Applicable To:

- ☑ Medicaid – excluding Arizona and Kentucky
- ☑ Florida CMS Health Plan

Claims and Payment Policy:
INHALED NITRIC OXIDE (iNO)THERAPY IN INFANTS

Policy Number: CPP- 135

Original Effective Date: 6/6/2019
Revised Effective Date(s): N/A

BACKGROUND

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. 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.

Persistent pulmonary hypertension (PPHN) occurs primarily in term or late preterm infants (gestational age [GA] ≥34 weeks). It is caused by abnormalities of the pulmonary vasculature that include underdevelopment, maldevelopment (ie, abnormally thick pulmonary arteriolar musculature), and maladaption (abnormal vasoconstriction that interferes with the normal postnatal fall in PVR).

Infants with PPHN generally present with cyanosis and respiratory distress (e.g., tachypnea). PPHN is associated with prenatal risk factors (fetal heart rate abnormalities and meconium-stained amniotic fluid), and a variety of primary respiratory disorders, such as meconium aspiration syndrome (MAS), pneumonia, respiratory distress syndrome (RDS), congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia.

Initial testing includes pulse oximetry assessment, which may demonstrate a significant difference (>10 percent) between pre- and postductal oxygen saturation, chest radiograph, which is typically normal in patients without another pulmonary condition, and an echocardiogram.

The diagnosis of PPHN should be considered in any neonate, especially term infants, with severe cyanosis, and is confirmed by echocardiography. In PPHN, the echocardiogram demonstrates normal structural cardiac anatomy and evidence of pulmonary hypertension (ie, flattened or displaced ventricular septum, or evidence of elevated pulmonary arterial pressure). The differential diagnosis of PPHN includes cyanotic congenital heart disease (CHD), primary pulmonary disorders, and sepsis.

Original Effective Date: 06/06/2019 - Revised: N/A
PRO_48154E Internal/State Approved 04022020 NA9PROWEB48154E_0000

The management of PPHN consists of general supportive cardiorespiratory care, therapy directed towards associated pulmonary conditions, and in patients with severe PPHN, pulmonary vasodilatory agents (eg, inhaled nitric oxide [iNO]) and extracorporeal membrane oxygenation (ECMO). The standard approach to treating infants with PPHN includes:

- Because oxygen is a pulmonary vasodilator, supplemental oxygen is recommended and should be initially administered in a concentration of 100 percent to infants with PPHN in an attempt to reverse pulmonary vasoconstriction (Grade 1A). PaO2 should be maintained subsequently in the range of 50 to 90 mmHg (preductal oxygen saturation 90 to 95 percent) to minimize lung toxicity. The oxygenation index (OI) is used to assess the severity of hypoxemia in PPHN and is used to determine whether additional interventions (e.g., iNO and ECMO) are warranted.
- Mechanical ventilation to initially maintain PaCO2 between 40 and 50 mmHg, as hypercarbia and acidosis increase PVR.
- Maintenance of adequate systemic blood pressure by providing sufficient vascular volume and the use of inotropic agents.
- For term and preterm infants with a gestational age greater than 34 weeks with severe PPHN (defined as an OI ≥25), iNO is recommended to be administered at a dose of 20 ppm.
- Because data regarding efficacy and safety are insufficient, we do not recommend enteral sildenafil as initial therapy if iNO is available (Grade 1C). It may be considered in a resource-limited setting.
- In those who have an OI ≥40 despite the use of iNO and high ventilatory support, ECMO is recommended.
- Blood cultures should be obtained and empiric antimicrobial therapy initiated.
- Survivors of severe PPHN and/or ECMO treatment are at increased risk of developmental delay, motor disability, and hearing deficits.

Oxygenation index — The oxygenation index (OI) is most commonly used in neonates with persistent pulmonary hypertension of the newborn to determine the severity of hypoxemia and to guide the timing of interventions, such as inhaled nitric oxide [9,10]. The OI is calculated as follows (calculator 2):
OI = [mean airway pressure x FiO2 ÷ PaO2] x 100
A high OI (eg, ≥25) indicates severe hypoxemic respiratory failure. (See "Persistent pulmonary hypertension of the newborn".)

POSITION STATEMENT

Coverage

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

1. Neonate must be term and near-term, >= 34 weeks gestational age; **AND,**
2. Cyanosis and respiratory distress with tachypnea; **AND,**
3. Hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension; **AND,**
4. Conventional therapies such as o2 support and mechanical ventilation failed; **AND,**
5. Pulmonary vascular resistance >=25 vs. 14 mm Hg in normal cases.

* 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.

Exclusions

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

Original Effective Date: 06/06/2019 - Revised: N/A
PRO_48154E Internal/State Approved 04022020 NA9PROWEB48154E_0000

- Neonate must be term and near-term, >= 34 weeks gestational age; AND,
- Oxygenation Index >= 25 associated with clinical or echocardiographic evidence of pulmonary hypertension; AND,
- Conventional therapies such as oxygen support and mechanical ventilation failed

CODING & BILLING

Covered ICD-10-CM Diagnosis Codes

P28.5 Respiratory failure of newborn
P29.3 Persistent fetal circulation
P07.36 Preterm newborn, gestational age 33 completed weeks
P07.37 Preterm newborn, gestational age 34 completed weeks
P07.38 Preterm newborn, gestational age 35 completed weeks
P07.39 Preterm newborn, gestational age 36 completed weeks
P22.0 Respiratory distress syndrome of newborn

CPT© Code – No applicable codes.

HCPCS Level II ©Code – No applicable codes.

ICD-10-PCS (Inpatient Only)

Refer to the following ICD-10-PCS table(s) for specific code assignment based on physician documentation.

NOTE: Per ICD-10-PCS Coding Guidelines, "ICD-10-PCS codes are composed of seven characters. Each character is an axis of classification that specifies information about the procedure performed. Within a defined code range, a character specifies the same type of information in that axis of classification. One of 34 possible values can be assigned to each axis of classification in the seven-character code".

3E0F3SD Introduction of Gas into respiratory tract, percutaneous approach
3E0F7SD Introduction of Gas into respiratory tract via natural or artificial opening
3E0F8SD Introduction of Gas into respiratory tract via natural or artificial opening endoscopic

Coding information is provided for informational purposes only. The inclusion or omission of a CPT, HCPCS, or ICD-10 code does not imply member coverage or provider reimbursement. Consult the member's benefits that are in place at time of service to determine coverage (or non-coverage) as well as applicable federal / state laws.

DEFINITIONS

Acidosis	Occurs when the body produces too much acid or elimination through the kidney is limited due to an underlying conditions like renal failure. Commonly noted symptoms are rapid breathing, confusion, tiredness, shock or even death in severe cases. Aim at treating the underlying health problem or use alkalinizing agents like sodium bicarbonate (baking soda) and fluids to restore acid-base balance.
Congenital heart disease	A malformation of the heart, aorta, or other large blood vessels that is the most frequent form of major birth defect in newborns.
Cyanosis	A bluish discoloration of the skin resulting from poor circulation or inadequate oxygenation of the blood.

Original Effective Date: 06/06/2019 - Revised: N/A
PRO_48154E Internal/State Approved 04022020 NA9PROWEB48154E_0000

Echocardiogram	A test of the action of the heart using ultrasound waves to produce a visual display, used for the diagnosis or monitoring of heart disease.
Extracorporeal membrane oxygenation (ECMO)	A treatment that uses a pump to circulate blood through an artificial lung back into the bloodstream of a very ill baby. This system provides heart-lung bypass support outside of the baby's body. It may help support a child who is awaiting a heart or lung transplant.
Hypercarbia	The presence of an abnormally high level of carbon dioxide in the circulating blood.
Hypoxemia	An abnormally low concentration of oxygen in the blood.
Maladaption	Failure to adjust adequately or appropriately to the environment or situation.
Maldevelopment	Faulty or imperfect development.
Meconium aspiration syndrome (MAS)	The aspiration of stained amniotic fluid**,** which can occur before, during, or immediately after birth. Meconium is the first intestinal discharge from newborns, a viscous, dark-green substance composed of intestinal epithelial cells, lanugo, mucus, and intestinal secretions (eg, bile).
Nitric oxide (NO) inhalation therapy	A minimally invasive treatment that involves inhalation of gaseous NO in conjunction with ventilatory support.
Persistent pulmonary hypertension (PPHN)	The failure of the normal circulatory transition that occurs after birth**.** It is a syndrome characterized by marked pulmonary hypertension that causes hypoxemia secondary to right-to-left shunting of blood at the foramen ovale and ductus arteriosus.
Preterm Infant	A premature infant is a baby born before 37 completed weeks of gestation (more than 3 weeks before the due date).
Pulmonary hypoplasia	An incomplete development of the lungs, resulting in an abnormally low number or size of bronchopulmonary segments or alveoli. A congenital

Original Effective Date: 06/06/2019 - Revised: N/A
PRO_48154E Internal/State Approved 04022020

	malformation, it most often occurs secondary to other fetal abnormalities that interfere with normal development of the lungs. Primary pulmonary hypoplasia is rare and usually not associated with other maternal or fetal abnormalities.
Pulmonary Vascular Resistance (PVR)	The resistance that must be overcome to push blood through the circulatory system and create flow. The resistance offered by the systemic circulation is known as the systemic vascular resistance (SVR) or may sometimes be called by the older term total peripheral resistance (TPR), while the resistance offered by the pulmonary circulation is known as the pulmonary vascular resistance (PVR).
Respiratory distress syndrome (RDS)	Formerly known as hyaline membrane disease, a syndrome of respiratory difficulty in newborn infants caused by a deficiency of a molecule called surfactant**.** RDS almost always occurs in newborns born before 37 weeks of gestation.
Respiratory failure of newborn	Results from inadequate gas exchange by the respiratory system, meaning that the arterial oxygen, carbon dioxide or both cannot be kept at normal levels. Respiratory failure is classified as either Type 1 or Type 2, based on whether there is a high carbon dioxide level. The definition of respiratory failure in clinical trials usually includes increased respiratory rate, abnormal blood gases, and evidence of increased work of breathing. Respiratory failure causes an altered mental status due to ischemia in the brain.
Tachypnea	abnormally rapid breathing
Sepsis	Sepsis is a potentially life-threatening condition caused by the body's response to an infection. The body normally releases chemicals into the bloodstream to fight an infection. Sepsis occurs when the body's response to these chemicals is out of balance, triggering changes that can damage multiple organ systems. If sepsis progresses to septic shock, blood pressure drops dramatically. This may lead to death.

REFERENCES

1. Inhaled nitric oxide for the treatment of respiratory failure in preterm newborns. Hayes Directory Web site. http://www.hayesinc.com. Published February 24, 2009 (archived February 15, 2014). Accessed March 12, 2019.
2. Inhaled nitric oxide for the treatment of pulmonary hypertension in term and near term newborns. Hayes Directory Web site. http://www.hayesinc.com. Published January 15, 2009 (archived February 15, 2014). Accessed February 6, 2018.
3. National Institutes of Health. (2010). Consensus development conference statement on inhaled nitric oxide therapy for premature infants. Retrieved from http://consensus.nih.gov/2010/docs/ino/iNO%20Final%20Statement.pdf. Accessed February 6, 2018.
4. Persistent pulmonary hypertension of the newborn. https://www.uptodate.com/contents/persistent-pulmonary-hypertension-of-the-newborn?csi=2d1354e9-6ca9-434a-9f36-c960e64ec663&source=contentShare April 2019.

IMPORTANT INFORMATION ABOUT THIS DOCUMENT

Claims and Payment Policies (CPPs) are policies regarding claims or claim line processing and/or reimbursement related to the administration of health plan benefits. They are not recommendations for treatment, nor should they be used as treatment guidelines. Providers are responsible for diagnosing, treating, and making clinical recommendations to the member. CPPs are subject to, but not limited to, the following:

- State and federal laws and regulations;
- Policies and procedures promulgated by the Centers for Medicare and Medicaid Services, including National Coverage Determinations and Local Coverage Determinations;
- The health plan's contract with Medicare and/or a state's Medicaid agency, as applicable;
- Other CPPs and clinical policies as applicable including, but not limited to, *Pre-Payment and Post-Payment Review*.
- The provisions of the contract between the provider and the health plan; and
- The terms of a member's particular benefit plan, including those terms outlined in the member's Evidence of Coverage, Certificate of Coverage, and other policy documents.

In the event of a conflict between a CPP and a member's policy documents, the terms of a member's benefit plan will always supersede the CPP.

The use of this policy is neither a guarantee of payment, nor a prediction of how a specific claim will be adjudicated. Any coding information is for informational purposes only. No inference should be made regarding coverage or provider reimbursement as a result of the inclusion, or omission, in a CPP of a CPT, HCPCS, or ICD-10 code. Always consult the member's benefits that are in place at time of service to determine coverage or non-coverage. Claims processing is subject to a number of factors, including the member's eligibility and benefit coverage on the date of service, coordination of benefits, referral/authorization requirements, utilization management protocols, and the health plan's policies. Services must be medically necessary in order to be covered.

References to other sources and links provided are for general informational purposes only, and were accurate at the time of publication. CPPs are reviewed annually but may change at any time and without notice, including the lines of business for which they apply. CPPs are available at www.wellcare.com. Select the "Provider" tab, then "Tools" and then "Payment Guidelines".

RULES, PRICING & PAYMENT COMMITTEE HISTORY AND REVISIONS

Date	Action
10/30/2019	• Approved by RGC

Original Effective Date: 06/06/2019 - Revised: N/A
PRO_48154E Internal/State Approved 04022020