiac output within 30 minutes of administration ($p<0.0001$), iloprost resulted in a significantly greater reduction in pulmonary vascular resistance ($p<0.013$) and mean pulmonary artery pressure ($p=0.0006$). Iloprost also caused a significantly greater increase in cardiac output ($p=0.002$) compared to INO. A limitation of the study is the small patient 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 ($n=58$) for mitral valve replacement. 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” including the fact that neither iPGI2 nor its metabolites have any toxic effects.

Chronic Lung Disease (CLD): CLD or bronchopulmonary dysplasia (BPD) 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. There is insufficient evidence to support INO for the treatment of CLD (Ichinose, et al., 2009; Marks and Schreiber; 2008; Truog, 2005; Clark, et al., 2000).

Mercier et al. (2010) conducted a European multicenter ($n=36$) randomized controlled trial to investigate the potential of INO ($n=399$) compared to placebo ($n=401$) in reducing the incidence of BPD in preterm infants. Inclusion criteria included: gestation age at birth of 24–28 weeks plus six days (inclusive), a weight of at least 500 grams and required surfactant or continuous positive airway pressure within 24 hours of birth. The primary endpoint was survival without BPD at 36 weeks postmenstrual age. Secondary endpoints included survival without substantial brain injury (i.e., grade 3 or 4 intraventricular hemorrhage; periventricular hemorrhage or periventricular leukomalacia as seen on ultrasound of the head). Mean duration of therapy was 16.3 ± 3.5 days in the INO group and 16.4 ± 6.5 days in the placebo group. There were no statistically significant differences between the two groups in the primary or secondary outcomes at days seven, 14 and 21. There were no significant differences in adverse events. INO as a preventative strategy in this patient population was unsuccessful.

Schreiber et al. (2003) conducted a randomized controlled trial ($n=207$) to determine if INO would decrease the incidence of CLD and death in infants less than 34 weeks gestation with respiratory distress syndrome who were treated with mechanical ventilation. Gestational age in the INO group was 27.4 ± 2.5 with a birth weight of 1017 ± 369 g and 27.0 ± 2.8 in the control group with a birth weight of 949 ± 387 . Infants in the INO group were treated with 10 ppm on day 1, followed by 5 ppm for six days. In addition, infants in each group were randomized to receive intermittent mandatory or high-frequency oscillatory ventilation. In the INO group, 51 infants had CLD or died (48.6%) compared to 65 infants (63.7%) in the placebo group. There were no significant differences between the groups in the overall incidence of intraventricular hemorrhage and periventricular leukomalacia, but the incidence was less severe in the INO group. Analysis of the data according to the mode of ventilation showed a significant decrease in the risk of chronic lung disease and death in the INO group and

intermittent mandatory ventilation. However, the authors noted that because the study did not have sufficient power to detect a significant interaction, conclusions could not be drawn regarding the question of whether the benefit of inhaled nitric oxide is restricted to infants receiving intermittent mandatory ventilation. The beneficial effect of INO on CLD or death and long-term neurologic outcomes may have been amplified by the high rate of CLD in the control group (63.7%) and more mature neonates in the INO group.

Heart and Lung Transplantation: INO has been proposed for use in heart and lung transplantations but there is insufficient evidence to support its efficacy. 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 following 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.

In addition to conducting a cost analysis, George et al. (2006) conducted a prospective review of 376 patients with pulmonary and right ventricular failure who were undergoing orthotopic heart transplantation (OHT) (n=67), orthotopic lung transplantation (OLT) (n=45), cardiac surgery (105), ventricular assist device (VAD) placement (n=66), and patients who experienced hypoxemia in other surgeries (n=34) and some medical patients (n=59) who received INO. The overall mortality was highest among medical patients and lowest after OHT and OLT. Although mortality in the VAD group was not significantly different than the cardiac surgery group, only five of the 66 cardiac patients required VAD. INO may have allowed avoidance of VAD. However, additional studies are needed to validate the outcomes of this study.

Left Ventricular Assist Device (LVAD): INO has been proposed to be of benefit in the intraoperative management of patients in the setting of right ventricular dysfunction after LVAD insertion. However, data supporting favorable clinical outcomes are lacking. Kukucka et al. (2011) conducted a randomized controlled trial to evaluate the acute effect of LVAD on right ventricular geometry and function and pulmonary circulation, as well as the effects of INO (n=24) compared to placebo (n=23). The study included elective patients without acute decompensation for chronic heart failure but with preoperative increased pulmonary vascular resistance. Following LVAD implantation, a significant decrease was seen in pulmonary capillary wedge pressure ($p<0.01$) and mean pulmonary artery pressure ($p<0.01$) in both groups with no significant difference between the INO and placebo groups. Significant improvements were also seen on transesophageal echocardiography of right ventricular geometry and function in both groups, but with no significant difference between the groups. Three INO patients and one placebo patient developed right ventricular failure due to different clinical problems. Even though it decreased pulmonary vascular resistance, INO added no measurable effect on right ventricular geometry and function.

Wagner et al. (2006) compared the postoperative hemodynamic and humoral responses of LVAD implantation (n=15) and heart transplantation (HTx) (n=10) in patients who were treated with INO during cardiopulmonary bypass. All patients had right ventricular dysfunction from secondary pulmonary hypertension. Regarding the hemodynamic parameters, 72 hours after weaning from INO, central venous pressure (CVP) ($p=0.04$) and pulmonary vascular resistance (PVR) ($p=0.03$) were significantly lower. Of the humoral parameters, the atrial natriuretic peptide (ANP) and the cyclic guanosine monophosphate (cGMP) were elevated in the HTx recipients compared to the LVAD study group. Brain natriuretic peptide (BNP) levels were also higher in the HTx group 72 hours following INO weaning. INO may decrease big endothelin (ET) and ET-1 in patients with secondary pulmonary hypertension after LVAD. There were no significant difference in the dosage and duration of INO between the two groups. The results of the study indicated that volume, hemodynamic status, INO therapy, and ET were not "responsible for the elevation of ANP and cGMP early after HTx as compared with LVAD recipients."

Sickle Cell Disease: INO has been proposed for the treatment of acute chest syndrome and pain associated with vaso-occlusive crisis in patients with sickle cell disease. However, favorable clinical outcomes have not been reported in the peer-reviewed scientific literature. Gladwin et al. (2011) conducted a prospective, multicenter (n=11), double-blind, randomized controlled trial to compare the outcomes of INO (n=75) to inhaled nitrogen placebo (n=75) for the treatment of vaso-occlusive crisis (VOC) due to sickle cell disease. Time to VOC resolution, the primary outcome, was not significantly different ($p=0.87$) in the study group compared to the placebo group. There were also no statistically significant differences in median length of hospital stay ($p=0.30$), mean visual analog scale (VAS) pain scores at 24 hours ($p=0.90$), decrease in mean VAS scores over 2-hour

intervals during the first eight hours of treatment ($p=0.90$), median total opioid use ($p=0.73$), or acute chest syndrome requiring transfusion ($p=0.79$). Although not statistically significant, the number of rehospitalizations within thirty days was higher in the placebo group. INO recipients had significantly higher nitrate levels in plasma ($p=0.03$) and levels of methemoglobin in the venous blood compared to placebo ($p=0.001$), but the levels were not toxic. INO did not improve time to crisis resolution.

Al Hajeri et al. (2010) conducted a systematic review of the literature to identify randomized or quasi-randomized trials that addressed the use of INO in the treatment of acute chest syndrome in patients with sickle cell disease. No studies met inclusion criteria.

Professional Societies/Organizations

American Academy of Pediatrics (AAP): The AAP Committee on Fetus and Newborn (2010)

recommendations for INO for the treatment of infants with hypoxic respiratory failure include the following:

- 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.

American Association for Respiratory Care (AACR): Based on a systematic review of the literature, the AACR (2010) published evidence-based clinical practice guidelines for INO for neonates with acute hypoxic respiratory failure. The recommendations included:

1. "A trial of INO is recommended in newborns (≥ 34 wk gestation, < 14 d [days] of age) with $P_{aO_2} < 100$ mm Hg [millimeters of mercury] on $F_{IO_2} 1.0$ and/or an oxygenation index (OI) > 25 .
2. It is recommended that INO therapy be instituted early in the disease course, which potentially reduces the length of mechanical ventilation, oxygen requirement, and stay within the intensive care unit.
3. It is recommended that INO should not be used routinely in newborns with congenital diaphragmatic hernia.
4. It is suggested that INO therapy should not be used routinely in newborns with cardiac anomalies dependent on right-to-left shunts, congestive heart failure, and those with lethal congenital anomalies.
5. It is suggested that there are insufficient data to support the routine use of INO therapy in postoperative management of hypoxic term or near-term infants with congenital heart disease.
6. The recommended starting dose for INO is 20 ppm [parts per million].
7. It is recommended that response to a short trial (30–60 min) of INO should be judged by an improvement in P_{aO_2} or oxygenation index (OI); if there is no response, INO should be discontinued.
8. For the newborn with parenchymal lung disease, it is recommended that optimal alveolar recruitment be established prior to initiation of INO therapy.

9. For newborns with a response to INO therapy, it is recommended that the dose should be weaned to the lowest dose that maintains that response.
10. It is recommended that INO should not be discontinued until there is an appreciable clinical improvement; that the INO dose should be weaned to 1 ppm before an attempt is made to discontinue; and that the F_{IO_2} should be increased prior to discontinuation of INO therapy.
11. It is recommended that FDA-approved INO delivery systems should be used to assure consistent and safe gas delivery during therapy.
12. During conventional mechanical ventilation, it is suggested that the INO gas injector module should be placed on the dry side of the humidifier.
13. During conventional ventilation, it is suggested that the sampling port be placed in the inspiratory limb of the ventilator, downstream from the site of injection, no greater than 15 cm [centimeters] proximal the patient connection/interface.
14. It is suggested that the F_{IO_2} be measured downstream from the injection of INO into the circuit.
15. It is suggested that the patient/ventilator system be continuously monitored for changes in ventilation parameters, with adjustments to maintain desired settings during INO therapy (Grade 2C).
16. It is suggested that the lowest effective doses of INO and O₂ be used, to avoid excessive exposure to NO, NO₂, and methemoglobinemia.
17. It is suggested that the INO delivery system be properly purged before use to minimize inadvertent exposure to NO₂.
18. It is suggested that the high NO₂ alarm be set at 2 ppm on the delivery system to prevent toxic gas exposure to the lungs.
19. It is suggested that methemoglobin be monitored approximately 8 hours and 24 hours after therapy initiation and daily thereafter.
20. It is suggested that the INO dose be weaned or discontinued if methemoglobin rises above 5%.
21. It is suggested that continuous pulse oximetry and hemodynamic monitoring be used to assess patient response to INO therapy.
22. It is suggested that scavenging of exhaled and unused gases during INO therapy is not necessary”.

American College of Chest Physicians (ACCP): In their evidence-based practice guidelines for the treatment of pulmonary arterial hypertension, ACCP (2007) stated 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, AACCP noted 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.”

American College of Critical Care Medicine (ACCCM): The 2007 update of the “Clinical Practice Parameters for the Hemodynamic Support of Pediatric and Neonatal Patients in Septic Shock” by the ACCCM (Brierley, et al., 2009) 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 (NaHCO₃) or tromethamine. Mild hyperventilation can also be instituted until 100% oxygen saturation and < 5% difference in preductal and postductal saturations are obtained. Inhaled nitric oxide should be administered as the first treatment when available.”

European Society of Intensive Care Medicine (ESICM): The European expert recommendations from the ESICM and the European Association of Cardiothoracic Anaesthesiologists (Germann, et al., 2005) identified 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.” INO is useful for testing for “pulmonary vasoreactivity in patients undergoing heart transplantation or in patients with pulmonary arterial hypertension.” According to the 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 recommended 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 stated 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.

European Society of Paediatric and Neonatal Intensive Care (ESPNIC): The consensus guidelines for the use of iNO in neonates and children from the ESPNIC, the European Society of Paediatric Research and the European Society of Neonatology (Macrae, et al., 2004) stated that iNO "appears to improve outcomes in hypoxemic term and near-term infants" with the exception of infants with congenital heart disease, and stated that sufficient data is lacking to recommend the routine use of iNO in preterm infants. ESPNIC also noted that iNO may be "justified as rescue therapy in life threatening hypoxaemia after lung recruitment has been optimized." As it relates to cardiac disease, the guidelines concluded that "there is insufficient evidence to recommend the routine use of prophylactic postoperative iNO in congenital heart patients at risk of pulmonary hypertension." 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."

European Society of Cardiology (ESC): In their guidelines on the management of pulmonary hypertension, the ESC (Galie, et al., 2009) stated that acute vasodilator testing including intravenous prostacyclin or adenosine and inhaled nitric oxide should be used at the time of initial right heart catheterization. It is "generally accepted" that acute vasodilator challenge can identify those individuals who may benefit from long-term calcium channel blockers.

Global Initiative for Chronic Obstructive Lung Disease (GOLD): The 2010 "Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease" stated that the administration of iNO in patients with COPD can worsen the gas exchange because of "altered hypoxic regulation of ventilation-perfusion balance" and is, therefore, contraindicated.

National Institutes of Health (NIH): A Consensus Panel for the NIH (2010) conducted a systematic review of the literature to evaluate iNO for the treatment of preterm infants ≤ 34 weeks gestation. The Panel included "experts" from neonatology, pediatric pulmonology, pediatric neurology, perinatal epidemiology, ethics, neurodevelopmental follow-up, nursing, and family-centered care. The conclusions of their investigation included the following statements:

- "Taken as a whole, the available evidence does not support use of inhaled nitric oxide (iNO) in early routine, early rescue, or later rescue regimens in the care of premature infants <34 weeks gestation who require respiratory support.
- There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants <34 weeks gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties."

The Panel also noted that future research is needed to understand iNO benefits on lung development and function in infants at high risk of BPD.

Summary

Evidence in the published peer-reviewed scientific literature and the American Academy of Pediatrics support inhaled nitric oxide (iNO) therapy for the treatment of term and preterm infants with a gestational age at birth of at least 34 weeks, who 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.

Although the published evidence for INO for other indications is not robust, there is some evidence in clinical trials, and support from professional societies and organizations for INO administration in the postoperative treatment of congenital heart disease in patients with pulmonary hypertension. INO may also be used as a vasodilating agent during heart catheterization to assess pulmonary vasoreactivity and aid in the diagnosis of pulmonary hypertension.

The evidence in the published peer-reviewed scientific literature does not support the safety and efficacy of INO for the treatment of hypoxic respiratory failure in neonates birth age < 34 weeks gestation, nor in the treatment of infants, children and adults with other conditions such as acute respiratory distress syndrome, chronic lung disease, and sickle cell anemia. INO is not indicated in the treatment of patients following heart and/or lung transplantation.

Coding/Billing Information

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

Covered when medically necessary:

CPT[®]* Codes	Description
93463	Pharmacologic agent administration (eg, inhaled nitric oxide, intravenous infusion of nitroprusside, dobutamine, milrinone, or other agent) including assessing hemodynamic measurements before, during, after and repeat pharmacologic agent administration, when performed (List separately in addition to code for primary procedure)
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

ICD-9-CM Procedure Codes	Description
00.12	Administration of inhaled nitric oxide

ICD-9-CM Diagnosis Codes	Description
416.0	Primary pulmonary hypertension
416.8	Other chronic pulmonary heart disease
747.83	Persistent fetal circulation
748.5	Agenesis, hypoplasia, and dysplasia of lung
748.60- 748.69	Other anomalies of the lung
748.8	Other specified anomalies of respiratory system
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
768.70- 768.73	Hypoxic-ischemic encephalopathy (HIE)
768.9	Unspecified birth asphyxia in liveborn infant
769	Respiratory distress syndrome
770.12	Meconium aspiration with respiratory symptoms

770.14	Aspiration of clear amniotic fluid with respiratory symptoms
770.16	Aspiration of blood with respiratory symptoms
770.84	Respiratory failure of newborn
770.88	Hypoxemia of newborn
771.81	Septicemia [sepsis] of newborn

Experimental/Investigational/Unproven/Not Covered when used in association with the administration of inhaled nitric oxide:

ICD-9-CM Diagnosis Codes	Description
282.41-282.42	Sickle-cell thalassemia
282.60-282.69	Sickle-cell disease
518.82	Other pulmonary insufficiency, not elsewhere classified
765.20	Unspecified weeks of gestation
765.21-765.27	Less than 24 completed weeks of gestation to 33-34 weeks of completed gestation
756.6	Anomalies of diaphragm
770.7	Chronic respiratory disease in the perinatal period
V42.1	Organ or tissue replaced by transplant; heart
V42.6	Organ or tissue replaced by transplant; lung
	All other codes

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Policy History

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

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