Molina Clinical Policy
Inhaled Nitric Oxide (iNO) for Neonatal Hypoxic Respiratory Failure: Policy No. 121

Last Approval: 10/12/2022
Next Review Due By: October 2023

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members.[1] References included were accurate at the time of policy approval and publication.

OVERVIEW

Inhaled nitric oxide (iNO) is a vasodilator used in conjunction with ventilatory support and other appropriate agents used in the treatment of term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

The Food and Drug Administration (FDA) approved iNOmax in 1999 for use in intubated full term and late preterm infants with hypoxemic respiratory failure. According to FDA labeling, the initial recommended starting dose for infants is 20 ppm with continued use for 14 days or until improvement in the underlying disease process results in normal oxygen saturations. The dose is weaned incrementally with improving oxygen saturations beginning as soon as four hours after the initiation of therapy, to 5 ppm before discontinuation. Doses above 20 ppm should not be used because of the risk of methemoglobinemia and elevated nitrogen dioxide (NO2), a toxic metabolite (FDA, 1999; AHRQ, 2010).

COVERAGE POLICY

Initial Criteria for Treatment (initial approval for 72 hours)

1. Inhaled nitric oxide (iNO) is indicated for the treatment of **term and near-term (>34 weeks gestational age at birth) neonates** who have severe documented hypoxic respiratory failure secondary to persistent primary pulmonary hypertension (PPHN) and **ALL** of the following:

   a. Oxygenation index (OI) recorded x 2 measurements taken 15 min apart that are >25 despite maximum medical therapy that includes **ALL** of the following:
      - FiO_2 concentration of 100%; **AND**
      - Failure to respond to additional optimal medical treatment which must include high frequency oscillatory ventilation (HFOV), cardiovascular support and attempts to correct the blood pH.

   AND

   b. Echocardiogram findings suggestive of PPHN; **AND**

   c. Absence of a congenital diaphragmatic hernia (CDH) except when used to repair a congenital diaphragmatic hernia and limited to patients with **ALL** of the following:
      - Suprasystemic pulmonary vascular resistance (PVR) with right-to-left shunting across the foramen ovale causing critical preductal hypoxemia; **AND**
      - After optimal lung inflation; **AND**
      - Adequate left ventricle (LV) performance is established.

   AND

d. Facility must have the availability of extracorporeal membrane oxygenation (ECMO) or an established mechanism for timely transfer of infants to an ECMO center; **AND**

e. Facility must have personnel trained in the administration of iNOmax.

2. Inhaled nitric oxide (iNO) is indicated for the postoperative management in **infants ≥34 weeks gestational age at birth and children who have one of the following indications:**

   a. Congenital heart defect and **ANY** of the following:
      - iNO therapy for vasodilation is used in response to cardiac bypass surgery to repair a congenital heart defect that is causing pulmonary arterial hypertension; **OR**
      - Postoperative stabilization and management of hypoxia.

   b. Pulmonary hypertensive crisis associated with heart or lung surgery (including immediately pre-operatively for congenital diaphragmatic hernia).

3. The recommended dose of INOmax is 20 ppm. Treatment should be maintained until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy.

NOTE: iNO should be administered using FDA-approved devices capable of administering iNO in constant concentration ranges in parts per million or less throughout the respiratory cycle.

Continuation of Therapy

1. Initial signs of improvement as documented by at least **TWO** of the following:
   a. Repeat echocardiogram demonstrating significantly lower pulmonary artery pressures; **OR**
   b. Lower O_2 requirements; **OR**
   c. Lower ventilator settings; **OR**
   d. Improved blood gases.

AND

2. Re-evaluation every 48 hours; **AND**

3. Neonates who cannot wean: 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, the dose of iNO should be weaned; **AND**

4. Neonates who cannot be weaned from iNO after seven days should be carefully evaluated for other forms of lung pathology and cardiac disease. Continuation of iNO beyond 7 days must be reviewed by a medical director.

Limitations and Exclusions

1. For the treatment of neonates with cardiac anomalies dependent on right-to-left shunts (e.g., patent ductus arteriosus [PDA-dependent heart lesions], congestive heart failure, and those with lethal congenital anomalies).
2. iNO therapy for any other indications such as preterm infants < 34 weeks gestation at birth, acute bronchiolitis, bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH) (except as noted above), 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 in the peer reviewed literature.
3. For the treatment of life-threatening conditions deemed by the neonatologist / medical team as it is likely to result in death or significant neurological impairment including genetic syndromes or conditions with a poor prognosis.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Systematic reviews, meta-analysis, and randomized controlled trials have reported that INO improved systematic oxygenation and that fewer term and near-term infants with birth age greater than 34 weeks gestation required ECMO and/or developed chronic lung disease. A summary of the most relevant studies is outlined below.

The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO) in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤14 days of age (mean, 1.7 days) with a mean PaO2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H2O / mm Hg were initially randomized to receive 100% O2 with (n=114) or without (n=121) 20 ppm nitric oxide for up to 14 days. Response to study drug was defined as a change from baseline in PaO2 30 minutes after starting treatment (full response = >20 mm Hg, partial = 10–20 mm Hg, no response = <10 mm Hg).

Neonates with a less than full response were evaluated for a response to 80 ppm nitric oxide or control gas. While the incidence of death by 120 days of age was similar in both groups (NO, 14%; control, 17%), significantly fewer infants in the nitric oxide group required ECMO compared with controls (39% vs. 55%, p = 0.014). The combined incidence of death and/or initiation of ECMO showed a significant advantage for the nitric oxide treated group (46% vs. 64%, p =0.006). The nitric oxide group also had significantly greater increases in PaO2 and greater decreases in the OI and the alveolar-arterial oxygen gradient than the control group (p<0.001 for all parameters). Significantly more patients had at least a partial response to the initial administration of study drug in the nitric oxide group (66%) than the control group (26%, p<0.001). Of the 125 infants who did not respond to 20 ppm nitric oxide or control, similar percentages of NO-treated (18%) and control (20%) patients had at least a partial response to 80 ppm nitric oxide for inhalation or control drug, suggesting a lack of additional benefit for the higher dose of nitric oxide. No infant had study drug discontinued for toxicity. Inhaled nitric oxide had no detectable effect on mortality. The adverse events collected in the NINOS trial occurred at similar incidence rates in both treatment groups. Follow-up exams were performed at 18–24 months for the infants enrolled in this trial. In the infants with available follow-up, the two treatment groups were similar with respect to their mental, motor, audiologic, or neurologic evaluations (NINOS, 1997).

CINRGI Study: This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was caused by MAS (35%), idiopathic PPHN (30%), pneumonia/sepsis (24%), or RDS (8%). Patients with a mean PaO2 of 54 mm Hg and a mean OI of 44 cm H2O / mm Hg were randomly assigned to receive either 20 ppm INOmax (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO2 >60 mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax or placebo. Significantly fewer neonates in the INOmax group required ECMO compared to the control group (31% vs. 57%, p<0.001). Although the number of deaths were similar in both groups (INOmax, 3%; placebo, 6%), the combined incidence of death and/or receipt of ECMO was decreased in the INOmax group (33% vs. 58%, p<0.001). In addition, the INOmax group had significantly improved oxygenation as measured by PaO2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with INOmax, 2 (2%) were withdrawn from study drug due to methemoglobin levels >4%. The frequency and number of adverse events reported were similar in the two study groups (Clark et al., 2000).

In a randomized, double-blind, parallel, multicenter study, 385 patients with moderately severe acute lung injury who had a PaO_2/FiO_2 less than 250 mmHg despite optimal oxygenation and ventilation, received either placebo (n = 193) or nitric oxide (n = 192), 5 ppm, for 4 hours to 28 days or until weaned off due to improvements in oxygenation. This

study found that despite acute improvements in oxygenation, there was no effect of nitric oxide on the primary endpoint of days alive and off ventilator support (Taylor et al., 2004).

A double-blind study done at 36 centers in nine countries in the European Union by Mercier et al. (2010) of 800 preterm infants with a gestational age at birth of between 24 weeks and 28 weeks plus 6 days (inclusive), weighing at least 500 g, requiring surfactant or continuous positive airway pressure for respiratory distress syndrome within 24 h of birth were randomly assigned in a one-to-one ratio to inhaled nitric oxide (5 parts per million) or placebo gas (nitrogen gas) for a minimum of 7 days and a maximum of 21 days. Care providers and investigators were masked to the computer-generated treatment assignment. The primary outcome was survival without development of bronchopulmonary dysplasia at postmenstrual age 36 weeks. Analysis was by intention to treat. Infants were assigned to inhaled nitric oxide, and 401 to placebo; 395 and 400, respectively, were analyzed. Treatment with inhaled nitric oxide and placebo did not result in significant differences in survival of infants without development of bronchopulmonary dysplasia (258 [65%] of 395 versus 262 [66%] of 400, respectively; relative risk 1.05, 95% CI 0.78-1.43); in survival at 36 weeks' postmenstrual age (343 [86%) of 399 versus 359 [90%] of 401, respectively); and in development of bronchopulmonary dysplasia (81 [24%] of 339 versus 96 [27%] of 358, respectively). The authors concluded that early use of low dose inhaled nitric oxide in very premature babies did not improve survival without bronchopulmonary dysplasia or brain injury, suggesting that such a preventive treatment strategy is unsuccessful.

A systematic review the evidence on the use of iNO in infants born at 34 weeks gestation who receive respiratory support was conducted by Donahue and colleagues in 2011. The review focused on mortality, bronchopulmonary dysplasia (BPD), the composite outcome of death or BPD, and neurodevelopmental impairment (NDI). Fourteen randomized controlled trials, 7 follow-up studies, and 1 observational study were eligible for inclusion. Mortality rates in the NICU did not differ for infants treated with iNO compared with controls. BPD at 36 weeks for iNO and control groups also did not differ for survivors A small difference was found in favor of iNO in the composite outcome of death or BPD. There was no evidence to suggest a difference in the incidence of cerebral palsy neurodevelopmental impairment or cognitive impairment. The authors concluded that there was no benefit or increased risk to preterm infants born at < 34 weeks' gestational age treated with iNO compared with control infants for mortality, BPD at 36 weeks post menstrual age, short-term risks (patent ductus arteriosus, sepsis, necrotizing enterocolitis, treated retinopathy of prematurity, pulmonary hemorrhage, air leak, brain injury), or NDI. There was a 7% reduction in the risk of the composite outcome of death or BPD at 36 weeks for infants treated with iNO compared with controls but no reduction in death alone or BPD.

A Cochrane Review determined the effect of treatment with iNO on death, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH)and neurodevelopmental disability in preterm newborn infants with respiratory disease. 17 randomised controlled trials of iNO therapy in preterm infants were reviewed. The trials were grouped into three categories on the basis of entry criteria: treatment during the first three days of life for impaired oxygenation, routine use in preterm babies along with respiratory support, and later treatment for infants at increased risk for bronchopulmonary dysplasia (BPD). Eight trials providing early rescue treatment for infants on the basis of oxygenation criteria demonstrated no significant effect of iNO on mortality or BPD (typical risk ratio (RR) 0.94, 95% confidence interval (CI) 0.87 to 1.01; 958 infants). Four studies examining routine use of iNO in infants with pulmonary disease reported no significant reduction in death or BPD (typical RR 0.94, 95% CI 0.87to 1.02; 1924 infants), although this small effect approached significance. Later treatment with iNO based on risk of BPD (three trials) revealed no significant benefit for this outcome in analyses of summary data (typical RR 0.92, 95% CI 0.85 to 1.01; 1075 infants). Investigators found no clear effect of iNO on the frequency of all grades of IVH nor severe IVH. Early rescue treatment was associated with a non-significant 20% increase in severe IVH. The authors found no effect on the incidence of neurodevelopmental impairment. The authors concluded that iNO does not appear to be effective as rescue therapy for the very ill preterm infant. Early routine use of iNO in preterm infants with respiratory disease does not prevent serious brain injury or improve survival without BPD. Later use of iNO to prevent BPD could be effective, but current 95% confidence intervals include no effect; the effect size is likely small (RR 0.92) and requires further study (Barrington et al., 2017).

A second Cochrane Review compared the effects of postoperative administration of iNO versus placebo or conventional management, or both, on infants and children with CHD and pulmonary hypertension. The primary outcome was mortality. Secondary outcomes included length of hospital stay; neurodevelopmental disability; number of pulmonary hypertensive crises (PHTC); changes in mean pulmonary arterial pressure (MPAP), mean arterial pressure (MAP), and heart rate (HR); changes in oxygenation measured as the ratio of arterial oxygen tension (PaO2)

to fraction of inspired oxygen (FiO2); and measurement of maximum methaemoglobin level as a marker of toxicity. In total four randomized trials involving 210 participants were included in this review. We observed no differences in mortality (OR 1.67, 95% CI 0.38 to 7.30; P = 0.50); PHTC (OR 0.80, 95% CI 0.15 to 4.18; P = 0.79); changes in MPAP (treatment effect -2.94 mm Hg, 95% CI -9.28 to 3.40; P = 0.36), MAP (treatment effect -3.55 mm Hg, 95% CI -11.86 to 4.76; P = 0.40), HR (treatment effect 0.02 bpm, 95% CI -8.13 to 8.18; P = 1.00), or PaO2:FiO2 (mean difference 17.18, 95% CI -28.21 to 62.57; P = 0.46). There was a significant increase in the methaemoglobin level (mean difference 0.30%, 95% CI 0.24 to 0.36; P < 0.00001) in patients treated with iNO, although levels did not reach toxicity levels. Data from long-term mortality, neurodevelopmental disability, and length of stay were not available. Two trials had a low risk of bias. Very low quality of the evidence was observed considering grading of the outcomes. No differences with the use of iNO in the outcomes reviewed. No data were available for several clinical outcomes including long-term mortality and neurodevelopmental outcome. We found it difficult to draw valid conclusions given concerns regarding methodologic quality, sample size, and heterogeneity (Bizzarro et al., 2014).

A third Cochrane Review found that 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 (Gebistorf et al., 2016).

National and Specialty Organizations

The **American Academy of Pediatrics (AAP)** published the following recommendations for iNO therapy:

- Results of randomized controlled trials and meta-analysis study indicate that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure.
- The majority of evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities
- The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants.
- Results of a multicenter, randomized controlled trial suggest that treatment with a high dose of iNO (20 ppm) beginning in the second postnatal week may provide a small reduction in the rate of BPD. However, these results need to be confirmed by other trials.
- An individual-patient data meta-analysis included 96% of preterm infants enrolled in all published iNO trials; they found no statistically significant differences in iNO effect according to any of the patient-level characteristics, including gestational age, race, oxygenation index, postnatal age at enrollment, evidence of pulmonary hypertension, and mode of ventilation.
- There are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood (Kumar & Committee on Fetus and Newborn, AAP, 2014).

The **American Association for Respiratory Care (AACR)** clinical practice guidelines on INO for neonates with acute hypoxic respiratory failure include the following recommendations:

- A trial of INO is recommended in newborns (≥ 34 wk gestation, < 14 d [days] of age) with PaO2 < 100 mm Hg [millimeters of mercury] on FIO2 1.0 and/or an oxygenation index (OI) > 25.
- INO therapy be instituted early in the disease course, which potentially reduces the length of mechanical ventilation, oxygen requirement, and stay within the intensive care unit.
- INO should not be used routinely in newborns with congenital diaphragmatic hernia.
- The recommended starting dose for INO is 20 ppm [parts per million].
- FDA-approved INO delivery systems should be used to assure consistent, safe gas delivery during therapy.
- INO therapy should not be used routinely in newborns with cardiac anomalies dependent on right-to-left shunts, congestive heart failure, and those with lethal congenital anomalies.
- INO therapy should not be used routinely in postoperative management of hypoxic term or near-term infants with congenital heart disease (DiBlasi et al., 2010).

The **American Heart Association and American Thoracic Society (AHA/ATS)** *Pulmonary Hypertension (PH) Guidelines* include the following recommendations for persistent PH of the newborn:

- Inhaled nitric oxide (iNO) is indicated to reduce the need for extracorporeal membrane oxygenation (ECMO) support in term and near-term infants with persistent PH of the newborn (PPHN) or hypoxemic respiratory failure who have an oxygenation index that exceeds 25 (Class I, Level A recommendation).
- iNO is indicated in postoperative 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 (Class 1, Level B recommendation) (Abman et al., 2015).

SUPPLEMENTAL INFORMATION

None.

CODING & BILLING INFORMATION

CPT Code

CPT	Description
94799	Unlisted pulmonary service or procedure

HCPCS Codes – N/A

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

10/13/2021	Policy reviewed, no changes to criteria; updated references. Coding reviewed on 6/8/2021 – added CPT 94799, removed CPT codes 94002, 94003 and 93463.
9/16/2020	Policy reviewed, no changes, updated references.
9/18/2019	Policy reviewed, clinical criteria updated based on new literature and guidelines. Added criteria for congenital heart defects causing PAH and pulmonary hypertensive crisis associated with heart or lung surgery. Updated the Continuation of Therapy section based on new guidelines and coverage exclusions; updated professional society guidelines and reference.
6/22/2017, 3/8/2018	Policy reviewed, no changes.
7/21/2016	Policy reviewed by staff from the NICU program and neonatologists Drs. Karotkin and Dubose. Changes to initiation of treatment criteria; includes OI index measured x2 15 min apart and failure to respond to optimal medical management. Initial approval will be granted for 72 hours with re-evaluation criteria required every 72 hours. Bronchopulmonary dysplasia added as an exclusion.
12/2015	Policy reviewed by staff from the NICU program and neonatologists Drs. Karotkin and Dubose. No changes to criteria.
10/30/2013	Policy reviewed, no changes.
10/4/2012	New policy.

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APPENDIX

Reserved for State specific information *(to be provided by the individual States, not Corporate). Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*