National Medical Policy

Subject: **Inhaled Nitric Oxide Therapy (iNO)**

Policy Number: **NMP420**

Effective Date*: **May 2008**

Updated: **December 2015**

This National Medical Policy is subject to the terms in the IMPORTANT NOTICE at the end of this document

For Medicaid Plans: Please refer to the appropriate State's Medicaid manual(s), publication(s), citations(s) and documented guidance for coverage criteria and benefit guidelines prior to applying Health Net Medical Policies

The Centers for Medicare & Medicaid Services (CMS)
For Medicare Advantage members please refer to the following for coverage guidelines first:

Use	Source	Reference/Website Link
	National Coverage Determination (NCD)	
	National Coverage Manual Citation	
	Local Coverage Determination (LCD)*	
	Article (Local)*	
	Other	
X	None	Use Health Net Policy

Instructions

- Medicare NCDs and National Coverage Manuals apply to ALL Medicare members in ALL regions.
- Medicare LCDs and Articles apply to members in specific regions. To access your specific region, select the link provided under "Reference/Website" and follow the search instructions. Enter the topic and your specific state to find the coverage determinations for your region. *Note: Health Net must follow local coverage determinations (LCDs) of Medicare Administration Contractors (MACs) located outside their service area when those MACs have exclusive coverage of an item or service. (CMS Manual Chapter 4 Section 90.2)
- If more than one source is checked, you need to access all sources as, on occasion, an LCD or article contains additional coverage information than contained in the NCD or National Coverage Manual.
- If there is no NCD, National Coverage Manual or region specific LCD/Article, follow the Health Net Hierarchy of Medical Resources for guidance.

Current Policy Statement

Please note, this policy addresses the therapeutic use of inhaled nitric oxide and does not address the use of inhaled nitric oxide in acute vasodilator testing of adults with pulmonary pulmonary arterial hypertension (PAH).

I. Health Net Inc. considers inhaled nitric oxide therapy medically necessary for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure* when both of the following criteria is met:

- Conventional therapies such as high concentrations of oxygen, hyperventilation, high-frequency ventilation, the induction of alkolosis, neuromuscular blockade and sedation have failed or are expected to fail; and

- Absence of a congenital diaphragmatic hernia.

Note: iNO should be administered using FDA-approved devices capable of administering iNO in constant concentration ranges in parts per million or less throughout the respiratory cycle.

*Note: Hypoxic respiratory failure is defined as an oxygenation index (OI) of at least 25 recorded on 2 measurements made at least 15 minutes apart. The OI is calculated as the mean airway pressure in cms water multiplied by the fraction of inspired oxygen divided by the partial pressure of arterial oxygen times 100. An OI of 25 is associated with a 50% risk of requiring extracorporeal membrane oxygenation (ECMO) or dying. An OI of 40 is often used as a criterion to initiate ECMO therapy.

I. Health Net Inc. considers treatment with inhaled nitric oxide for all other indications, including but not limited to, the treatment of premature neonates (< 34 weeks of gestation), treatment of acute lung injury, adult respiratory distress syndrome and severe malaria, investigational. Although studies are still being done, there is insufficient evidence in the peer review literature to support its use outside of clinical trials.

Abbreviations

ARDS	Acute respiratory distress syndrome
ALI	Acute lung injury
ECMO	Extracorporeal membrane oxygenation
iNO	Inhaled nitric oxide
ppm	Parts per million

Codes Related To This Policy (may not be all inclusive)

NOTE:
The codes listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit documents and medical necessity criteria. This list of codes may not be all inclusive.

On October 1, 2015, the ICD-9 code sets used to report medical diagnoses and inpatient procedures will be replaced by ICD-10 code sets. Health Net National Medical Policies will now include the preliminary ICD-10 codes in preparation for this transition. Please note that these may not be the final versions of the codes and that will not be accepted for billing or payment purposes until the October 1, 2015

implementation date.

ICD-9 Codes

747.83	Persistent fetal circulation (primary pulmonary hypertension of newborn)
748.5	Agenesis, hypoplasia, and dysplasia of lung
748.60	Anomaly of lung, unspecified
748.8	Other specified anomalies of respiratory system
765.27	Weeks of gestation; 33-34 completed weeks of gestation
765.28	Weeks of gestation; 35-36 completed weeks of gestation
765.29	Weeks of gestation; 37 or more completed weeks of gestation
769	Respiratory distress syndrome (newborn)
770.10-770.9	Other respiratory conditions of fetus and newborn
771.81	Septicemia [sepsis] of newborn
786.00-786.9	Symptoms involving respiratory system and other chest symptoms

ICD-10 Codes

P29.3	Persistent fetal circulation
Q33.0-Q33.9	Congenital malformations of lung
Q34.0-Q34.9	Other congenital malformations of respiratory system
PØ7.36	Preterm newborn, gestational age 33 completed weeks
PØ7.37	Preterm newborn, gestational age 34 completed weeks
PØ7.38	Preterm newborn, gestational age 35 completed weeks
PØ7.39	Preterm newborn, gestational age 36 completed weeks
P22.0-P22.9	Respiratory distress of newborn
P36.0-P36.9	Bacterial sepsis of newborn
R06.00-R06.9	Abnormalities of breathing

CPT Codes

94799	Unlisted pulmonary service or procedure

HCPCS Codes

N/A

Scientific Rationale – Update December 2015

Maitre et al (2015) reported that previous clinical trials suggested that inhaled nitric oxide (iNO) could have beneficial effects in sickle cell disease (SCD) patients with acute chest syndrome (ACS). The authors sought to determine whether iNO reduces treatment failure rate in adult patients with ACS. They conducted a prospective, double-blind, randomized, placebo-controlled clinical trial. iNO (80 ppm, N = 50) gas or inhaled nitrogen placebo (N = 50) was delivered for 3 days. The primary end point was the number of patients with treatment failure at day 3, defined as any one of the following: death from any cause, need for endotracheal intubation, decrease of PaO2/FiO2 ≥ 15 mmHg between days 1 and 3, augmented therapy defined as new transfusion or phlebotomy. The two groups did not differ in age, gender, genotype, or baseline characteristics and biological parameters. iNO was well tolerated, although a transient decrease in nitric oxide concentration was mandated in one patient. There was no significant difference in the primary end point between the iNO and placebo groups [23 (46 %) and 29 (58 %); odds ratio (OR), 0.8; 95 % CI, 0.54-1.16; p = 0.23]. A post hoc analysis of the 45 patients with hypoxemia showed that those in the iNO group were less likely to experience treatment failure at day 3 [7 (33.3 %) vs 18 (72 %); OR = 0.19; 95 % CI, 0.06-0.68; p = 0.009].

The authors concluded iNO did not reduce the rate of treatment failure in adult SCD patients with mild to moderate ACS. Future trials should target more severely ill ACS patients with hypoxemia.

Ternan et al (2015) evaluated the effectiveness and safety of iNO in adult patients with severe hypoxemia before and during transport to a tertiary care center. Prospective data were examined in a retrospective cohort study. Patients with severe hypoxemia and cardiopulmonary failure (n=139) at referring hospitals in whom conventional therapy was unsuccessful were treated with iNO in the intensive care units in anticipation of transfer to a tertiary center. Treatment with iNO was initiated by the critical care transport team in 114 patients and continued in 25 patients. Arterial blood gas analysis was done before and after iNO treatment. Patients treated with iNO had significant improvement in oxygenation: mean (SD) for PaO2 increased from 60.7 (20.2) to 72.3 (40.6) mm Hg (P=.008), and mean (SD) for ratio of PaO2 to fraction of inspired oxygen (P:F) increased from 62.4 (26.1) to 73.1 (42.6) (P= .03). Use of iNO was continued through transport in 102 patients, all of whom were transported without complication. The P:F continued to improve, with a mean (SD) of 109.7 (73.8) from 6 to 8 hours after arrival at the tertiary center (P< .001 relative to values both before and after treatment). Among patients treated with iNO, 60.2% survived to discharge. In 35 nonresponders, iNO was discontinued, and 15 patients could not be transferred owing to life-threatening hypoxemia; 2 were later transferred on extracorporeal membrane oxygenation. Of 18 patients transported without iNO, 9 (50%) survived. The authors concluded use of iNO significantly improves oxygenation of patients with severe hypoxemia and allows safe transfer to a tertiary care center.

Bronicki et al (2015) sought to test the hypothesis that iNO would lead to improved oxygenation and a decrease in duration of mechanical ventilation in pediatric patients with acute respiratory distress syndrome. A total of 55 children with acute respiratory distress syndrome were enrolled from 9 centers. Patients were randomized to iNO or placebo and remained on the study drug until death, they were free of ventilator support, or day 28 after the initiation of therapy. Mean baseline oxygenation indexes (OIs) were 22.0 ± 18.4 and 25.6 ± 14.9 (iNO and placebo groups, respectively, P = .27). There was a trend toward an improved OI in the iNO group compared with the placebo group at 4 hours that became significant at 12 hours. There was no difference in the OI between groups at 24 hours. Days alive and ventilator free at 28 days was greater in the iNO group, 14.2 ± 8.1 and 9.1 ± 9.5 days (iNO and placebo groups, respectively, P = .05). Although overall survival at 28 days failed to reach statistical significance, 92% (22 of 24) in the iNO group and 72% (21 of 29) in the placebo group (P = .07), the rate of extracorporeal membrane oxygenation-free survival was significantly greater in those randomized to iNO 92% (22 of 24) vs 52% (15 of 29) for those receiving placebo (P < .01). The authors concluded the use of iNO was associated with a significantly reduced duration of mechanical ventilation and significantly greater rate of extracorporeal membrane oxygenation-free survival.

Scientific Rationale – Update December 2014

Kumar et al. (2014) completed a clinical report by the American Academy of Pediatrics (AAP). This included a review of existing data for the use of INO in preterm infants and provided guidance regarding its use in this population. The only information regarding the safety of inhaled Nitric oxide (iNO) use in preterm infants is derived from the NOCLD trial. (i.e., Truog et al. (2007), Ballard et al. (2007, 2008), and (Posencheg et al. 2010). The limited data suggest that iNO is safe and does not increase lung inflammation or oxidative stress. The following summary was provided:

- The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure (Evidence quality, A; Grade of recommendation, strong).
- The preponderance of evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities (Evidence quality, A; Grade of recommendation, strong).
- The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants (Evidence quality, A).
- The results of 1 multicenter, randomized controlled trial suggest that treatment with a high dose of iNO (20 ppm) beginning in the second postnatal week may provide a small reduction in the rate of BPD. However, these results need to be confirmed by other trials.
- An individual-patient data meta-analysis that included 96% of preterm infants enrolled in all published iNO trials found no statistically significant differences in iNO effect according to any of the patient-level characteristics, including gestational age, race, oxygenation index, postnatal age at enrollment, evidence of pulmonary hypertension, and mode of ventilation.
- There are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood.

There have been reviews on inhaled nitric oxide therapy for neonates for hypoxic respiratory failure, by various authors:

Kumar, worked with the AAP, (20104) states: "Nitric oxide, an important signaling molecule with multiple regulatory effects throughout the body, is an important tool for the treatment of full-term and late-preterm infants with persistent pulmonary hypertension of the newborn and hypoxemic respiratory failure. Several randomized controlled trials have evaluated its role in the management of preterm infants ≤34 weeks' gestational age with varying results. The purpose of this clinical report is to summarize the existing evidence for the use of inhaled nitric oxide in preterm infants and provide guidance regarding its use in this population".

Dr. Sukumar, neonatologist (2014) states: "I read the recent Clinical Report on the use of inhaled Nitric Oxide in Preterm infants, with great interest. Although it supports the recommendations of the NIH Consensus published in October 2010, it fails to address the possible benefit of inhaled nitric oxide in preterm infants with pulmonary hypoplasia and/or severe PPHN. Although there is scant published data that supports this practice, nitric oxide is being widely used in these critically ill infants in many NICU's and it is important that the Committee acknowledges this fact as done in the NIH Consensus".

Schreiber et al., pediatric professor (2014) states: "We read with interest the review of the use of iNO in premature infants recently published by Dr. Kumar on behalf of the AAP Committee on Fetus and Newborn. Along with the recent NIH Consensus opinion, this article provides practicing neonatologists with direction on the use of iNO in premature infants, a population in which well-performed clinical trials have failed to produce consensus about its overall efficacy".

The American Academy of Pediatrics (2014) also notes: "Nitric oxide, an important signaling molecule with multiple regulatory effects throughout the body, is an important tool for the treatment of full-term and late-preterm infants with persistent pulmonary hypertension of the newborn and hypoxemic respiratory failure."

In summary, there is insufficient evidence in published peer-reviewed studies demonstrating the safety and efficacy of INO for any use, other than as a component of the treatment of hypoxic respiratory failure in term and near-term (born at 34 or more weeks of gestation) neonates under specific circumstances.

Scientific Rationale – Update December 2013

Hypoxic respiratory failure is defined as an oxygenation index (OI) of at least 25 recorded on 2 measurements made at least 15 minutes apart. The OI is calculated as the mean airway pressure in cms water multiplied by the fraction of inspired oxygen divided by the partial pressure of arterial oxygen times 100. An OI of 25 is associated with a 50% risk of requiring extracorporeal membrane oxygenation (ECMO) or dying. An OI of 40 is often used as a criterion to initiate ECMO therapy.

Scientific Rationale – Update March 2011

Per the 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 (http://www.fda.gov). 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.

Per the Journal of American Medical Association (JAMA, 2010) "Inhaled nitric oxide therapy should not be used routinely to treat infants born at or before 34 weeks of gestation, according to an independent consensus panel appointed by the National Institutes of Health. We found that there has been considerable work on the use of nitric oxide in infants born more than 6 weeks early, but we don't find sufficient evidence to warrant routine use." The panel noted that clinical trials to date have not clearly demonstrated the effect of the therapy on pulmonary outcomes, survival, and neurodevelopment. Cole also noted the trials have used complex and varied

designs that make it difficult to compare results. More studies are needed to determine if routine use is warranted. Additionally, the panel noted that such therapy maybe beneficial in infants born before 34 weeks of gestation with pulmonary hypertension and lung hypoplasia, but that these uses have not been adequately studied.

Mercier et al. (2010) 800 preterm infants with a gestational age at birth of between 24 weeks and 28 weeks plus 6 days (inclusive), weighing at least 500 g, requiring surfactant or continuous positive airway pressure for respiratory distress syndrome within 24 h of birth were randomly assigned in a one-to-one ratio to inhaled nitric oxide (5 parts per million) or placebo gas (nitrogen gas) for a minimum of 7 days and a maximum of 21 days in a double-blind study done at 36 centers in nine countries in the European Union. Care providers and investigators were masked to the computer-generated treatment assignment. The primary outcome was survival without development of bronchopulmonary dysplasia at postmenstrual age 36 weeks. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00551642. 399 infants were assigned to inhaled nitric oxide, and 401 to placebo. 395 and 400, respectively, were analyzed. Treatment with inhaled nitric oxide and placebo did not result in significant differences in survival of infants without development of bronchopulmonary dysplasia (258 [65%] of 395 versus 262 [66%] of 400, respectively; relative risk 1.05, 95% CI 0.78-1.43); in survival at 36 weeks' postmenstrual age (343 [86%) of 399 versus 359 [90%] of 401, respectively; 0.74, 0.48-1.15); and in development of bronchopulmonary dysplasia (81 [24%] of 339 versus 96 [27%] of 358, respectively; 0.83, 0.58-1.17). Early use of low-dose inhaled nitric oxide in very premature babies did not improve survival without bronchopulmonary dysplasia or brain injury, suggesting that such a preventive treatment strategy is unsuccessful.

Scientific Rationale – Update May 2010

Inhaled Nitric oxide is well established and widely accepted for use in acute vasodilator testing in adults with PAH. Vasodilator testing is performed to determine whether the patient might derive clinical benefit from calcium channel blocker therapy (eg, nifedipine). During the vasoreactivity trial, inhaled NO is administered after baseline hemodynamic parameters are measured. Hemodynamic measurements are repeated after inhalation of NO for five to ten minutes at doses between 10 and 80 parts per million. The ability of vasoreactivity testing with inhaled NO to predict nifedipine-induced vasodilation of the pulmonary vasculature has been confirmed in several small studies. Ricciardi et al (1998) demonstrated that vasodilation of the pulmonary vasculature induced by inhaled NO at a dose of 80 ppm predicted an acute hemodynamic response to nifedipine with a sensitivity, specificity, and predictive accuracy of 88, 100, and 94 percent, respectively. An advantage of using inhaled NO for vasodilator testing is its selective effect on the pulmonary vasculature. As a result, systemic hemodynamic effects (eg, hypotension) that can occur with some other forms of vasodilators are not seen when inhaled NO is used.

The potential therapeutic role of inhaled nitric oxide in adults remains uncertain at this time and FDA approved indications are restricted to pediatric practice.

Kahn et al (2009) compared inhaled nitric oxide and inhaled prostacyclin in the treatment of pulmonary hypertension, refractory hypoxemia, and right ventricular dysfunction in thoracic transplant recipients in a prospective, randomized, crossover pilot trial. Heart transplant and lung transplant recipients were randomized to nitric oxide or prostacyclin as initial treatment, followed by a crossover to the other agent after 6 hours. Pulmonary vasodilators were initiated in the operating room for pulmonary hypertension, refractory hypoxemia, or right ventricular dysfunction.

Nitric oxide was administered at 20 ppm, and prostacyclin was administered at 20,000 ng/mL. Hemodynamic and oxygenation parameters were recorded before and after initiation of pulmonary vasodilator therapy. At 6 hours, the hemodynamic and oxygenation parameters were recorded again, just before discontinuing the initial agent. Crossover baseline parameters were measured 30 minutes after the initial agent had been stopped. The crossover agent was then started, and the hemodynamic and oxygenation parameters were measured again 30 minutes later. Heart transplant and lung transplant recipients (n = 25) were randomized by initial treatment (nitric oxide, n = 14; prostacyclin, n = 11). Nitric oxide and prostacyclin both reduced pulmonary artery pressure and central venous pressure, and improved cardiac index and mixed venous oxygen saturation on initiation of therapy. More importantly, at the 6-hour crossover trial, there were no significant differences between nitric oxide and prostacyclin in the reduction of pulmonary artery pressures or central venous pressure, or in improvement in cardiac index or mixed venous oxygen saturation. Nitric oxide and prostacyclin did not affect the oxygenation index or systemic blood pressure. There were no complications associated with nitric oxide or prostacyclin.

Elahi et al (2009) studied the impact of inspired NO gas on physiological function and markers of inflammation-oxidative stress for 15 individuals scheduled for coronary artery bypass graft (CABG) operation. Outcomes from individuals that received 5 ppm and 20 ppm of inspired NO (n=5/group) were compared to those not given NO gas. Breath-to-breath measurement commenced at the start of intubation and continued up to 4h later. Indices of cardiovascular function, alveolar-capillary gas exchange and haematological parameters were not significantly different in outcomes for the inspired NO groups as compared with control. A reduction in mean systemic arterial in all subjects at 30 min and 4h after bypass when compared with pre bypass values was observed. Markers of systemic inflammatory response and oxidative stress increased during cardiopulmonary bypass particularly at 4h and 24h after the initiation of bypass. In contrast, a reduction in expired NO, at 24h after surgery in the groups given inspired NO was observed. IThere was also a significant reduction in oxidative stress markers in blood at 24h after surgery for the groups given inspired NO as compared with the control group. In contrast, cytokines response remained similar in all the three groups at all time points. The authors concluded results suggest that inspired NO gas has an antioxidant property that reduces the levels of cell death, and is not associated with significantly worse-off physiological outcomes.

Winterhalter et al (2008) compared the efficacy of inhaled iloprost and nitric oxide (iNO) in reducing pulmonary hypertension (PHT) during cardiac surgery immediately after weaning from cardiopulmonary bypass (CPB) in a prospective randomized study. Forty-six patients with PHT (mean pulmonary artery pressure (mPAP) $\geq$ 26 mmHg preoperatively at rest, after anesthesia induction, and at the end of CPB) scheduled to undergo cardiac surgery were enrolled. Patients were randomly allocated to receive iloprost (group A, n = 23) or iNO (group B, n = 23) during weaning from CPB. Heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure (PAP), pulmonary capillary wedge pressure, and left atrial pressure were recorded continuously. Iloprost and iNO were administered immediately after the end of CPB before heparin reversal. Both substances caused significant reductions in mean PAP (mPAP) and pulmonary vascular resistance (PVR) and significant increases in cardiac output 30 minutes after administration. However, in a direct comparison, iloprost caused significantly greater reductions in PVR ($p = 0.013$) and mPAP ($p = 0.0006$) and a significantly greater increase in cardiac output ($p = 0.002$) compared with iNO.

Clinical trial evaluating the use of inhaled nitric oxide for numerous indications are ongoing.

Scientific Rationale Initial

Hypoxic respiratory failure in neonates born at or near term may be caused by such conditions as primary persistent pulmonary hypertension, respiratory distress syndrome, aspiration syndromes, pneumonia or sepsis, and congenital diaphragmatic hernia. According to the American Academy of Pediatrics, conventional therapies, which have not been validated by randomized controlled trials, include administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, the induction of alkalosis, neuromuscular blockade, and sedation.

Nitric oxide is a gas that is administered by inhalation that relaxes pulmonary vessels, producing pulmonary vasodilation without affecting systemic blood pressure and improves oxygenation. Nitric oxide is most often administered to patients receiving mechanical ventilation, however, it may be given through a face mask or nasal cannula. Inhaled nitric oxide (e.g., INOmax) is FDA approved for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure, in conjunction with ventilatory support and other appropriate agents, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO). The American Academy of Pediatrics supports the indications for inhaled nitric acid (iNO) for the treatment of this population. The FDA approval was based on results from several double-blind, randomized, placebo-controlled, multicenter trials. The Neonatal Inhaled Nitric Oxide Study Group trial documented that iNO reduced the need for ECMO without increasing neurodevelopmental, behavioral, or medical abnormalities at 2 years of age. The Clinical Inhaled Nitric Oxide Research Group trial, reported that iNO reduced the need for ECMO and the incidence of chronic lung disease. In clinical trials, iNO was not effective for infants with congenital diaphragmatic hernia. Avoidance of ECMO is a clinically desirable outcome, however, if iNO therapy fails, ECMO is usually initiated. It is recommended that institutions that offer iNO therapy should have ECMO capability or have the ability for the timely transfer of infants to a collaborating ECMO center.

Inhaled nitric oxide (iNO) therapy has also been proposed as a potential therapy for acute respiratory distress syndrome (ARDS). The diagnosis of ARDS is made on clinical grounds, according to the following criteria set forth by the American-European Consensus Conference:

- Acute onset
- Bilateral infiltrates
- Pulmonary artery wedge pressure less than 19 mm Hg (or no clinical signs of congestive heart failure) and PaO2/FIO2 ratio less than 200 (ARDS) or less than 300 acute lung injury.

Acute lung injury (ALI) is a milder clinical expression of the injury of ARDS that may or may not progress to ARDS. ARDS is associated with severe hypoxemia thus high inspired oxygen concentrations are required to maintain adequate tissue oxygenation. Unfortunately, oxygen toxicity may promote further lung injury. ARDS is associated with pulmonary hypertension and the development of progressive pulmonary hypertension is associated with a poor prognosis. Patients with ARDS are likely to have prolonged hospital courses, and they frequently develop nosocomial infections, especially ventilator-associated pneumonia. The most common cause of death in ARDS is not hypoxemia or pulmonary failure, but rather multiple organ failure.

Supportive treatment of ARDS may include mechanical ventilation, oxygen and fluid management, use of sedatives and neuromuscular blockade, careful hemodynamic management, nutritional support, control of blood glucose, evaluation and treatment of nosocomial pneumonia, and prophylaxis against deep vein thrombosis and gastrointestinal bleeding. Effective pharmacotherapy for ARDS is limited. Glucocorticoids have been the most investigated treatment, however, their definitive role in the treatment of ARDS in adults remains controversial. Studies suggest a possibility of reduced mortality and increased ventilator free days with steroids started after the onset of ARDS. Several randomized trials of patients with acute lung injury or ARDS demonstrated that prolonged treatment with glucocorticoids in moderate doses consistently improved gas exchange, lung injury score, and dramatically shortened duration of mechanical ventilation. A multicenter trial reported by Steinberg et al did not show any evidence for a survival benefit, and even suggested that when glucocorticoids are administered very late after 2 weeks of progression of the disease, they may cause harm. Prone positioning appears to improve oxygenation in many patients with ALI and ARDS, and may reduce the incidence of ventilator-associated pneumonia, however, studies have not shown a advantage in survival or duration of mechanical ventilation. Prone positioning may be associated with harmful effects such as decubitus ulcers and self-extubation. At this time, there appears to be insufficient evidence to support its routine use in patients with ALI or ARDS.

Inhaled Nitric oxide has been studied in patients with acute lung injury and ARDS. Inhaled NO is typically administered at a dose between 1.25 and 40 parts per million (ppm). There is evidence that patients treated with continuous iNO might become sensitized. Potential harms of iNO include methemoglobinemia during acute or prolonged NO inhalation; cytotoxity; immunosuppression; and mutagenesis.

Studies suggest iNO has beneficial physiological effects, but there is little evidence that patient outcome improves. In a multicenter trial, Taylor et al (2004) randomly assigned 385 patients with moderate to severe acute lung injury to either placebo or inhaled NO at 5 ppm. The acute lung injury was not caused by sepsis, and significant nonpulmonary organ dysfunction was absent. Inhaled NO induced short-term improvement of oxygenation; however, there was no improvement in the duration of mechanical ventilation, 28-day mortality, or one-year survival.

Angus et al (2006) also investigated the long-term outcomes of 385 previously healthy adults with ARDS randomized to 5 ppm inhaled nitric oxide or placebo gas. The investigators reported that one-year survival was no different by treatment arm for inhaled nitric oxide vs. placebo. There were also no differences in length of stay or Therapeutic Intervention Scoring System points. At 1 year, survivors reported low quality of life and poor function with no differences by treatment arm.

In addition, a meta-analysis of ten randomized controlled trials (1237 patients) reported by Adhikari et al. (2007) compared iNO versus placebo or conventional management. Inhaled NO did not improve hospital mortality, duration of ventilation, or ventilator-free days. It did increase the PAo2/Fio2 ratio on the first day of therapy, and some evidence suggested improvements in oxygenation until day four, however, there was no effect on mean pulmonary arterial pressure. The authors concluded that nitric oxide is associated with limited improvements in oxygenation in patients with ALI or ARDS but confers no mortality benefit. The authors recommended against its use in these severely ill patients.

In summary, acute, short-term benefits in physiologic parameters have been demonstrated in numerous studies of iNO inhalation therapy for ARDS, but randomized controlled trials have failed to show improvement in mortality rates.

The potential therapeutic role of inhaled NO in adults remains uncertain. Randomized controlled clinical trials are necessary to investigate the benefit of inhaled NO in the treatment of ALI/ARDS.

Review History

May 2008	Medical Advisory Council, initial approval
May 2010	Update – no revision
March 2011	Update. Added Medicare Table. No revisions.
December 2011	Update – no revisions
December 2012	Update – no revisions
December 2013	Update – no revisions. Codes updated.
December 2014	Update – no revisions. Codes updated.
December 2015	Update – no revisions.

This policy is based on the following evidence-based guidelines:

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4. Hayes Health Technology Brief. Inhaled Nitric Oxide for Acute Respiratory Distress Syndrome (ARDS) in Adults. Nov. 2010. Updated Oct 2011. Updated March 31, 2014. Update Mar 2015
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5. Teman NR, Thomas J, Bryner BS, et al. Inhaled nitric oxide to improve oxygenation for safe critical care transport of adults with severe hypoxemia. Am J Crit Care. 2015 Mar;24(2):110-7.

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Important Notice

General Purpose.
Health Net's National Medical Policies (the "Policies") are developed to assist Health Net in administering plan benefits and determining whether a particular procedure, drug, service or supply is medically necessary. The Policies are based upon a review of the available clinical information including clinical outcome studies in the peer-reviewed published medical literature, regulatory status of the drug or device, evidence-based guidelines of governmental bodies, and evidence-based guidelines and positions of select national health professional organizations. Coverage determinations are made on a case-by-case basis and are subject to all of the terms, conditions, limitations, and exclusions of the member's contract, including medical necessity requirements. Health Net may use the Policies to determine whether under the facts and circumstances of a particular case, the proposed procedure, drug, service or supply is medically necessary. The conclusion that a procedure, drug, service or supply is medically necessary does not constitute coverage. The member's contract defines which procedure, drug, service or supply is covered, excluded, limited, or subject to dollar caps. The policy provides for clearly written, reasonable and current criteria that have been approved by Health Net's National Medical Advisory Council (MAC). The clinical criteria and medical policies provide guidelines for determining the medical necessity criteria for specific procedures, equipment, and services. In order to be eligible, all services must be medically necessary and otherwise defined in the member's benefits contract as described this "Important Notice" disclaimer. In all cases, final benefit determinations are based on the applicable contract language. To the extent there are any conflicts between medical policy guidelines and applicable contract language, the contract language prevails. Medical policy is not intended to override the policy that defines the member's benefits, nor is it intended to dictate to providers how to practice medicine.

Policy Effective Date and Defined Terms.
The date of posting is not the effective date of the Policy. The Policy is effective as of the date determined by Health Net. All policies are subject to applicable legal and regulatory mandates and requirements for prior notification. If there is a discrepancy between the policy effective date and legal mandates and regulatory requirements, the requirements of law and regulation shall govern. * In some states, prior notice or posting on the website is required before a policy is deemed effective. For information regarding the effective dates of Policies, contact your provider representative. The Policies do not include definitions. All terms are defined by Health Net. For information regarding the definitions of terms used in the Policies, contact your provider representative.

Policy Amendment without Notice.
Health Net reserves the right to amend the Policies without notice to providers or Members. In some states, prior notice or website posting is required before an amendment is deemed effective.

No Medical Advice.
The Policies do not constitute medical advice. Health Net does not provide or recommend treatment to members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

No Authorization or Guarantee of Coverage.
The Policies do not constitute authorization or guarantee of coverage of particular procedure, drug, service or supply. Members and providers should refer to the Member contract to determine if exclusions, limitations, and dollar caps apply to a particular procedure, drug, service or supply.

Policy Limitation: Member's Contract Controls Coverage Determinations.
Statutory Notice to Members: The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illnesses or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. The determination of coverage for a particular procedure, drug, service or supply is not based upon the Policies, but rather is subject to the facts of the individual clinical case, terms and conditions of the member's contract, and requirements of applicable laws and regulations. The contract language contains specific terms and conditions, including pre-existing conditions, limitations, exclusions, benefit maximums, eligibility, and other relevant terms and conditions of coverage. In the event the Member's contract (also known as the benefit contract, coverage document, or evidence of coverage) conflicts with the Policies, the Member's contract shall govern. The Policies do not replace or amend the Member's contract.

Policy Limitation: Legal and Regulatory Mandates and Requirements
The determinations of coverage for a particular procedure, drug, service or supply is subject to applicable legal and regulatory mandates and requirements. If there is a discrepancy between the Policies and legal mandates and regulatory requirements, the requirements of law and regulation shall govern.

Reconstructive Surgery
CA Health and Safety Code 1367.63 requires health care service plans to cover reconstructive surgery. "Reconstructive surgery" means surgery performed to correct or repair abnormal structures of the body caused by congenital defects, developmental abnormalities, trauma, infection, tumors, or disease to do either of the following:

(1) To improve function or

(2) To create a normal appearance, to the extent possible.

Reconstructive surgery does not mean "cosmetic surgery," which is surgery performed to alter or reshape normal structures of the body in order to improve appearance.

Requests for reconstructive surgery may be denied, if the proposed procedure offers only a minimal improvement in the appearance of the enrollee, in accordance with the standard of care as practiced by physicians specializing in reconstructive surgery.

Reconstructive Surgery after Mastectomy
California Health and Safety Code 1367.6 requires treatment for breast cancer to cover prosthetic devices or reconstructive surgery to restore and achieve symmetry for the patient incident to a mastectomy. Coverage for prosthetic devices and reconstructive surgery shall be subject to the co-payment, or deductible and coinsurance conditions, that are applicable to the mastectomy and all other terms and conditions applicable to other benefits. "Mastectomy" means the removal of all or part of the breast for medically necessary reasons, as determined by a licensed physician and surgeon.

Policy Limitations: Medicare and Medicaid
Policies specifically developed to assist Health Net in administering Medicare or Medicaid plan benefits and determining coverage for a particular procedure, drug, service or supply for Medicare or Medicaid members shall not be construed to apply to any other Health Net plans and members. The Policies shall not be interpreted to limit the benefits afforded Medicare and Medicaid members by law and regulation.