



MEDICAL COVERAGE POLICY

SERVICE: Inhaled Nitric Oxide in Preterm Infants

Policy Number: 217

Effective Date: 01/01/2020

Last Review: 10/31/2019

Next Review Date: 10/31/2020

Important note:

Unless otherwise indicated, this policy will apply to all lines of business.

Even though this policy may indicate that a particular service or supply may be considered medically necessary and thus covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage (EOC) or Summary Plan Description (SPD) to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Medicare-linked plan members, this policy will apply unless there are Medicare policies that provide differing coverage rules, in which case Medicare coverage rules supersede guidelines in this policy. Medicare-linked plan policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS's Coverage Issues Manual can be found on the CMS website. Similarly, for Medicaid-linked plans, the Texas Medicaid Provider Procedures Manual (TMPPM) supersedes coverage guidelines in this policy where applicable.

SERVICE: Inhaled Nitric Oxide Use in Preterm Infants

PRIOR AUTHORIZATION: Not required.

POLICY:

Inhaled nitric oxide (iNO) may be considered medically necessary as a component of treatment of hypoxic respiratory failure in neonates born at more than 34 weeks of gestation and in the absence of congenital diaphragmatic hernia.

Use of iNO therapy for more than 4 days is subject to medical necessity review.

Other indications for iNO are unproven or investigational, including, but not limited to, its use in premature neonates born at less than or equal to 34 weeks of gestation, adults and children with acute hypoxemic respiratory failure.

OVERVIEW:

Nitric oxide is a colorless, odorless, gas. iNO is a selective pulmonary vasodilator whose mechanism of action involves guanylyl cyclase activation leading to production of cyclic guanosine monophosphate and subsequent smooth muscle relaxation. There are several physiologic effects that make iNO an appealing therapy for infants with pulmonary hypertension: iNO can decrease pulmonary vascular resistance, improve ventilation-perfusion inequalities, and reduce right-to-left intra-cardiac shunting of blood through the foramen ovale and ductus arteriosus, all of which can contribute to improved arterial oxygenation and hemodynamic stability.

INOMax™, a commercially available inhaled nitric oxide product, is FDA-approved for use in term and near-term neonates with hypoxic respiratory failure along with respiratory support and other appropriate treatments. INOMax™ received U.S. Food and Drug Administration (FDA) approval in 1999 for the following indication: "INOMax™, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension."

The primary clinical indication for iNO, in conjunction with ventilatory support and other medical interventions, is hypoxic respiratory failure secondary to persistent pulmonary hypertension in the

MEDICAL COVERAGE POLICY

SERVICE: Inhaled Nitric Oxide in Preterm Infants

Policy Number: 217

Effective Date: 01/01/2020

Last Review: 10/31/2019

Next Review Date: 10/31/2020

neonate born at more than 34 weeks gestation. 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.

The American Academy of Pediatrics (AAP) Committee on Fetus and Newborn (2000) recommendations for iNO for the treatment of neonates born at or near term with hypoxic respiratory failure included 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 (AARC): Based on a systematic review of the literature, the AARC (2010) published evidence-based clinical practice guidelines for iNO for neonates with acute hypoxic respiratory failure. Some of the recommendations included:

1. A trial of iNO is recommended in newborns (≥ 34 wk gestation, < 5 days old and treated for a maximum of 14 days) with $\text{PaO}_2 < 100$ mm Hg on $\text{FiO}_2 1.0$ 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.



MEDICAL COVERAGE POLICY

SERVICE: Inhaled Nitric Oxide in Preterm Infants

Policy Number:	217
Effective Date:	01/01/2020
Last Review:	10/31/2019
Next Review Date:	10/31/2020

- It is recommended that iNO should not be used routinely in newborns with congenital diaphragmatic hernia as some research has shown that INO may cause outcomes to be worse in newborns with congenital diaphragmatic hernia.
- 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.
- It is suggested that there is insufficient data to support the routine use of iNO therapy in postoperative management of hypoxic term or near-term infants with congenital heart disease.

MANDATES: None

CODES:

Important note:

CODES: Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.

CPT Codes:	
CPT Not Covered:	
ICD10 codes:	I27.0 Primary pulmonary hypertension I27.2 Secondary pulmonary hypertension P07.37- P07.39 Preterm newborn 34-36 complete weeks P28.5 Respiratory failure of newborn P29.30 Pulmonary hypertension of newborn P29.38 Other persistent fetal circulation
ICD10 Not covered:	P27.x Chronic respiratory disease originating in the perinatal period

CMS: There is no NCD or LCD for use of Inhaled Nitric Oxide at this time.

POLICY HISTORY:

Status	Date	Action
New	09/24/2015	New policy
Reviewed	09/29/2016	No changes in coverage
Reviewed	09/19/2017	No changes
Reviewed	08/14/2018	No changes
Reviewed	10/31/2019	No changes

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. SWHP will continue to review clinical evidence related to this policy and may modify it at a later date based upon the evolution of the published clinical evidence. Should additional scientific studies become available and they are not included in the list, please forward the reference(s) to SWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

- American Academy of Pediatrics. Committee on Fetus and Newborn. Use of Inhaled Nitric Oxide. Recommendations. Pediatrics Vol 106, No.2, August 2000. Available @: pediatrics.aappublications.org/content/pediatrics/106/2/344.full. accessed 9/11/2017.



MEDICAL COVERAGE POLICY

SERVICE: Inhaled Nitric Oxide in Preterm Infants

Policy Number: 217

Effective Date: 01/01/2020

Last Review: 10/31/2019

Next Review Date: 10/31/2020

2. American Academy of Pediatrics. Committee on Fetus and Newborn. Use of inhaled nitric oxide in preterm infants. *Pediatrics* 2014;133:1 165-170.
3. American Association for Respiratory Care (AARC). Evidence-based clinical practice guideline: inhaled nitric oxide for neonates with acute hypoxic respiratory failure. 2010. Accessed 9/8/17. Available at URL address: <http://www.rcjournal.com/cpgs/index.cfm>
4. Cole FS, Alleyne C, Barks JD, et al. NIH Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. *Pediatrics*. 2011;127(2):363–369
5. Kinsella JP, Cutter GR, Steinhorn RH, Nelin LD, Walsh WF, Finer NN, Abman SH. Noninvasive inhaled nitric oxide does not prevent bronchopulmonary dysplasia in premature newborns. *J Pediatr*. 2014 Dec;165(6):1104-1108.
6. Recommendations for the Use of Inhaled Nitric Oxide Therapy in Premature Newborns with Severe Pulmonary Hypertension. Kinsella JP, Steinhorn RH, Krishnan US, Feinstein JA, Adatia I, Austin ED, Rosenzweig EB, Everett AD, Fineman JR, Hanna BD, Hopper RK, Humpl T, Ivy DD, Keller RL, Mullen MP, Raj JU, Wessel DL, Abman SH. *J Pediatr*. 2016 Mar;170:312-4. doi: 10.1016/j.jpeds.2015.11.050. Epub 2015 Dec 15. PMID: 26703869
7. Early inhaled nitric oxide in preterm infants <34 weeks with evolving bronchopulmonary dysplasia. Jiang Q, Gao X, Liu C, Chen D, Lin X, Xia S, Zhuang D, Yang C, Zhu W, Liu L, Chen C, Sun B. *J Perinatol*. 2016 Jul 21. doi: 10.1038/jp.2016.112. PMID: 27442155
8. American Academy of Pediatrics. Maduekwe E, DeCristofaro JD., *Neoreviews*, March 2017, Volume 18/Issue 3 section on Inhaled Nitric Oxide. Available at http://neoreviews.aappublications.org/content/18/3/e173?utm_source=TrendMD&utm_medium=TrendMD&utm_campaign=NeoRev_TrendMD_0. Accessed 9/11/2017.
9. Carey WA, Weaver AL, Mara KC, Clark RH. Inhaled Nitric Oxide in Extremely Premature Neonates With Respiratory Distress Syndrome. *Pediatrics* March 2018, 141 (3) e20173108; DOI: <https://doi.org/10.1542/peds.2017-3108>