



**INHALED NITRIC OXIDE (iNO)  
THERAPY IN INFANTS  
HS-063**



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**Inhaled Nitric Oxide (iNO)  
Therapy in Infants**

**Policy Number: HS-063**

**Original Effective Date: 11/24/2008**

**Revised Date(s): 9/17/2009; 9/24/2010;  
7/21/2011**

**DISCLAIMER**

The Clinical Coverage Guideline is intended to supplement certain standard WellCare benefit plans. The terms of a member's particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member's benefit plan may contain specific exclusions related to the topic addressed in this Clinical Coverage Guideline. When a conflict exists between the two documents, the Member's Benefit Plan always supersedes the information contained in the Clinical Coverage Guideline. Additionally, Clinical Coverage Guidelines relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

**APPLICATION STATEMENT**

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

## **BACKGROUND**

In some newborn infants, the decrease in pulmonary vascular resistance and increase in pulmonary blood flow that normally takes place at birth does not occur, causing persistent pulmonary hypertension of the newborn (PPHN). PPHN can occur either as a primary developmental defect or secondary to conditions such as pneumonia, sepsis, hyaline membrane disease, meconium aspiration syndrome (MAS), congenital diaphragmatic hernia (CDH), or pulmonary hypoplasia. In these states, pulmonary vascular resistance is high ( $\geq 25$  vs 14 mm Hg in normal cases), resulting in hypoxemia. The baby presents clinically with cyanosis and respiratory distress with tachypnea. Since the infant's chest radiograph may be normal or may demonstrate various abnormalities indicative of MAS, CDH, pneumonia, or hyaline membrane disease, the diagnosis of PPHN is often confirmed with echocardiography. When conventional therapies such as oxygen support and mechanical ventilation fail, extracorporeal membrane oxygenation (ECMO) is initiated. During ECMO, the jugular vein and/or carotid artery is surgically bisected and connected to a heart-lung machine with a cannula to oxygenate the infant's blood. Although ECMO has been highly effective, it is highly invasive.

Nitric oxide (NO) inhalation therapy is a minimally invasive treatment that involves inhalation of gaseous NO in conjunction with ventilatory support. INOmax® is a blend of compressed NO (0.1% or 0.8%) and nitrogen (99.9% or 99.2%) gases supplied in aluminum cylinders. Treatment with INOmax is indicated for term and near-term neonates,  $\geq 34$  weeks gestational age, who have hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. In these neonates, NO inhalation at doses of 20 dilates pulmonary blood vessels, improving blood oxygenation and reducing the likelihood that ECMO will be required. Gradual weaning from NO is essential to prevent a rebound increase in arterial pressure and insufficient oxygenation of pulmonary tissue.

### *Dose and Duration of Treatment*

Studies of iNO Therapy show that inhalation of nitric oxide of 20 ppm were found to be effective in most neonates. Increasing the dose to 40 ppm does not increase the efficacy of treatment seen at 20 ppm. Sustained inhalation of NO doses at 80 ppm increases the risk of methemoglobinemia.

Multi-center clinical trials of iNO therapy had a typical duration of less than 5 days, which parallels the clinical resolution of pulmonary hypertension. If iNO therapy is required more than 4 days, medical necessity review is required and an investigation into other possible causes of pulmonary hypertension should be considered (e.g. alveolar capillary dysplasia).

### *Weaning and Discontinuation of Therapy*

Two approaches to weaning off iNO therapy exist and are recommended in the literature.

The first approach recommends that iNO be reduced to 5 ppm in the first 4 to 24 hours after initiating therapy.

- a. iNO is started at 20 ppm. Arterial blood gas and methemoglobin are measured at 4, 24, and 96 hours
- b. Dose of iNO is decreased to 5 ppm if the neonate's condition is stable, partial pressure of arterial oxygen (PaO<sub>2</sub>) is at least 60 mm Hg, and pH is 7.55 or lower
- c. If these criteria are not met, dose is maintained at 20 ppm until the criteria are met or until the
- d. neonate has been treated for 24 hours

- e. After 24 hours, dose is decreased to 5 ppm
- f. Treatment is continued at 5 ppm until fraction of inspired oxygen (FIO<sub>2</sub>) is less than 0.7, the neonate has been treated for 96 hours, or the neonate is 7 days old, whichever comes first

An alternative approach recommends that iNO be reduced in a stepwise fashion to as low as 1 ppm before discontinuation in order to minimize reduction in PaO<sub>2</sub>.

- a. After the neonate is classified as a treatment success (PaO<sub>2</sub> ≥60 mm Hg, FIO<sub>2</sub> <0.6, mean airway pressure <10 cm H<sub>2</sub>O), iNO is reduced by 20%
- b. An arterial blood gas with a record of hemodynamic and ventilatory status is obtained, and further 20% reductions can be made immediately or within 4 hours
- c. This weaning process is continued until iNO is turned off
- d. iNO can be increased back up to 20% with appropriate increases in FIO<sub>2</sub> if PaO<sub>2</sub> becomes <40 mm Hg during a weaning step

Note: Sudden discontinuation of iNO will cause rebound pulmonary hypertension that may be severe. This probably results from suppression by iNO of endogenous NO production. Rebound pulmonary hypertension is a risk with cessation of iNO from even low doses (i.e., <5 ppm), after only a few hours of iNO therapy, and regardless of whether the infant initially responded to iNO.

## **POSITION STATEMENT**

Inhaled nitric oxide (iNO) therapy **is considered medically necessary** when the following criteria are met:

- Therapy is intended for term and near-term neonates, ≥ 34 weeks gestational age, with hypoxic respiratory failure\* associated with clinical or echocardiographic evidence of persistent pulmonary hypoplasia of the newborn and/or pulmonary hypertension; **AND**,
- Conventional therapies such as administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, the induction of alkalosis, neuromuscular blockade and sedation have failed, are expected to fail, or are contraindicated;

\* Hypoxic respiratory failure 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 ECMO or dying. An OI of 40 is often used as a criterion to initiate ECMO therapy.

The use of inhaled nitric oxide therapy **is considered experimental and investigational** in the following circumstances:

- Treating premature infants < than 34 weeks of gestation; **OR**,
- For the treatment of any indication not listed above

## **CODING**

**CPT® Code** - No applicable code

**ICD-9-CM Procedure Code**

**00.12** Administration of inhaled nitric oxide

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## **HCPCS Level II ©Code**

**S1025** Deleted / Invalid code effective 2009

## **Covered ICD-9-CM Diagnosis Codes when criteria are met**

- 747.83** Persistent fetal circulation (primary pulmonary hypertension of newborn)
- 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
- 770.84** Respiratory failure of newborn

## **Experimental/Investigational/Unproven/Not Covered**

For the procedure code listed above, when criteria are not met, for all other diagnoses not listed; or when the code describes a procedure indicated in the Policy section as investigational/not medically necessary.

## **Non-Covered ICD-9-CM Diagnosis Codes**

**765.20 - 765.26** Weeks of gestation; unspecified or 1-32 completed weeks of gestation.

\*Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.

## **REFERENCES**

### **Peer Reviewed**

1. Angus DC, Clermont G, Watson RS, et al. Cost-effectiveness of inhaled nitric oxide in the treatment of neonatal respiratory failure in the United States. *Pediatrics*. 2003; 112 (6 Pt 1):1351-1360.
2. Ballard RA, Truog WE, Cnaan A, Martin RJ, Ballard PL, Merrill JD, Walsh MC, Durand DJ, Mayock DE, Eichenwald EC, Null DR, Hudak ML, Puri AR, Golombek SG, Courtney SE, Stewart DL, Welty SE, Phibbs RH, Hibbs AM, Luan X, Wadlinger SR, Asselin JM, Coburn CE. Inhaled Nitric Oxide in Preterm Infants Undergoing Mechanical Ventilation. *N Engl J Med* 355:343, July 27, 2006.
3. Clark RH, Kueser TJ, Walker MW, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *Clinical Inhaled Nitric Oxide Research Group*. *N Engl J Med*. 2000; 342 (7):469-474.
4. Ellington M Jr, O'Reilly D, Allred EN, et al. Child health status, neurodevelopmental outcome, and parental satisfaction in a randomized, controlled trial of nitric oxide for persistent pulmonary hypertension of the newborn. *Pediatrics*. 2001; 107(6):1351-1356.
5. Field D, Elbourne D, Truesdale A, et al. Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: the INNOVO multicentre randomised controlled trial (ISRCTN 17821339). *Pediatrics*. 2005; 115(4):926-936.
6. Hayes Directory. Inhaled Nitric Oxide for the Treatment of Respiratory Failure in Preterm Newborns. February 24, 2009.
7. Hayes Directory. Inhaled Nitric Oxide for the Treatment of Pulmonary Hypertension in Term and Near Term Newborns. January 15, 2009.
8. Hayes Brief, Technology at a Glance. INOmax® (INO Therapeutics) for the Treatment of Pediatric Pulmonary Hypertension. September 9, 2005.
9. Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. *N Engl J Med*. 2006; 355(4):354-364.
10. Kinsella, JP and Abman, SH (2000). Clinical approach to inhaled nitric oxide therapy in the newborn with hypoxemia. *Journal of Pediatrics*, 136 (6) (June, 2000).

11. Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. *J Pediatr*. 1997b; 131(1 Pt 1):55-62.
12. Kinsella, JP, Neish, SR, Shaffer, E, Abman, SH. Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn, *Lancet*, 340, 819-20, 1992.
13. Martin RJ, Walsh MC. Inhaled Nitric Oxide for Preterm Infants — Who Benefits? *N Engl J Med* 353:82, July 7, 2005 *Editorial*.
14. Use of Inhaled Nitric Oxide. Committee on Fetus and Newborn. *Pediatrics*, 106 (2), 344, 2000.
15. Van Meurs KP, Wright LL, Ehrenkranz RA, Lemons JA, Ball MB, Poole WK, Perritt R, Higgins RD, Oh W, Hudak ML, Lupton AR, Shankaran S, Finer NN, Carlo WA, Kennedy KA, Fridriksson JH, Steinhorn RH, Sokol GM, Konduri GG, Aschner JL, Stoll BJ, D'Angio CT, Stevenson DK. Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure. *N Engl J Med* 353:13, July 7, 2005.

#### **Government Agencies, Professional and Medical Organizations**

1. UCSF Children's Hospital at UCSF Medical Center. Intensive Care Nursery House Staff manual. Inhaled Nitric Oxide (iNO). 2004.

#### **Other**

1. INO Therapeutics White Paper. Weaning Neonates from Inhaled Nitric Oxide. 2004.

#### **HISTORY AND REVISIONS**

<b>Date</b>	<b>Action</b>
12/1/2011	<ul style="list-style-type: none"><li>• New template design approved by MPC.</li></ul>
7/21/2011	<ul style="list-style-type: none"><li>• Approved by MPC. No changes.</li></ul>