Prior Authorization Review Panel

CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 11/012018**
Policy Number: PA.CP.MP.87	**Effective Date: 1/1/2019** **Revision Date: 10/2018**
Policy Name: Inhaled Nitric Oxide	**HC Approval Date:**

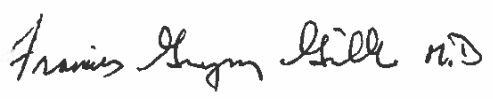
Type of Submission – Check all that apply:

- ☒ **New Policy**
- ☐ **Revised Policy***
- ☐ **Annual Review – No Revisions**
- ☐ **Attestation of HC PARP Policy –** *This option should only be used during Readiness Review for Community HealthChoices. The policy must be identical to the PARP approved policy for the HealthChoices Program, with the exception of revisions/clarifications adding the term "Community HealthChoices" to the policy.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

New Policy/ PHW acknowledges that under current CHC agreement we are not caring for Neonates. For 1/1/2019 PHW will have a Health Care Reform product and is adopting this policy for that population, and as supportive for staff addressing delivery issues for high risk pregnancies in current PHW CHC population

Name of Authorized Individual (Please type or print):	**Signature of Authorized Individual:**
Francis G. Grillo, MD	

Clinical Policy: Inhaled Nitric Oxide

Reference Number: PA.CP.MP.87
Effective Date: 11/18
Last Review Date: 10/18 Revision Log

Description
Inhaled Nitric Oxide (iNO) is a selective pulmonary vasodilator in which its mechanism of action results in smooth muscle relaxation. Several studies have suggested that iNO improves oxygenation, particularly in trials of term and near-term neonates with hypoxic respiratory failure. iNO has been shown to reduce the need for ECMO (extracorporeal membrane oxygenation) without increasing neurodevelopmental, behavioral, or medical abnormalities at 2 years of age.

Policy/Criteria

I. It is the policy of Pennsylvania Health and Wellness (PHW) that iNO therapy is **medically necessary** for the following indications:

A. *Initiation* of therapy

1. Hypoxic respiratory failure in newborns ≥ 34 weeks gestational age at birth with all:
   a. Pulmonary artery hypertension (PAH) diagnosed by echocardiogram that excluded congenital heart disease (CHD), *and*
   b. Conventional therapies such as mechanical ventilation, administration of high concentrations of oxygen (80-100%), high-frequency ventilation, induction of alkalosis, neuromuscular blockade, and sedation have failed or are expected to fail; *and*
   c. Oxygen index (OI) ≥ 25. The OI is calculated as the mean airway pressure divided by the partial pressure of arterial oxygen times 100; *and*
   d. Response seen with administration of up to 40 ppm trial of iNO (defined as a PaO2 increase ≥ 20 mm Hg or a 20% decrease in OI.
2. Perioperative management of pulmonary hypertension in infants and children with CHD, must meet all:
   a. iNO therapy for vasodilation is used in response to cardiac bypass surgery to repair a congenital heart defect that is causing PAH, *and*
   b. iNO is delivered directly to the lungs via endotracheal tube.
3. Perioperative management of pulmonary hypertensive crises associated with heart or lung surgery in infants or children.

B. Continuation of iNO therapy in newborns

1. Member continues to require iNO as evidenced by a continued O2 requirement of 80-100%, or
2. A weaning protocol is being initiated after a 4-6 hour period of stability indicated by O2 requirement decreased to 60-80% or OI ≤ 10; *and*
   a. The iNO has been used for 1 week or less.

II. It is the policy of PHW that iNO is **not medically necessary** for any other indications such as preterm infants < 34 weeks gestation, acute bronchiolitis, bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH), adult respiratory distress syndrome or acute

lung injury, treatment in adults with positive vaso-reactivity testing, post-op cardiac surgery in adults, and vaso-occlusive crises in members with sickle cell disease because safety and effectiveness have not been established.

Treatment Regimen
The American Academy of Pediatrics (AAP) recommends that iNO should only be administered according to a formal protocol that has been approved by the Food and Drug Administration (FDA) and the institutional review board and with informed consent. Use should be limited to sites with multisystem support, including on-site ECMO capability. If ECMO is not available on-site, a timely transfer needs to be arranged to a collaborating ECMO center without interruption of iNO therapy.

Since no one standard protocol has been issued for iNO treatment, the following is one guideline to assist in determining appropriate initiation and continuation of treatment. The recommended starting dose of iNO for term infants is 20ppm. A positive response generally occurs in less than 30 minutes with a PaO_2 increase ≥20 mmHg (or 20% decrease in OI). If there is no response, the dose may be increased up to 40 ppm. In premature infants, the initial dose used in studies was 10 ppm with an increase up to 20 ppm in non-responders. Doses of up to 80 ppm have been used, but the potential for increasing toxicity without additional benefits occurs at doses greater than 40 ppm.

Per Peliowski, weaning can occur following improvement in oxygenation and after a 4 to 6 hour period of stability, during which the inspired oxygen concentration is decreased to 60% to 80%, or the OI falls to ≤10. At 4-6 hour intervals, the dose can be decreased by 50%, as long as the OI remains ≤10. When stability is maintained at iNO dose of 5 ppm, weaning should occur by 1 ppm every 4 hours and discontinued at 1 ppm if oxygenation status remains with <60% oxygen with PaO_2 consistently >50 mmHg. If deterioration occurs during or after weaning occurs, the dose should be increased to the previous level or iNO restarted. Once the infant stabilizes again, weaning should occur more slowly, taking place over a 24 to 48 hour period.

In general, patients who responded to iNO therapy typically require treatment for 3-4 days, with randomized trials demonstrating 90% of treated infants were off iNO therapy within one week of initiation. Patients should be monitored for potential toxic effects by measuring the serum methemoglobin concentration, levels of nitrogen dioxide at the airway opening, and ambient air contamination. Decreased platelet aggregation, increased risk of bleeding and surfactant dysfunction can also occur from iNO toxicity.

Background
A large and well-designed multicenter trial was conducted by the Neonatal Research Network in 235 infants with gestational age ≥34 weeks who had severe hypoxic respiratory failure (OI ≥25) and did not have CDH. Infants were randomly assigned to iNO or control (100% oxygen). Fewer infants in the treatment group died within 120 days or received ECMO therapy, (46% versus 64%; relative risk 0.72, 95% CI 0.57-0.91) compared to control. This difference was entirely due to decreased requirement for ECMO (39% versus 54%); there was no difference between groups in mortality.

In a systemic review by the Cochrane database, similar findings of fewer requirements for ECMO and no difference in mortality were noted. Fourteen randomized trials were found in term or near term infants with hypoxia. iNO improved oxygenation in approximately 50% of the treated infants. Within 30 to 60 minutes of beginning therapy, PaO_2 increased by a mean of 53 mmHg and OI decreased by a mean of 15.1. Outcome did not appear to be affected by whether infants had echocardiographic evidence of persistent pulmonary hypertension. No benefit was noted in those with CDH, indeed there is a suggestion that outcome was slightly worsened.

In preterm infants <35 weeks gestation, a systematic review by the Cochrane database found 14 randomized controlled trials of iNO. The authors concluded that iNO as a rescue therapy for the very ill ventilated preterm infant does not appear to be effective and may increase the risk of severe intraventricular hemorrhage. Later use to prevent BPD does not appear to be effective. Early routine use of iNO in mildly sick preterm infants may improve survival without BPD and decrease serious brain injury; further studies are needed to confirm these findings.

Furthermore, a 2018 retrospective analysis of 993 extremely preterm infants (born at 22 to 29 weeks' gestation) compared infants receiving iNO with propensity-matched controls, and did not find a significant association between iNO exposure and mortality.

iNO has been well-studied in patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS). While iNO may improve oxygenation temporarily, it has not been shown to improve clinically important outcomes such as duration of mechanical ventilation, 28-day mortality or one-year survival. Furthermore, iNO does not improve oxygenation in all patients and the factors that may predict a good response are still uncertain.

In an updated Cochrane database review, the evidence was insufficient to support iNO in any category of critically ill adults and children with acute respiratory distress syndrome. Although iNO results in a transient improvement in oxygenation, it does not reduce mortality and may be harmful, as it seems to increase renal impairment.[22]

A Cochrane Summary for the use of iNO for pulmonary hypertension (PH) following surgery in infants and children with congenital heart disease found no benefit of it to assist in recovery. In the four randomized trials reviewed, there was no difference found in mortality or other outcomes reviewed. Due to the minimal data that was available, the authors found it difficult to draw valid conclusions regarding effectiveness and safety of this treatment in the select population. In a later study, iNO was effective in reducing the risk of development of PH crisis in PAH-CHD patients after cardiac repair in a placebo-controlled study [16] . Infants with PAH-CHD receiving iNO had fewer PH crises and shorter postoperative courses without concomitant side effects related to the medication.

2015 guidelines on pediatric pulmonary hypertension, issued by the American Heart Association and American Thoracic Society, make a class 1, level B recommendation for use of iNO in post-operative pulmonary hypertensive crises. The guidelines state that iNO is an established therapy for postoperative pulmonary hypertension due to its selective pulmonary vasodilator properties, rapid effect onset, and ease of administration.

Research on iNO use in adults with PH is limited to case reports and small case series, which leaves the impact of iNO on survival uncertain. It has been found to successfully stabilize a variety of acutely ill and hemodynamically compromised patients with severe PH, but the outcomes data are limited and thus cannot be considered standard of care. Acute vasodilator testing is the only well established and widely accepted use of iNO in patients with PAH. Patients with a positive vasoreactivity test are candidates for a trial of calcium channel blocker therapy

INO has numerous potential harms that must be considered when determining the risks and benefits of treatment. These potential harms include renal dysfunction, DNA strand breakage and base alterations which are potentially mutagenic, immunosuppression that could increase the risk of nosocomial infection, and a possible increase in methemoglobin and NO2 concentrations, which must be monitored frequently. Also, iNO may produce toxic free radicals; however, it is unknown if these are more harmful than ongoing exposure to high fractions of inspired oxygen.

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2018, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

CPT® Codes	Description
94799	Unlisted pulmonary service or procedure

HCPCS Codes	Description
N/A	

ICD-10-CM Diagnosis Codes that Support Coverage Criteria

ICD-10-CM Code	Description
I27.0	Primary pulmonary hypertension
I27.2	Other secondary pulmonary hypertension
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
P28.5	Respiratory failure of newborn
P29.3	Persistent fetal circulation
Q21.0	Ventricular septal defect
Q21.2	Atrial septal defect

Reviews, Revisions, and Approvals	Date	Approval Date
Policy developed.	10/18	

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