MN.028.A Inhaled Nitric Oxide

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Thank you for being a valued provider for members in one or more of our health plans: Jefferson Health Plans Medicare Advantage, Jefferson Health Plans Individual and Family Plans, Jefferson Health Plans CHIP, and/or Jefferson Health Plans EverWell (our Medicaid plan).

PRODUCT VARIATIONS

This policy applies to all Jefferson Health Plans lines of business.

POLICY STATEMENT

Inhaled nitric oxide is considered **medically necessary** for **any** of the following indications:

1. Neonatal Respiratory Failure: Term or near-term infants (at least 34 weeks gestation at birth) with hypoxic respiratory failure or echocardiographic evidence of persistent pulmonary hypertension of the newborn (PPHN) and all of the following:

    - There is failure, intolerance, or contraindication to conventional therapy (e.g., 100% oxygen, mechanical ventilation, sedation), AND
    - There is no evidence of congenital diaphragmatic hernia.

2. Postoperative Management of Pulmonary Hypertension:

    - Use following surgical repair of congenital heart disease, OR
    - Use during management of a pulmonary hypertensive crisis in the postoperative setting.

3. Pulmonary Vasoreactivity Testing:
   - During right heart catheterization in adults or children with suspected pulmonary arterial hypertension (PAH) being evaluated for:
     - Suitability for vasodilator therapy, OR
     - Lung or heart-lung transplantation.

Inhaled nitric oxide for the following indications (not an all-inclusive list) is considered not medically necessary due to insufficient evidence of safety and efficacy:

- Acute bronchiolitis; *or*
- Premature neonates less than or equal to 34 weeks of gestation; *or*
- Acute hypoxemic respiratory failure in children (other than those who meet the medical necessity criteria above) and in adults; *or*
- Acute pulmonary embolism, *or*
- Acute respiratory distress syndrome (including mechanically ventilated individuals) or acute lung injury; *or*
- Bronchopulmonary dysplasia, prevention in preterm infants without hypoxic respiratory failure; *or*
- Improvement of post-operative outcomes in cardiovascular surgeries (except for post-operative management of pulmonary hypertensive crisis in infants and children with congenital heart disease); *or*
- Patients following elective LVAD insertion surgery; *or*
- In lung transplantation, during and/or after graft reperfusion; *or*
- Combined ECMO and iNO treatment; *or*
- Treatment beyond 2 weeks; *or*
- Malaria, adjunctive treatment; *or*
- Sickle cell disease, treatment of vaso-occlusive crises or acute chest syndrome (sickle cell vasculopathy); *or*

- Treatment of COVID-19 related pneumonia, pulmonary hypertension, and respiratory hypoxemia/failure; *or*
- Treatment of mycobacterium and pseudomonas aeruginosa infections in persons with cystic fibrosis; *or*
- Treatment of persons with congenital diaphragmatic hernia; *or*
- Treatment of post-cardiac arrest syndrome; *or*
- Treatment of pulmonary hypertension associated with pulmonary fibrosis; *or*
- Treatment of right heart failure after hemorrhagic shock and trauma pneumonectomy; *or*
- Treatment of traumatic brain injury.

POLICY GUIDELINES

The medical record must reflect the medical necessity for the care provided.

Inhaled nitric oxide (iNO) therapy should be initiated only after all other aspects of care have been optimized, to ensure an accurate assessment of therapeutic response. The goal of therapy should be to wean to the minimum effective dose and discontinue treatment as soon as clinically tolerated, consistent with best practices for all medications. Inhaled nitric oxide has a rapid onset and a very short duration of action; intolerance to dose reduction typically becomes evident within 10 to 15 minutes. Transient declines in oxygenation beyond this window are common and may be attributable to other clinical factors.

Inhaled Nitric Oxide is considered medically necessary for no longer than 14 days if the oxygen desaturation has been resolved.

Use in preterm infants <34 weeks or for longer than 2 weeks will require individual consideration due to exceptional circumstances.

Monitoring during inhaled nitric oxide (iNO) therapy is essential to detect risks such as methemoglobinemia, nitrogen dioxide (NO_2) toxicity, and rebound pulmonary hypertension from abrupt withdrawal.

Inhaled nitric oxide is performed in centers with Level 3 or Level 4 neonatal intensive care units and referral access to extracorporeal membrane oxygenation.

CODING

Note: The Current Procedural Terminology (CPT®), Healthcare Common Procedure Coding System (HCPCS), and the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes that may be listed in this policy are for reference purposes only. Listing of a code in this policy does not imply that the service is covered and is not a guarantee of payment. Other policies and coverage guidelines may apply. When reporting services, providers/facilities should code to the highest level of specificity using the code that was in effect on the date the service was rendered. This list may not be all inclusive.

CPT® is a registered trademark of the American Medical Association.

CPT Code	Description
93463	Pharmacologic agent administration (e.g., 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)

HCPCS Code	Description
N/A	

ICD-10 Codes	Description
I27.0	Primary pulmonary hypertension
I27.20-I27.29	Other secondary pulmonary hypertension
I27.83	Eisenmenger's syndrome
I27.9	Pulmonary heart disease, unspecified
P07.30	Preterm newborn, unspecified weeks of gestation
P07.37-P07.39	Preterm newborn, gestation age 34/35/36 completed weeks

ICD-10 Codes	Description
P22.0-P22.9	Respiratory distress syndrome of newborn
P24.01	Meconium aspiration with respiratory symptoms
P24.11	Neonatal aspiration of (clear) amniotic fluid and mucus with respiratory symptoms
P24.81	Other neonatal aspiration with respiratory symptoms
P24.9	Neonatal aspiration, unspecified
P28.0	Primary atelectasis of newborn
P28.5	Respiratory failure of newborn
P28.9	Respiratory condition of newborn, unspecified
P29.30	Pulmonary hypertension of newborn
P29.38	Other persistent fetal circulation
P36.0-P36.9	Bacterial sepsis of newborn
P84	Other problems with newborn [birth asphyxia]
P91.60-P91.63	Hypoxic ischemic encephalopathy [HIE]
Q33.1	Accessory lobe of lung
Q33.2	Sequestration of lung
Q33.3	Agenesis of lung
Q33.4	Congenital bronchiectasis
Q33.5	Ectopic tissue in lung
Q33.6	Congenital hypoplasia and dysplasia of lung
Q33.8	Other congenital malformations of lung
Q33.9	Congenital malformation of lung, unspecified

BENEFIT APPLICATION

Medical policies do not constitute a description of benefits. This medical necessity policy assists in the administration of the members' benefits which may vary by line of business. Applicable benefit documents govern which services/items are eligible for coverage, subject to benefit limits, or excluded completely from

coverage. This policy is invoked only when the requested service is an eligible benefit as defined in the Member's applicable benefit contract on the date the service was rendered. Services determined by the Plan to be investigational or experimental, cosmetic, or not medically necessary are excluded from coverage for all lines of business.

DESCRIPTION OF SERVICES

Inhaled nitric oxide (iNO) therapy involves the administration of gaseous nitric oxide which dilates pulmonary vessels in ventilated areas and decreases pulmonary vascular resistance. Because nitric oxide affects vascular muscle tone regulation in the pulmonary system, it has become a treatment for hypoxemic respiratory failure which is associated with high pulmonary vascular pressure.

iNO is used as one of the treatments for newborns with hypoxic respiratory failure to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO). iNO may be a treatment option for the postoperative management of pulmonary hypertension associated with heart or lung surgery in infants. While iNO is generally considered safe, it results in increased levels of methemoglobin and has been associated with a more than eight-fold risk of childhood cancer (Dixon et al., 2018). These possible harms should be weighed against the demonstrated benefits in selected populations of infants.

Hypoxic respiratory failure can occur in infants of all gestational ages. In the preterm infant, respiratory failure typically presents secondary to an insufficiency of surfactant, a soap-like material that lines the air-spaces of the lungs. Respiratory failure in the term and near-term newborn can result from conditions such as sepsis, meconium aspiration at birth, pulmonary hypoplasia, or congenital diaphragmatic hernia (CDH). These conditions can cause elevated pressure in the pulmonary vessels. The classic characteristics of persistent pulmonary hypertension of the newborn (PPHN) include increased pulmonary vascular resistance, right-to-left shunting, and severe hypoxemia (McLaughlin et al., 2009).

Treatment of the preterm infant (born at less than 34 weeks gestation) with respiratory failure usually involves administration of exogenous surfactant and mechanical ventilation. In the term and near-term (≥ 34 weeks gestation) newborn, management of acute respiratory failure could also include administration of oxygen, continuous positive airway pressure, conventional or high-frequency ventilation, pharmacological intervention, or ECMO using a heart/lung machine.

For the above conditions, iNO has not been scientifically demonstrated to be as safe and effective as conventional treatment.

Hypoxic respiratory failure is defined as an oxygenation index (OI) of at least 25 on 2 measurements done 15 minutes apart.

The oxygenation index [OI] is calculated as the mean airway pressure times 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. It is used in iNO research trials to identify study participants with severe hypoxic respiratory failure.

In clinical practice, an OI may not be available in neonates due to lack of arterial access. Alternative non-invasive measures such as pulse oximetry, ventilator data, transcutaneous CO2 monitoring, and echocardiograms are often used to define respiratory failure and pulmonary hypertension to avoid multiple invasive arterial blood draws.

Contraindications

Neonates dependent on right-to-left shunting of blood

Precautions/Warnings

Rebound Pulmonary Hypertension Syndrome following Abrupt Discontinuation: Wean from nitric oxide. Abrupt discontinuation of nitric oxide may lead to worsening oxygenation and increasing pulmonary artery pressure, i.e., Rebound Pulmonary Hypertension Syndrome. Signs and symptoms of Rebound Pulmonary Hypertension Syndrome include hypoxemia, systemic hypotension, bradycardia, and decreased cardiac output. If Rebound Pulmonary Hypertension occurs, reinstate nitric oxide therapy immediately.

Hypoxemia from Methemoglobinemia: Nitric oxide combines with hemoglobin to form methemoglobin, which does not transport oxygen. Methemoglobin levels increase with the dose of nitric oxide; it can take 8 hours or more before steady-state methemoglobin levels are attained. Monitor methemoglobin and adjust the dose of nitric oxide to optimize oxygenation. If methemoglobin levels do not resolve with decrease in dose or discontinuation of nitric oxide, additional therapy may be warranted to treat methemoglobinemia.

Airway Injury from Nitrogen Dioxide: Nitrogen dioxide (NO2) forms in gas mixtures containing NO and O2. Nitrogen dioxide may cause airway inflammation and damage to lung tissues. If there is an unexpected change in NO2 concentration, or

if the NO2 concentration reaches 0.5 ppm when measured in the breathing circuit, then the delivery system should be assessed in accordance with the Nitric Oxide Delivery System's Manual troubleshooting section, and the NO2 analyzer should be recalibrated. The dose of nitric oxide and/or FiO2 should be adjusted as appropriate.

Worsening Heart Failure: Patients with left ventricular dysfunction treated with nitric oxide may experience pulmonary edema, increased pulmonary capillary wedge pressure, worsening of left ventricular dysfunction, systemic hypotension, bradycardia and cardiac arrest. Discontinue nitric oxide while providing symptomatic care.

CLINICAL EVIDENCE

Efficacy:

The efficacy of iNO in the treatments for newborns with hypoxic respiratory failure setting is supported by randomized trials and meta-analyses demonstrating that iNO improves oxygenation and reduces the need for ECMO in term and late preterm infants with severe PPHN (OI ≥25) . In a meta-analysis of seven trials involving 815 term and near term neonates with severe hypoxic respiratory failure, iNO reduced the need for ECMO compared with control (31 versus 51 percent; risk ratio [RR] 0.6, 95% CI 0.5-0.71) .Mortality was similar in both groups (11 versus 12 percent, respectively). In the two trials (n=301) that reported outcomes at 18 to 24 months of age, both treatment groups had similar rates of neurodevelopmental disability (26 and 27 percent, respectively).

DEFINITIONS

Inhaled Nitric Oxide (iNO) is a selective pulmonary vasodilator used to reduce pulmonary artery pressure and improve oxygenation, particularly in neonates with hypoxic respiratory failure or in other critically ill patients when rapid, targeted pulmonary vasodilation is needed.

Pulmonary Hypertension is abnormally elevated blood pressure within the pulmonary circulation.

Methemoglobinemia is a blood disorder where there's a higher-than-normal level of methemoglobin in the blood. Methemoglobin is a form of hemoglobin that can't carry oxygen effectively, leading to reduced oxygen delivery to the body's tissues.

DISCLAIMER

Approval or denial of payment does not constitute medical advice and is neither intended to guide nor influence medical decision making. Policy Bulletins are developed to assist in administering plan benefits and constitute neither offers of coverage nor medical advice. This Policy Bulletin may be updated and therefore is subject to change.

For Jefferson Health Plans EverWell and Jefferson Health Plans CHIP products: Any requests for services that do not meet criteria set in PARP will be evaluated on a case-by-case basis.

POLICY HISTORY

This section provides a high-level summary of changes to the policy since the previous version.

Summary	Version	Version Date
2026 Annual Review. Revisions to policy guideline statement. References updated.	A	02/09/2026
New Policy	A	02/09/2026

REFERENCES

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2. Mayo clinic Nitric oxide (inhalation route): https://www.mayoclinic.org/drugs-supplements/nitric-oxide-inhalation-route/description/drg-20060881

3. National Library of Medicine (NIH) Inhaled nitric oxide: https://pmc.ncbi.nlm.nih.gov/articles/PMC6295404/

4. Guidelines for Rational and Cost-Effective Use of iNO Therapy in Term and Preterm Infants https://pmc.ncbi.nlm.nih.gov/articles/PMC3743146/

5. INOMAX:https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020845s020lbl.pdf

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7. 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 1997; 131:55.

8. Kinsella JP, Steinhorn RH, Krishnan US, et al. Recommendations for the Use of Inhaled Nitric Oxide Therapy in Premature Newborns with Severe Pulmonary Hypertension. J Pediatr 2016; 170:312.

9. Cole FS, Alleyne C, Barks JD, et al. NIH Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. Pediatrics 2011; 127:363.

10. Persistent pulmonary hypertension of the newborn (PPHN): Management and outcome- Ann R Stark, MD, Eric C Eichenwald, MD; UpToDate; last updated: Mar27, 2026