POLICY AND PROCEDURE MANUAL

Policy Title: Inhaled Nitric Oxide	**Policy Number: B.07**
Primary Department: Medical Management **Affiliated Department(s): N/A**	**NCQA Standard: N/A** **URAC Standard: N/A**
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Applicable Lines of Business: ☐MeridianCare ☒MeridianHealth ☐MeridianComplete ☒MeridianChoice	
Applicable States: ☐All ☒MI ☒IL ☐OH ☐_____ ☐_____	
Applicable Programs: ☒All ☐Other _____	
Policy is to be published: Internally Only ☐ Internally & Externally ☒	

Definitions:

Inhaled Nitric oxide(iNO)	Acts as a vasodilator which increases blood flow to the tissues and regulates the binding and releasing of oxygen to hemoglobin. When used as an inhalant to treat persistent pulmonary hypertension (PPHN) nitric oxide produces selective pulmonary vasodilatation and redistributes pulmonary blood flow from areas of the lung with low gas exchange capability (decreased ventilation capacity) to the healthier lung tissue with better gas exchange capability, thus improving oxygenation. The effect of iNO and ventilator support on improved oxygenation also reduces the need for the use of extracorporeal membrane oxygenation(ECMO), a more surgically invasive treatment
Acute Respiratory Distress Syndrome (ARDS)	A type of pulmonary (lung) failure that may result from any disease that causes large amounts of fluid to collect in the lungs. ARDS is not itself a specific disease, but a syndrome.
Bronchopulmonary Dysplasia	A chronic lung condition that is caused by tissue damage to the lungs, is marked by inflammation, exudate, scarring, fibrosis, and emphysema, and usually occurs in immature infants who have received mechanical ventilation and supplemental oxygen as treatment for respiratory distress syndrome
Neonate	A neonate is classified as an infant from birth up to 28 days of age.
Hypoxic respiratory failure:	May result from respiratory distress syndrome (RDS), persistent pulmonary hypertension, meconium aspiration, pneumonia, or sepsis. Its treatment typically includes oxygen support, mechanical ventilation, and induction of alkalosis, neuromuscular blockade, or sedation. It is 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 extracorporeal membrane oxygenation

	(ECMO) or dying. An OI of 40 is often used as a criterion to initiate ECMO therapy.
ECMO	Extracorporeal membrane oxygenation is an invasive technique that may be considered in neonates when other therapies fail. It is a procedure that uses a machine to take over the work of the lungs and sometimes the heart. The blood circulates outside of the body with the help of a machine that puts oxygen into the blood and takes out carbon dioxide just like the lungs. The goal of ECMO is to insure that body has enough oxygen by taking over the workload of reversible heart and/or lung disorders. The member can be on ECMO for several days to a few weeks. When the heart or the lungs have healed and can work on their own, the support from ECMO is gradually removed. Members with severe but reversible heart or lung disorders that have not responded to the usual treatments of mechanical ventilation, medications and oxygen therapy are candidates for ECMO.

Policy:
Inhaled nitric oxide may be medically necessary when administered as a component of treatment of hypoxic respiratory failure in neonates born at 34 or more weeks of gestation.

Criteria for Coverage:
Inhaled nitric oxide (iNO) is considered therapy medically necessary as a component of the treatment of hypoxic respiratory failure in term and near-term (born at 34 or more weeks of gestation) neonates with clinical and or echocardiographic evidence of persistent pulmonary hypertension of the newborn syndrome when both of the following criteria are met:

1. When conventional therapies such as administration of high concentrations of oxygen, hyperventilation, high-frequency ventilation, the induction of alkalosis, neuromuscular blockade, and sedation have failed or are expected to fail; *or*
2. Have pulmonary hypertension in the acute phases of recovery following surgery for cyanotic congenital heart defects *and*
3. Neonates that do not have a congenital diaphragmatic hernia (CDH). If the neonate does have CDH, iNO can be considered appropriate for use if
    a. iNO is required to stabilize a patient during transition to ECMO (Usually required for a few hours before)
    b. iNO is required during transition off of ECMO when pulmonary arterial pressures are high (this can be a period of time ranging from hours to several days)

Note: Use of iNO therapy for more than 4 days is subject to medical necessity review. Treatment should be maintained for no longer than 14 days or less if the oxygen desaturation has been resolved. **Medical director review required for use beyond 14 days.**
The recommended initial dose of iNO is 20 ppm. Abrupt discontinuation of the therapy can lead to worsening of PaO2 and increasing pulmonary artery pressure. Clinical input from academic medical centers and specialty societies obtained in 2012 indicated that:

- Prolonged use of INO [inhaled NO] beyond 1-2 weeks has not been shown to improve outcomes. Use of INO beyond 2 weeks of treatment is therefore not recommended.
- If ECMO is initiated in near-term neonates, inhaled NO should be discontinued as there is no benefit to combined treatment.

The diagnostic use of iNO is considered medically necessary as a method of assessing pulmonary vaso-reactivity in persons with pulmonary hypertension. Thus, members may be eligible for the use of iNO for acute vasodilator testing in pulmonary hypertension

Specific Diagnoses:
Inhaled nitric oxide (iNO) is an effective treatment in the near-term to full-term neonate diagnosed with persistent pulmonary hypertension (PPHN) as an isolated condition or as an associated condition resulting from any of the following:

- Respiratory distress syndrome (hyaline membrane disease)
- Meconium aspiration syndrome
- Pneumonia
- Sepsis
- Repaired congenital diaphragmatic hernia *or*
- Lung hypoplasia
- Hypoxic respiratory failure in a term or near-term infant (i.e., born at more than 34 weeks gestation) in the absence of an unrepaired congenital diaphragmatic hernia when there is failure, contraindication orintolerance to conventional therapy (e.g., high concentrations of oxygen, hyperventilation, sedation)
- Postoperative management of pulmonary hypertension following repair of congenital heart disease
- Postoperative management of pulmonary hypertensive crisis following pediatric heart or lung surgery
- Pulmonary hypertension during heart catheterization to determine pulmonary vasoreactivity

Absolute Contraindications:
Inhaled nitric oxide is **investigational** in all other instances, including, but not limited to the following:

- Adults and children with acute hypoxemic respiratory failure, *or* for premature neonates born at less than or equal to 34 weeks of gestation. There is insufficient clinical evidence to support the use of inhaled nitric oxide for any indication in preterm infants less than 34 weeks gestation. This includes routine administration in intubated infants, early rescue based on decreased oxygenation levels, and late rescue based on the risk of bronchopulmonary dysplasia BPD.
- There is insufficient clinical evidence to support the use of inhaled nitric oxide for treatment of chronic lung conditions.

iNO therapy is considered **experimental and investigational** for all other indications, because of insufficient evidence in the peer-reviewed literature, including any of the following:

- Premature neonates (less than 34 weeks of gestation);
- Acute bronchiolitis;
- Adult acute respiratory distress syndrome or acute lung injury;
- Acute pulmonary embolism
- Acute hypoxemic respiratory failure in children (other than those who meet the medical necessity criteria above) and in adults;
- Bronchopulmonary dysplasia, prevention in preterm infants without hypoxic respiratory failure;
- Prevention of ischemia-reperfusion injury/acute rejection following lung or liver transplantation;
- Treatment of vaso-occlusive crises or acute chest syndrome in persons with sickle cell disease (sickle cell vasculopathy);
- Post-operative management of pulmonary hypertension in infants and children with congenital heart disease*; or*
- Treatment of persons with congenital diaphragmatic hernia.
- As adjunctive therapy of malaria
- In lung or liver transplantation, during and/or after graft reperfusion.
- Postoperative use in adults and children with congenital heart disease; Treatment of right heart failure after hemorrhagic shock and trauma pneumonectomy.

Although studies are still being done, there is insufficient evidence in the peer review literature to support its use outside of clinical trials for the above conditions.

iNO therapy is not without harmful side effects. When oxygen and nitric oxide mix together, they chemically react to form nitrogen dioxide (NO2), which is toxic to the lungs. Nitrogen dioxide concentrations greater than 10 parts per million (ppm) have been known to induce pulmonary edema, alveolar hemorrhage, changes in the surface tension properties of surfactant, and death. NO2 is dose- dependent and its concentrations should be maintained below 3 ppm by decreasing the iNO concentration if its level increases. Methemoglobinemia (MetHb), which impairs the ability of the

hemoglobin molecule to bind with oxygen, is another harmful side effect of iNO therapy. MetHb is dose-dependent and its levels must be carefully monitored. Significant methemoglobinemia has been reported after accidental overdose of iNO, and a level greater than 10% may cause cyanosis, headaches, muscle weakness, and tissue hypoxia. Laboratory and clinical studies have suggested that high doses of inhaled nitric oxide may increase the risk of bleeding, which is a serious concern because of the predisposition of premature newborns to intracranial hemorrhage (Kinsella 2006, Finer 2009, Henry 2012).

There is evidence from a systematic review of randomized controlled trials that inhaled nitric oxide improves the net health outcome in hypoxic term or near-term infants. Other systematic reviews of randomized controlled trials did not find evidence of a net benefit from inhaled nitric oxide among preterm infants when used in the first 3 days of life for severe respiratory failure or after the first 3 days of life to prevent bronchopulmonary dysplasia. For preterm infants, the largest trial published to date had 800 participants and did not find that use of inhaled nitric oxide in preterm infants improved survival without bronchopulmonary dysplasia or survival without brain injury. In children and adults with acute hypoxemic respiratory failure, a systematic review of randomized controlled trials (RCT) did not find that inhaled nitric oxide treatment improved the net health outcome; there was no significant effect on all-cause mortality or duration of mechanical ventilation. There was no significant difference in adverse events overall, but there was a significantly higher rate of renal impairment with inhaled nitric oxide treatment.
The literature indicates that iNO does not appear to increase the incidence of adverse neurodevelopmental, behavioral, or medical sequelae in these high-risk neonates. Infants with unrepaired congenital diaphragmatic hernia have been shown not to benefit from iNO therapy. Furthermore, iNO therapy has not shown to be associated with significant benefits in pre-term infants.

Finally, for postoperative management of children with congenital heart disease, one RCT reported an improvement in pulmonary hypertensive episodes, but a systematic review of RCTs found no significant mortality reduction and a paucity of data on other outcomes. Thus, inhaled nitric oxide may be considered medically necessary to treat term and near-term infants and investigational for other indications.

Line of Business Applicability:
This policy applies to Michigan Medicaid, Illinois Medicaid, and Individual plans.

For **Medicaid/Medicaid Expansion Plan** members, this policy will apply. Coverage is based on medical necessity criteria being met and the codes being submitted and considered for review being included on either the Michigan Medicaid Fee Schedule (located at: http://www.michigan.gov/mdch/0,1607,7-132-2945_42542_42543_42546_42551-159815--,00.html), or the Illinois Medicaid Fee Schedule (located at: http://www.illinois.gov/hfs/MedicalProviders/MedicaidReimbursement/Pages/default.aspx). If there is a discrepancy between this policy and either the Michigan Medicaid Provider Manual (located at: http://www.michigan.gov/mdch/0,1607,7-132-2945_5100-87572--,00.html), or the Illinois Medicaid Provider Manual (located at: http://www.illinois.gov/hfs/MedicalProviders/Handbooks/Pages/default.aspx the applicable Medicaid Provider Manual will govern.

For **Individual** members, consult the individual insurance policy. If there is a discrepancy between this policy and the individual insurance policy document, the guidelines in the individual insurance policy will govern.

State specific special instructions:

None: ☒

MI/ Medicaid: When a facility us utilizing iNO for a period of more than 4 days check special pricing for this item, notify the facility that that MHP covers 4 days of iNO, and request that records be sent for review upon discharge

IL/ Medicaid: When a facility us utilizing iNO for a period of more than 4 days check special pricing for this item, notify the facility that that MHP covers 4 days of iNO, and request that records be sent for review upon discharge

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References:

1. American Heart Association/American Thoracic Society Guideline. "Pediatric Pulmonary Hypertension – Guidelines form the AHA and ATS." Published: November 3, 2015.Sponsored by the National Heart, Lung, and Blood Institute (NHLBI). Examining the use of noninvasive inhaled nitric oxide to reduce chronic lung disease in premature newborns (NCT00955487). Available online at: www.clinicaltrials.gov. Accessed: September 14, 2016.
2. Cole FS, Alleyne C, Barks JD et al. NIH Consensus Development Conference statement: inhaled nitric-oxide therapy for premature infants. Pediatrics 2011; 127(2):363-9.
3. American Academy of Pediatrics. Committee on Fetus and Newborn. Use of inhaled nitric oxide. Pediatrics 2000; 106(2 Pt 1):344-5.
4. American Academy of Pediatrics: Use of Inhaled Nitric Oxide (2000, reaffirmed 2009 and 2014)
5. Kumar P; Committee on Fetus and Newborn; American Academy of Pediatrics. Use of inhaled nitric oxide in preterm infants. Pediatrics. 2014;133(1):164-170. American Association of Respiratory Care: Evidence-based clinical practice guidelines: inhaled nitric oxide for neonates with acute hypoxic respiratory failure (2010)
6. National Institute of Health (NIH): Consensus Development Conference Statement on Inhaled Nitric Oxide Therapy for Premature Infants (2010)
7. Canadian Pediatric Society: Inhaled Nitric Oxide Use in Newborns (2012, reaffirmed 2015)
8. Allen MC, Donohue P, Gilmore M, et al. Inhaled Nitric Oxide in Preterm Infants. Evidence Report/Technology Assessment No. 195. (Prepared by Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-1). AHRQ Publication No. 11-E001. Rockville, MD: Agency for Healthcare Research and Quality. October 2010. Available at: http://www.ahrq.gov/downloads/pub/evidence/pdf/inoinfants/inoinfants.pdf.
9. 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; 170:312-314.
10. Inhaled Nitric Oxide for the Treatment of Persistent Pulmonary Hypertension in Term and Near-Term Newborns, Hayes, Inc, published June 16, 2016, archived Jul 17,2017
11. Inhaled Nitric Oxide for the Treatment of Respiratory Failure in Preterm Newborns, Hayes, Inc published Feb 24, 2009, archived March 19, 2014
12. Nitric oxide: Pediatric drug information. UpToDate.com.
13. American Association for Respiratory Care (AACR): The 2010 clinical practice guidelines on INO for neonates with acute hypoxic respiratory failure

Medicare Managed Care Manual:				
Medicaid CFR:				
State Administrative Codes:				
Contract Requirements:				
Related Policies:				
Related Desk Level Procedures/ Job Aids/Template Letters:				
Related Algorithms/Flowcharts /Attachments				