Clinical Policy: Inhaled Nitric Oxide

Reference Number: CP.MP.87
Date of Last Revision: 07/21

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 health plans affiliated with Centene Corporation® that *initiation* of inhaled nitric oxide (iNO) therapy is **medically necessary** when meeting the following:

A. iNO will be administered via endotracheal tube or tracheostomy;
B. One of the following indications:
   1. Hypoxic respiratory failure in newborns ≥ 34 weeks gestational age **at birth** with all:
      a. Evidence of pulmonary artery hypertension (PAH), one of the following:
         i. Well-documented, clear clinical evidence of pulmonary hypertension despite maximal respiratory support;
         ii. Echocardiogram suggestive of PAH;
      b. Absence of unrepaired congenital diaphragmatic hernia except when used as a bridge to surgical repair of congenital diaphragmatic hernia;
      c. Conventional therapies such as mechanical ventilation, administration of high concentrations of oxygen (80-100%), high-frequency ventilation, induction of alkalosis, neuromuscular blockade, and/or sedation have failed or are expected to fail;
      d. Oxygen index (OI) ≥ 25. The OI is calculated as the mean airway pressure (cm H20) times the fraction of inspired oxygen (FiO2) times 100 divided by the partial pressure of arterial oxygen (mm Hg);
      e. 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 in children, and infants ≥ 34 weeks gestational age **at birth**, both of the following:
      a. One of the following indications:
         i. Congenital heart defect and one of the following:
            a) iNO therapy for vasodilation is used in response to cardiac bypass surgery to repair a congenital heart defect that is causing PAH;
            b) Perioperative stabilization and management of hypoxia;
         ii. Pulmonary hypertensive crisis associated with heart or lung surgery (including immediately pre- or post-operatively for congenital diaphragmatic hernia);
      b. Initiation of alternative vasodilator therapies (e.g. sildenafil or others) during iNO administration with the intent to wean iNO (see continuation criteria in section III);

3. COVID-19 diagnosis**, both of the following:
   a. Severe acute respiratory distress syndrome (ARDS);
   b. Hypoxemia despite optimized ventilation and other rescue strategies.

Note: If no rapid improvement in oxygenation is observed, treatment should be tapered off.

II. It is the policy of health plans affiliated with Centene Corporation that that while the medical literature predominantly does not support the use of iNO in premature infants <34 weeks gestational age at birth, requests for initiation of iNO therapy in these infants may be **reviewed on a case-by-case basis** for potential benefit and, if approved for an initial trial period, reviewed closely thereafter for proof of therapeutic success. Requests must meet all of the following:

A. iNO will be administered via endotracheal tube or tracheostomy;
B. One of the following indications:
   1. Hypoxic respiratory failure and all of the following:
      a. Evidence of pulmonary artery hypertension (PAH), one of the following:
         i. Well-documented, clear clinical evidence of pulmonary hypertension despite maximal respiratory support;
         ii. Echocardiogram suggestive of PAH;
      b. Absence of unrepaired congenital diaphragmatic hernia except when used as a bridge to surgical repair of congenital diaphragmatic hernia;
      c. Conventional therapies such as mechanical ventilation, administration of high concentrations of oxygen (80-100%), high-frequency ventilation, induction of alkalosis, neuromuscular blockade, and/or sedation have failed or are expected to fail;
      d. Oxygen index (OI) ≥ 25. The OI is calculated as the mean airway pressure (cm H20) times the fraction of inspired oxygen (FiO2) times 100 divided by the partial pressure of arterial oxygen (mm Hg);
      e. Response seen *within two hours* 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, both of the following:
      a. One of the following indications:
         iii. Congenital heart defect and one of the following:
            c) iNO therapy for vasodilation is used in response to cardiac bypass surgery to repair a congenital heart defect that is causing PAH;
            d) Perioperative stabilization and management of hypoxia;
         iv. Pulmonary hypertensive crisis associated with heart or lung surgery (including immediately pre- or post-operatively for congenital diaphragmatic hernia);
      b. Initiation of alternative vasodilator therapies (e.g. sildenafil or others) during iNO administration with the intent to wean iNO (see continuation criteria in section III).

III. It is the policy of health plans affiliated with Centene Corporation that *continuation* of inhaled nitric oxide (iNO) therapy is **medically necessary** when meeting the following:

A. Member/enrollee has previously met initial approval criteria, and one of the following*:
   1. Continues to require iNO as evidenced by a continued O2 requirement of 80-100%;
   2. A weaning protocol has been initiated after a 4-6 hour period of stability, indicated by O2 requirement decreased/decreasing to 60-80% or OI ≤ 10.

***Note:** Extended administration of iNO beyond 48 hours requires secondary review by a medical director.

IV. It is the policy of health plans affiliated with Centene Corporate that iNO is **not medically necessary** for any other indications, such as acute bronchiolitis, bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH) (except as noted above), adult respiratory distress syndrome (except as noted above) or acute lung injury, treatment in adults with positive vaso-reactivity testing, post-op cardiac surgery in adults, and vaso-occlusive crises in member/enrollees with sickle cell disease because safety and effectiveness have not been established.

Treatment Regimen
In 2000, the American Academy of Pediatrics (AAP) recommended 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.

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 only 3-4 days, with randomized trials demonstrating that 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 (including intracranial hemorrhage), 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 congenital diaphragmatic hernia. Infants were randomly assigned to iNO or to 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 congenital diaphragmatic hernia, 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. Extremely preterm infants and infants with pulmonary hypoplasia may develop pulmonary hypertension. No clinical trials are available to guide prediction of response to iNO in these cohorts. A trial of iNO in preterm infants with documented pulmonary hypertension or in infants with pulmonary hypoplasia may be beneficial,[30] however, the evidence remains inconclusive. In addition, patient selection criteria has not been defined. Additional studies are needed to identify the subset of preterm infants for whom iNO is beneficial.[1,12]

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-congenital heart defect patients after cardiac repair in a placebo-controlled study.[16] Infants with PAH-congenital heart defects 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.

Due to the rapidly evolving COVID-19 pandemic, the National Institutes of Health (NIH) has developed treatment guidelines, relying heavily on experience with other diseases, supplemented with evolving personal clinical experience with COVID-19, and incorporating the rapidly growing published scientific literature on COVID-19. The guidelines will be updated frequently as published data and other authoritative information becomes available.

In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet the oxygen needs of the patient. Options include high-flow nasal cannula oxygen, noninvasive positive pressure ventilation, or intubation and invasive mechanical ventilation.

The recommendations for mechanically ventilated adults include the following:

- For mechanically ventilated adults with COVID-19 and ARDS, the Panel recommends using low tidal volume (Vt) ventilation (Vt 4–8 mL/kg of predicted body weight) over higher tidal volumes (Vt >8 mL/kg) (AI). (strong recommendation, one or more randomized trials with clinical outcomes and/or validated laboratory endpoints)
- For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation (moderate recommendation, one or more well-designed, nonrandomized trials or observational cohort studies).
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies, the Panel recommends a trial of inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the patient should be tapered off treatment (optional recommendation, expert opinion).
- There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation for patients with COVID-19 and refractory hypoxemia (moderate recommendation, expert opinion).[28]

Potential risks and challenges with COVID-19 patients include aerosolization and clogging of bacterial/viral filters used in ventilator circuits when pulmonary vasodilators are being administered. iNO may be preferred since it is associated with a lower need to change filters with resultant reduction in the risk to the respiratory healthcare provider.[29]

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 2020, 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
I16.0-I16.9	Hypertensive crisis
I27.0	Primary pulmonary hypertension

ICD-10-CM Code	Description
I27.20 - I27.29	Other secondary pulmonary hypertension
J80	Acute respiratory distress syndrome
J96.01	Acute respiratory failure with hypoxia
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
P29.30-P29.38	Persistent fetal circulation
Q21.0	Ventricular septal defect
Q21.2	Atrial septal defect
U07.1	COVID-19, confirmed by laboratory testing
U07.2	Clinical or epidemiological diagnosis of COVID-19, laboratory confirmation inconclusive or not available
Z98.890	Other specified postprocedural states

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed, Neonatologist reviewed	08/13	08/13
Split criteria into initiation and continuation of therapy Added Treatment Regimen section Neonatologist reviewed	08/14	09/14
Literature researched and bibliography updated Converted to new template Neonatologist reviewed	09/15	09/15
Updated template and disclaimer language	03/16	
Added criteria for iNO therapy in perioperative management for PAH in pediatrics. Reviewed by Pediatric Cardiology, Adult Cardiology, and Neonatologist.	08/16	09/16
References reviewed and updated. ICD-10 and CPT codes added.	09/17	09/17
Added indication for pediatric post-op management of pulmonary hypertension associated with heart or lung surgery. Background updated. Reviewed by pediatric pulmonologist.	09/18	09/18

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Newborn hypoxic respiratory failure: removed exclusion of infant with congenital heart defect; added clinical evidence of PH as a diagnostic option; added that congenital diaphragmatic hernia is excluded except when a bridge to surgical repair. Perioperative criteria: combined indications into I.A.2; specified criteria applies to infants ≥34 weeks of age and children; removed restriction that congenital heart defect criteria applies only in the presence of pulmonary hypertension; added perioperative stabilization and management of hypoxia as an indication for member/enrollees with congenital heart defect; removed requirement that iNO be delivered via endotracheal tube; for pulmonary hypertensive crisis associated with heart or lung surgery, added immediate pre-op treatment of congenital diaphragmatic hernia; to all perioperative criteria, added requirement that alternative vasodilators must be initiated with the intent to wean iNO. For Continuation criteria: removed restriction to newborns only; removed restriction to one week of iNO or less. Added note applying to all indications that iNO administration beyond 48 hours requires medical director review. Reviewed by a pediatric pulmonologist, pediatric critical care physician, and pediatric emergency medicine physicians. Added ICD-10- CM codes I16.0-I16.9 and Z98.890.	04/19	04/19
Added requirement that iNO be delivered via endotracheal tube or tracheostomy.	05/19	05/19
In continuation criteria, clarified that member/enrollee must have previously met initial approval criteria.	01/20	
Annual review completed. Codes and references checked and updated. P29.3 changed to P29.30-P29.38 and I27.2 changed to I27.20 - I27.29.	04/20	4/20
Added iNO as medically necessary for COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies. Updated background. Added the following ICD-10 codes: J80, J96.01, U07.1 and U07.2	04/20	05/20
Corrected calculation of Oxygen Index in I.A.2.IV. Updated background with no impact on criteria. References added. Replaced "member" with "member/enrollee."	11/20	
References reviewed and updated.	04/21	04/21
Added indications for case by case review of iNO initiation for preterm infants <34 weeks at birth to section II. Split continuation criteria into section III, and not medically necessary indications are now section IV. Minor rewording of background. Added reference 35. Changed "Review Date" in policy header to "Date of Last Revision," and "Date" in the revision log table header to "Revision Date."	07/21	07/21

References

1. Stark AR, Eichenwald EC. Persistent pulmonary hypertension of the newborn. In: UpToDate: Garcia-Prats JA (Ed), UpToDate, Waltham, MA. Accessed April 6, 2021.

2. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database of Systematic Reviews 2016 Jun 27;(6):CD002787. doi: 10.1002/14651858.CD002787.pub3.
3. Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Database Syst Rev. 2017 Jan 3;1:CD000509. doi: 10.1002/14651858
4. Bizzarro M, Gross I, Barbosa FT. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. Cochrane Database of Systematic Reviews. 2014 Jul 3;(7):CD005055. doi: 10.1002/14651858.CD005055.pub3.
5. Breuer J, Perin W, Gebhardt S, et al. Inhaled nitric oxide treatment of children with pulmonary hypertension after cardiac surgery. Progress in Pediatric Cardiology, 1998, 2(9): 73-83.
6. Barrington KJ, Finer N, Pennaforte T, Altit G. Nitric oxide for respiratory failure in infants born at or near term. Cochrane review abstract and plain language summary. The Cochrane Database of Systematic Reviews 2017 Jan 5;1:CD000399. doi: 10.1002/14651858.
7. Guthrie SO, et al. Initial dosing of inhaled nitric oxide in infants with hypoxic respiratory failure. J Perinatal. 2004 May;24(5):290-4.
8. Granton J, Langleben D, Kutryk MJ, et al. Endothelial NO-Synthase Gene-Enhanced Progenitor Cell Therapy for Pulmonary Arterial Hypertension: the PHACeT Trial. Circ Res July 2015. 117:645-654 Available at: http://circres.ahajournals.org/content/117/7/645.long
9. Hopkins W, Rubin LJ. Treatment of pulmonary hypertension in adults. In: UpToDate, Mandel J (Ed), UpToDate, Waltham, MA. Accessed April 6, 2021.
10. Ichinose F, Roberts JD Jr, Zapol WM. A selective pulmonary vasodilator: Current uses and therapeutic potential. Circulation 2004; 109: 3106-3111.
11. Kumar P, Committee on Fetus and Newborn. Use of inhaled nitric oxide in preterm infants. Pediatrics 2014;133;164-170.
12. Martin, R. Prevention and treatment of respiratory distress syndrome in preterm infants. In: UpToDate, Garcia-Prats JA (Ed), UpToDate, Waltham, MA. Accessed April 6, 2021.
13. Miller OI, Tang SF, Keech A, et al. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomized double-blind study. Lancet 2000;356(9240):1464–1469.
14. Morales-Blanhir J, Sanos S, de Jover L, et al. Clinical value of vasodilator test with inhaled nitric oxide for predicting long-term response to oral vasodilators in pulmonary hypertension. Respir Med, 2004: 98(3): 225.
15. Peliowski A, Canadian Paediatric Society, Fetus and Newborn Committee. Inhaled nitric oxide use in newborns. Paediatr Child Health. 2012 February; 17(2): 95-97. Reaffirmed Jan 30, 2017.
16. Soll RF. Inhaled nitric oxide in the neonate. Journal of Perinatology (2009) 29, S63-S67.
17. Gebistorf F, Karam O, Wetterslev J, Afshari A. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) in children and adults. Cochrane Database Syst Rev. 2016 Jun 27;(6):CD002787
18. Siegel MD. Acute respiratory distress syndrome: Supportive care and oxygenation in adults. UpToDate, Waltham, MA. Accessed April 7, 2021.
19. Klinger JR, Inhaled nitric oxide in adults: Biology and indications for use. UpToDate, Waltham, MA. Accessed April 6, 2021.

20. Carey WA, Weaver AL, Mara KC, Clark RH. Inhaled nitric oxide in extremely premature neonates with respiratory distress syndrome. Pediatrics. 2018 Feb 9. pii: e20173108. doi: 10.1542/peds.2017-3108
21. Abman SH, Hansmann G, Archer SL, et al. Pediatric Pulmonary Hypertension: Guidelines from the American Heart Association and American Thoracic Society. Circulation. 2015 Nov 24;132(21):2037-99. doi: 10.1161
22. Sardo S, Osawa EA, Finco G, et al. Nitric oxide in cardiac surgery: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth. 2018 Dec; 32(6): 2512-2519.
23. Collura CA, Mara KC, Weaver AL, Clark RH, Carey WA. Outcomes of early inhaled nitric oxide use in premature African American neonates. J Perinatol. 2018 Dec; 38(12): 1657-1665.
24. Clark RH, Kueser TJ, Walker MW, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. N Engl J Med. 2000;342(7):469-474.
25. Putnam LR, Tsao K, Morini F, et al. Evaluation of Variability in Inhaled Nitric Oxide Use and Pulmonary Hypertension in Patients With Congenital Diaphragmatic Hernia. JAMA Pediatr. 2016 Dec 1;170(12):1188-1194.
26. Hayes. Inhaled Nitric Oxide for the Treatment of Respiratory Failure in Preterm Newborns. Hayes Medical Technology Directory. November 6, 2018. Update November 13, 2019.
27. DiBlasi RM, Dupras D, Kearner C, Costa E, Griebel JL. Nitric Oxide Delivery by Neonatal Noninvasive Respiratory Support Devices. Respiratory Care February 2015, 60 (2) 219-230.
28. National Institute of Health. Coronavirus Disease 2019. (Covid-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/. Updated December 17, 2020. Accessed April 6, 2021.
29. Anesi GL. COVID-19: Critical care and airway management issues. UpToDate. Manaker S (Ed). Updated March 26, 2021. Accessed April 6, 2021.
30. 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 March; 170:312-314.
31. Ellsworth KR, Ellsworth Ma, Weaver AL, et al. Association of Early Inhaled Nitric Oxide with the Survival of Preterm Neonates with Pulmonary Hypertension. JAMA Pediatr 2018 July; 172(7):e180761.
32. Soll RF. Inhaled Nitric Oxide for Preterm Infants: What Can Change our Practice? Pediatr 2018 March;141(3): e20174214.
33. Carey WA, Weaver AL, Mara KC, Clark RS. Inhaled Nitric Oxide in Extremely Premature Neonates with Respiratory Distress Syndrome. Pediatr 2018 March;141(3):e20173108.
34. Mandell EW, Kratimenos P, Abman SH, Steinhorn RH. Drugs for the Prevention and Treatment of Bronchopulmonary Dysplasia. Clin Perinatol 2019;46:291-310.
35. Chandrasekharan P, Lakshminrusimha S, Abman SH. When to say no to inhaled nitric oxide in neonates? Semin Fetal Neonatal Med. 2021;26(2):101200. doi:10.1016/j.siny.2021.101200.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program

approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

 Providers, member/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, member/enrollees and their representatives agree to be bound by such terms and conditions by providing services to member/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take

precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.