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Subject: Inhaled Nitric Oxide

THIS MEDICAL COVERAGE GUIDELINE IS NO T AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Inhaled nitric oxide (INO) is a natural vasodilator and has been studied for a variety of types of respiratory failure. Three products have been approved by the US Food and Drug Administration (FDA) – INOmax (December 1999), Noxivent (October 2018), and GeNOsyl (December 2019). Noxivent is a "generic" version of INOmax and was approved via an abbreviate new drug application (ANDA) and is considered therapeutically equivalent. However, Noxivent is only to be administered using a NOxBOXi system. GeNOsyl was approved via a new drug application (NDA) and must only be administered using a calibrated Genosyl Delivery System (a tankless, portable INO system that eliminates the need for large nitric oxide tanks). In June 2022, the first nitric oxide generator and delivery system, LungFit PH, was approved by the FDA as a medical device. LungFit PH generates on-demand nitric oxide from ambient air using patented ionizer technology and delivers it to a ventilator circuit, regardless of dose or flow. Using a compressor, LungFit PH drives room air through a plasma chamber of electrical pulses equivalent to a 60 W lightbulb to ionize the nitrogen and oxygen molecules to create nitric oxide, which is then passed through a filter removing the toxic nitrogen dioxide. For all four products, the only FDA-approved indication is "to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents. It is also proposed as a treatment for premature infants, critically ill children and adults with respiratory failure, as well as in the postoperative management of children undergoing repair of congenital heart disease and patients after lung transplantation to prevent or reduce reperfusion injury.

Hypoxic respiratory failure may result from respiratory distress syndrome, persistent pulmonary hypertension, meconium aspiration, pneumonia, or sepsis. Its treatment typically includes oxygen support, mechanical ventilation, induction of alkalosis, neuromuscular blockade, or sedation. INO is both

a vasodilator and a mediator in many physiologic and pathologic processes. INO has also been proposed for use in preterm infants less than 34 weeks of gestation.

There are several potential uses for INO in surgery. One is the proposed use of INO to manage pulmonary hypertension after cardiac surgery in infants and children with congenital heart disease. In congenital heart disease patients, increased pulmonary blood flow can cause pulmonary hypertension. Cardiac surgery can restore the pulmonary vasculature to normal, but there is the potential for complications, including postoperative pulmonary hypertension, which can prevent weaning from ventilation and is associated with substantial morbidity and mortality. Another potential surgical application is use of INO in lung transplantation to prevent or reduce reperfusion injury.

Inhaled nitric oxide (INO) appears to be of greatest benefit in individuals for whom primary or secondary pulmonary hypertension is a component of hypoxic respiratory failure. The benefit of INO appears limited in term or near-term infants whose hypoxic respiratory failure is due to diaphragmatic hernia.

POSITION STATEMENT:

Inhaled nitric oxide (including nitric oxide generated from room air by a device such as the LungFit PH system) **meets the definition of medical necessity** for **ALL** of the following indications:

- As a component of treatment for hypoxic respiratory failure in neonates born at more than 34 weeks of gestation* **AND BOTH** of the following:
    - The neonate does **NOT** have an unrepaired congenital diaphragmatic hernia
    - Conventional therapies (e.g., administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, induction of alkalosis, neuromuscular blockade, and sedation) have failed or are expected to fail
- Management of post-operative pulmonary hypertension in infants and children following heart or lung surgery during the acute recovery phase*
- As a method of assessing pulmonary vasoreactivity in children and adults with pulmonary hypertension

  **NOTE: Inhaled nitric oxide should be discontinued if no clinical improvement or echocardiographic improvement (e.g., reduced estimated pulmonary artery pressure, improved right ventricle function, decreased right-to-left shunting) is observed within 24 hours of beginning treatment (i.e., use of inhaled nitric oxide beyond 24 hours requires evidence of initial clinical or echocardiographic improvement)*

Inhaled nitric oxide (including nitric oxide generated from room air by a device such as the LungFit PH system) is considered **experimental or investigational** for all other indications, including but not limited to the conditions below, as data in published medical literature are inadequate to permit scientific conclusions on long-term and net health outcomes:

- Treatment of premature neonates born at less than or equal to 34 weeks of gestation with hypoxic respiratory failure
- Treatment of adults and children (other than those who meet the medical necessity criteria above) with acute hypoxemic respiratory failure
- Treatment of acute respiratory distress syndrome (ARDS) or acute lung injury

- Acute treatment of sickle cell vaso-occlusive crisis (pain crises)
- Postoperative use in adults with congenital heart disease
- In lung transplantation, during and/or after graft reperfusion

DOSAGE/ADMINISTRATION:

FDA-approved

INO Gases

- Indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents
- The recommended dose is 20 ppm, maintained for up to 14 days or until the underlying oxygen desaturation has resolved. Doses greater than 20 ppm are not recommended. Avoid abrupt discontinuation.

LungFit PH System

- Indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.
- The LungFit PH is intended to deliver nitric oxide (NO), a vasodilator, generated by the device into the inspiratory limb of the patient breathing circuit of a ventilator in a way that provides a constant concentration of nitric oxide, as set by the user, to the patient throughout the inspired breath. The LungFit PH provides continuous integrated monitoring of inspired oxygen (O2), nitrogen dioxide (NO2) and nitric oxide (NO), and a comprehensive alarm system. The LungFit PH system includes an integrated backup NO delivery system that is a completely independent backup NO generating system; it has its own NO generator and gas flow delivery system. The backup flow is delivered at 1 L/min at 220ppm NO to either a ventilator circuit or to a bagging system, depending upon the user selected setting.

Drug Availability

- Genosyl
    - 800 ppm concentration ion 216 liter-containing delivery system cassettes
- INOmax
    - 800 ppm concentration in 353 liter-containing (Size D) and 1963 liter-containing (Size 88) cylinders
- LungFit PH System
    - The device consists of an NO generator module for generating nitric oxide from room air and delivering it to a ventilator breathing circuit in a controlled concentration, a nitric oxide delivery module (NDM) for measuring the gas flow rate in the ventilator breathing circuit, a gas monitoring module for measuring the gas concentrations of NO, nitrogen dioxide (NO2) and oxygen (O2) in the breathing circuit just prior to inhalation by the patient and an integrated

backup NO delivery module used to bag the patient or in case the main NO generator module fails. In addition, there is an NO2 filter that removes NO2 from the NO gas prior to delivering it to the breathing circuit. The NO2 filter has a radio-frequency identification (RFID) tag that keeps a record of how much time is left on the filter before it needs to be changed and communicates that information to the main delivery system.

- Noxivent
  - 100 ppm concentration in 323 liter-containing and 2082 liter-containing cylinders
  - 800 ppm concentration in 323 liter-containing and 2082 liter-containing cylinders

PRECAUTIONS:

Boxed Warning

- None

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.

BILLING/CODING INFORMATION:

HCPCS Coding:

J3490	Unclassified drugs [for the nitric oxide gases ONLY]

ICD-10 Diagnoses Codes That Support Medical Necessity

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
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

ICD-10-PCS Procedure Code

3E0F7SD	Introduction of Nitric Oxide Gas into Respiratory Tract, Via Natural or Artificial Opening

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

Congenital diaphragmatic hernia (CDH): Herniation (bulging, looping) of the abdominal or retroperitoneal structures into the thorax, present at birth.

Hypoxic respiratory failure: A condition of under-oxygenation; an inadequate level of tissue oxygenation for cellular metabolism. Symptoms include dyspnea and tachypnea.

Hypoxemia: abnormally low arterial oxygen levels.

Meconium: A fetus or newborn's first feces (a dark green mucous material); typically passed in the uterus during early pregnancy and again in the first few days after birth.

Meconium aspiration syndrome (MAS): Inhalation of meconium by the fetus or newborn, which may block the newborn's airways right after birth. It can cause respiratory difficulty due to inflammation in the lungs after birth.

Pulmonary hypertension: High blood pressure in the arteries to the lungs. The blood vessels that carry blood from the heart to the lungs become hard and narrow, causing the heart to work harder to pump the blood. Over time, the heart weakens and cannot do its job, resulting in heart failure.

Neonatal respiratory distress syndrome (RDS): Condition of the newborn marked by dyspnea with cyanosis, often caused by a lack of surfactant in the lungs, or by genetic problems with lung development.

RELATED GUIDELINES:

None

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 09/11/24.

GUIDELINE UPDATE INFORMATION:

04/15/01	New Medical Coverage Guideline.
09/27/01	Medical Coverage Guideline reviewed.
01/01/02	HCPCS changes.
10/15/03	Scheduled review; no change in coverage statement.
01/15/06	Revision - additional reference added.
04/01/07	2nd Quarter HCPCS coding update; deleted S1025.
12/15/17	Medical Coverage Guideline returned to active status. Revised MCG title, description section, position statement, program exceptions, and definitions. Updated references.
10/15/18	Unscheduled review. Revised position statement; added coverage for post-operative pulmonary hypertension and assessment of pulmonary vasoreactivity. Updated references.
10/15/19	Scheduled review. Maintained position statement, revised index terms, and updated references.
10/15/20	Review and revision to guidelines consisting of updating the description, position statement, billing/coding, and references. Added new sections of dosage/administration and precautions. Policy number changed due to transition to a pharmacy MCG.
01/01/22	Review and revision to guidelines consisting of updating the references.
10/15/22	Review and revision to guidelines consisting of updating the references.
10/15/23	Review and revision to guidelines consisting of updating the position statement, dosage/administration, billing/coding, and references. Clarified the appropriate timing for post-op INO use in infants and children following heart or lung surgery. Added the LungFit PH nitric oxide generating system as in scope of this guideline.
10/15/24	Review and revision to guidelines consisting of updating the billing/coding and references.