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

Last Approval: 10/09/2024
Next Review Due By: October 2025

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. References included were accurate at the time of policy approval and publication.

OVERVIEW

Inhaled nitric oxide (iNO) is a gas that is used in conjunction with respiratory support and other appropriate agents in the treatment of pulmonary hypertension. iNO is a selective and potent pulmonary vasodilator when administered via inhalation (Klinger 2022). iNO may be administered by a variety of respiratory support modalities, including low-flow and high flow nasal cannula, continuous positive airway pressure, non-invasive positive pressure ventilation, conventional mechanical ventilation, and high-frequency ventilation (high-frequency oscillatory ventilation [HFOV] and high-frequency jet ventilation [HFJV]) (Stark & Eichenwald 2023). iNO is used in the treatment of neonates that are ≥34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension (FDA 2020), where it may improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) (Stark & Eichenwald 2023).

According to Stark & Eichenwald (2023), “persistent pulmonary hypertension of the newborn (PPHN) occurs when pulmonary vascular resistance remains abnormally elevated after birth, resulting in right-to-left shunting of blood through fetal circulatory pathways.” The result of PPHN is severe hypoxemia that may or may not respond to respiratory support (Stark & Eichenwald 2023). The severity of hypoxemia may be determined by calculating the oxygenation index (OI). The OI is used to determine when to utilize specific interventions for the management of hypoxemia (Theodore 2023). An OI < 15 is considered mild hypoxemia, an OI ≥ 15 and < 25 is considered moderate hypoxemia, an OI ≥ 25 and < 40 is considered severe hypoxemia, and an OI ≥ 40 is considered very severe hypoxemia (Stark & Eichenwald 2023). A single OI measurement provides a “snapshot in time” of the current severity of hypoxemia and serial OI measurements are obtained to trend the severity of hypoxemia over time (DiBlasi et al. 2010). If the severity of hypoxemia is increasing and there is concern that an intervention needs to be performed, at least two OI measurements will be obtained at least 15 minutes apart. Administration of oxygen at 100% fraction of inspired oxygen (FiO_2) is typically the first treatment for PPHN due to the pulmonary vasodilatory effects of oxygen (Stark & Eichenwald 2023). iNO is typically recommended as an intervention once the OI is > 25 and/or there is evidence of severe right ventricular dysfunction as a result of PPHN that has not responded to administration of oxygen at 100% FiO_2 (Stark & Eichenwald 2023).

The initial recommended starting dose of iNO is 20 parts per million (ppm) (FDA 2015; Stark & Eichenwald 2022). The infant is monitored for an adequate response to iNO following initiation of therapy. An adequate response to iNO is noted as an improvement in the partial pressure of oxygen in the arterial blood (PaO_2) on an arterial blood gas or a 20% increase in oxygen saturation (SpO_2) within the first 15 minutes from initiation of therapy (Stark & Eichenwald 2023). Once adequate oxygenation is achieved, the dosage of iNO is weaned incrementally, typically in “halves” until the dosage is at 5 ppm (20 ppm to 10 ppm to 5 ppm). Once at 5 ppm, the dosage is weaned in increments of 1 ppm. The dosage is then turned off from 1 ppm. The dosage of iNO may be weaned as soon as 4 hours from the initiation of therapy provided that the FiO2 has been decreased to at least 60% (Stark & Eichenwald 2022). However, the infant must be monitored for rebound hypoxemia with every dosage decrease. Rebound hypoxemia is typically a result of the delivery of iNO disrupting the body’s natural production of nitric oxide (McGlothlin et al. 2022). Rebound hypoxemia may be corrected by returning to the set dosage prior to the last wean. Subsequent dosage weans may occur less frequently or at lower dosage decreases (McGlothlin et al. 2022). Recurrent rebound hypoxemia may be an indication

that additional medical management, such as sildenafil, intravenous fluids, vasopressors, or inotropic agents, may be indicated to successfully discontinue administration of iNO (McGlothlin et al. 2022; Stark & Eichenwald 2023).

Overall data suggests that routine usage of iNO in infants born with a congenital diaphragmatic hernia (CDH) is not recommended based on a lack of long-term benefits noted in most studies (Hedrick & Adzick 2024). Additionally, early usage of iNO in infants born with a CDH has been associated with increased mortality and use of ECMO (Noh et al. 2023). However, researchers note that infants with a CDH that also have normal left ventricular function and right-to-left shunting may benefit from iNO (Hedrick & Adzick 2024).

Regulatory Status

The Food and Drug Administration (FDA) approved the INOmax iNO delivery system (INO Therapeutics/Mallinckrodt Manufacturing LLC) in 1999 for use in intubated infants in the neonatal intensive care unit with hypoxemic respiratory failure (FDA 1999). Subsequent FDA approvals have expanded coverage to include multiple respiratory support devices, including high-flow nasal cannula and CPAP device and transport ventilators ([1]FDA 2020), Subsequent FDA approval has also incorporated neonatal transport as a secondary targeted clinical setting ([1]FDA 2020). According to FDA labeling, the initial recommended starting dose for infants is 20 ppm with continued use for up to 14 days or until improvement in the underlying disease process results in adequate oxygenation.

Additional iNO delivery devices have received FDA approval. The AeroNOx Universal, AeroNOx Bedside, and AeroNOx Transport systems (Pulmonox Medical Corp) received initial FDA approval on August 4, 2000 (FDA 2000). The NOxBOXi Nitric Oxide Delivery System (Praxair Distribution, Inc.) received initial FDA approval on October 2, 2018 (FDA 2018). The AeroNOx 2.0 Nitric Oxide Titration & Monitoring System (International Biomedical) received FDA approval on March 10, 2020 ([2]FDA 2020). The Ulspira TS Nitric Oxide Therapy System (Airgas Therapeutics) received FDA approval on June 30, 2023 (FDA 2023) and the Evolve Nitric Oxide Delivery System (Mallinckrodt Manufacturing LLC) received FDA approval on May 28, 2024 (FDA 2024). All iNO delivery devices have received FDA approval for use in the neonatal intensive care unit and neonatal transport settings with the same indications as the INOmax. Additional FDA regulatory decisions for iNO delivery systems may be obtained by searching product code "MRN" in the FDA 510(k) Premarket Notification database.

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 documented severe hypoxic respiratory failure secondary to persistent pulmonary hypertension and **ALL** the following:
    a. Respiratory failure despite appropriate maximum medical therapy that includes **ALL** the following:
        i. FiO2 concentration of 100%
        ii. Failure to respond to additional optimal medical treatments which must include advanced cardiovascular support, attempts to correct acid-base balance, and high-frequency ventilation (high-frequency oscillatory or high-frequency jet)
    b. Echocardiogram findings suggestive of persistent pulmonary hypertension
    c. Absence of a congenital diaphragmatic hernia except when used during the repair of a congenital diaphragmatic hernia and limited to patients with **ALL** the following:
        i. Suprasystemic pulmonary vascular resistance with right-to-left shunting across the foramen ovale causing critical preductal hypoxemia
        ii. After optimal lung inflation
        iii. Adequate left ventricle performance is established.
    d. Facility must have the availability of ECMO or an established mechanism for timely transfer of infants to an ECMO center
    e. Facility must have personnel trained in the administration of iNO

2. iNO is indicated for 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:
        i. iNO therapy for vasodilation is used in response to cardiac bypass surgery to repair a congenital heart defect that is causing pulmonary hypertension
        ii. 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 iNO is 20 ppm. Treatment should be maintained until the underlying hypoxemia has resolved, and the neonate is ready to be weaned from iNO therapy.

NOTE: iNO should be administered using FDA-approved devices capable of administering iNO in constant concentration ranges in parts per million 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
    b. Lower oxygen requirements
    c. Lower ventilator settings
    d. Improved blood gases

2. Re-evaluation every 48 hours

3. Neonates who cannot wean: The dose of iNO should be weaned following a 4- to 6-hour period of stability and an improvement in oxygenation during which the FiO_2 is decreased to 60% to 80%

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-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, congenital diaphragmatic hernia (except as noted above), adult respiratory distress syndrome or acute lung injury, treatment in adults with positive vasoreactivity testing, post-operative 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 (RCTs) have reported that iNO improved systemic 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 due to the administration of iNO. A summary of the most relevant studies is outlined below.

Randomized Controlled Trials

The Neonatal Inhaled Nitric Oxide Study (NINOS) (1997) 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 PaO_2 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 PaO_2 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 PaO_2 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.

Systematic Reviews and Meta-Analyses

Zheng et al. (2023) completed a meta-analysis to determine "the significance of iNO on the potential occurrence and outcomes of [bronchopulmonary dysplasia] in premature infants" ≤ 34 weeks gestation at birth. A total of 11 RCTs were included with a total of 3651 preterm infants. Outcomes measured included rates of in-hospital mortality, bronchopulmonary dysplasia, grade 3 or 4 intraventricular hemorrhage, pulmonary hemorrhage, and necrotizing enterocolitis. All 11 studies evaluated the rate of in-hospital mortality and analysis revealed no statistically significant difference between the iNO and control groups (p = 0.79). All 11 studies also evaluated the rate of bronchopulmonary dysplasia and found a statistically significant difference in favor of the iNO group (p = 0.006), particularly when the iNO dose was ≥ 10 ppm (p = 0.03). Eight of the studies evaluated the rate of intraventricular hemorrhage and analysis revealed no statistically significant difference between the iNO and control groups (p = 0.34). Four of the studies evaluated the rate of pulmonary hemorrhage and found no statistically significant difference between the iNO and control groups (p = 0.37). Nine of the studies evaluated the rate of necrotizing enterocolitis and analysis revealed a statistically significant difference between the iNO and control groups that indicated iNO was associated with higher rates of necrotizing enterocolitis when an initial dose of 5 ppm was used (p = 0.03). Researchers concluded "that iNO at an initial dosage of 10 ppm seemed more effective in reducing the risk of [bronchopulmonary dysplasia] than conventional treatment and iNO at an initial dosage of 5 ppm in preterm infants at a gestational age of ≤ 34 weeks who required respiratory support. However, the incidence of in-hospital mortality and adverse events between the overall iNO group and control were similar."

Wang et al. (2019) completed a meta-analysis to determine the effects of iNO on the rates of death and usage of ECMO as well as the change in oxygenation (reported as a change in PaO_2). The meta-analysis included 8 RCTs with a total of 856 participants. Of the 856 participants, 463 were included in the iNO group and 393 were included in the control group. The control group received either a placebo gas (such as nitrogen) or no gas. Inclusion criteria for the meta-analysis included 1) newborn infants > 34 weeks gestational age and < 1 month of age that had hypoxemia that was suspected to be due to lung disease, pulmonary hypertension with right-to-left shunting, or a combination of lung disease and pulmonary hypertension with right-to-left shunting, 2) a comparison of iNO to a control group (either no

gas or a placebo gas), and 3) the primary outcomes reported were the rate of death or ECMO usage, death before hospital discharge, and the usage of ECMO before hospital discharge. Exclusion criteria included 1) infants with intracardiac shunting due to a structural CHD, 2) gestational age < 34 weeks, 3) infants with hypoxemia not related to lung disease, and 4) articles with insufficient data and review articles or case reports. The total number of events related to death or the use of ECMO was reported in 8 studies. Results showed that the iNO group had a significantly lower number of events related to either death or usage of ECMO with 162 events across 463 participants compared to 211 events across 393 participants for the control group. Death before hospital discharge was reported by 8 studies and showed that iNO tended to reduce death before hospital discharge. However, there was no significant difference between either group. The use of ECMO before hospital discharge was reported by 7 studies and showed that the iNO group had a significantly lower usage of ECMO before hospital discharged compared to the control group. There were 131 events across 447 participants in the iNO group compared to 189 events across 368 participants in the control group. Change in oxygenation following treatment was reported by 2 studies was divided into a subgroup comparing infants without a CDH and a subgroup comparing infants with a CDH. Analysis of the subgroup without a CDH showed that iNO significantly improved PaO_2 compared to the control group. Analysis of the subgroup with a CDH showed that iNO tended to increase PaO_2 compared to the control group but there was no overall significant difference between either group.

Barrington et al. (2017) completed a systematic review and meta-analysis of 17 studies to "determine the effects of treatment with iNO on death, BPD, intraventricular hemorrhage (IVH) or other serious brain injury, and adverse long-term neurodevelopmental outcomes in preterm newborn infants with hypoxic respiratory failure." Preterm infants were defined as having a gestational age < 35 weeks for this meta-analysis. All infants included in this analysis were diagnosed with respiratory failure after adequate treatment that included surfactant. The meta-analysis included 4780 participants across all studies. Inclusion criteria included randomized and quasi-randomized studies that included preterm infants with respiratory disease. The studies had to compare the effects of iNO to a control group but did not need to include a placebo. Participants were divided into 3 groups for analysis: 1) infants treated over the first 3 days of life due to defects in oxygenation, 2) preterm infants with evidence of pulmonary disease treated routinely with iNO, and 3) infants treated with iNO after 3 days of age because of an elevated risk of BPD. The primary outcomes analyzed were death before hospital discharge, the rate of BPD (defined as oxygen dependence at 36 weeks corrected gestational age), the rate of death or BPD, and the incidence of any grade of IVH and grade 3 or 4 IVH. Secondary outcomes analyzed included periventricular leukomalacia, neurodevelopmental disability, and any stage of retinopathy of prematurity and ≥ stage 3 retinopathy of prematurity. A total of 10 studies were included in group 1 (treated in first 3 days of life), 4 studies were included in group 2 (evidence of pulmonary disease treated routinely with iNO), and 3 studies were included in group 3 (infants treated after 3 days of age). Survival to discharge was reported by all included trials and analysis showed no significant difference across all 3 groups. Death before 36 weeks corrected gestational age was reported by 9 studies with 5 of those studies reporting for group 1 and 1 study reporting for group 3. Analysis showed no significant effect across either group. Diagnosis of BPD among survivors at 36 weeks corrected gestational age was reported by 15 studies and analysis revealed no significant effect across all groups. Combined death and BPD outcomes were available in all studies and there was no significant effect noted for all groups. IVH outcomes were noted to only be reported for group 1 as a result of "most cases of IVH occur[ring] in [the] first three days of life; therefore, studies with later entry would not be expected to report an effect on IVH." There was no evidence to suggest an impact on the overall frequency of IVH (grades 1-4). However, there was an "almost significant" increase in the incidence of severe IVH (grades 3 and 4). Neurodevelopmental outcomes were reported in 7 studies with 6 studies showing no significant effect and 1 study describing a significant reduction in the frequency of cerebral palsy, bilateral blindness, and bilateral hearing loss. Overall, this meta-analysis showed no significant effects of iNO at improving survival or reducing lung injury in preterm infants.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Noh et al. (2023) completed a multicenter cohort study to determine if the early use of iNO (within the first 3 days of life) affected mortality or the use of ECMO in infants born with a CDH. A total of 1777 infants were included in the study with 863 receiving early iNO and 914 receiving routine care. Researchers noted that infants that received early iNO typically had a lower birth weight, larger CDH defect size, abnormal ventricular size and function, and more severe pulmonary hypertension compared to those in the routine care group. Even after accounting for these variables, researchers noted that infants receiving early iNO had significantly increased rates of mortality and ECMO usage compared to the routine care group.

National and Specialty Organizations

The **Canadian Congenital Diaphragmatic Hernia Collaborative (CCDHC)** published a 2023 update to their clinical practice guidelines for the diagnosis and management of CDH (Puligandla et al. 2024). The update states the following regarding the use if iNO in infants with a CDH: "The use of targeted pulmonary vasodilator therapy is recommended in the context of CDH-associated pulmonary hypertension when standard cardiorespiratory maneuvers fail to maintain adequate oxygenation or cardiac function. iNO may be considered as part of the treatment regimen but only in the context of demonstrable echocardiographic and clinical evidence of improvement, which, if lacking, should lead to its cessation."

The **Canadian Pediatric Society (CPS)** published a practice point for the use of iNO in newborns. The practice point makes the following recommendations (CPS 2023):

- The use of iNO is recommended for late pre-term and term infants with hypoxic respiratory failure, specifically with an OI > 15 to 20 or a PaO_2 < 100mmHg while receiving 100% oxygen.
- iNO therapy can be safely initiated during neonatal transport.
- iNO should be initiated at 20 ppm in near-term and term infants. A clinical response should be achieved within 30 minutes of initiation.
- Routine use of iNO for preterm infants is not recommended. However, "iNO may be considered as a rescue modality in preterm infants with early-onset refractory hypoxic respiratory failure when associated with premature rupture of membranes or oligohydramnios."
- A trial of iNO may be considered in infants with a CDH and hypoxic respiratory failure "despite optimal lung recruitment and with echocardiographic evidence of supra-systemic pulmonary hypertension and adequate left ventricular function."

The **European Pediatric Pulmonary Vascular Disease Network (EPPVDN)** published an updated consensus statement in 2019 with recommendations for the diagnosis and treatment of pediatric pulmonary hypertension. Recommendations are assigned a class of recommendation (I-III) and a level of recommendation (A-C) based on published evidence and member voting. The consensus statement had the following recommendations for supportive measures and pharmacotherapy in PPHN and pulmonary hypertension associated with BPD and neonatal chronic lung disease (Hansmann et al. 2019):

- iNO is an indicated treatment for PPHN in mechanically ventilated near-term and term infants to improve oxygenation and reduce the need for ECMO if the PaO2 is < 100 mmHg while receiving oxygen at 100% FiO2 or the OI exceeds 25 (Class I, Level A).
- The administration of intravenous sildenafil is effective for weaning iNO (Class I, Level C).
- Evidence is not well-established for the usage of iNO in preventing the incidence of BPD in preterm infants that are < 34 weeks gestational age (Class IIB, Level C).
- iNO may be considered as a treatment option for infants < 34 weeks gestation with respiratory failure and confirmed pulmonary hypertension (Class IIB, Level C).
- iNO may be considered post-operatively for the treatment of pulmonary hypertension to improve oxygenation and reduce the risk of a pulmonary hypertensive crisis in mechanically ventilated patients (Class IIB, Level B).

The **National Institute for Health and Care Excellence (NICE)** published guidelines in 2019 recommending against the routine use of iNO for "preterm babies who need respiratory support for respiratory distress syndrome…unless there are other indications such as pulmonary hypoplasia or pulmonary hypertension." NICE cited a lack of evidence of benefit in preterm infants. In addition, the use of iNO in infants less than 34 weeks gestation is considered off-label use (NICE 2019).

The **American Heart Association and American Thoracic Society (AHA/ATS)** published guidelines in 2015 for the treatment of pediatric pulmonary hypertension that include the following recommendations for PPHN (Abman et al. 2015):

- iNO is indicated to reduce the need for ECMO support in term and near-term infants with PPHN or hypoxemic respiratory failure who have an OI > 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 vasodilatory properties, rapid effect onset, and ease of administration (Class 1, Level B recommendation).

The **American Academy of Pediatrics (AAP)** published the following recommendations for iNO therapy (Kumar et al. 2014):

- Results of RCTs and meta-analyses indicate that neither rescue nor routine use of iNO improves survival in preterm infants (< 34 weeks gestational age) 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 IVH, 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, RCT 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, OI, 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.

The **American Association for Respiratory Care (AARC)** clinical practice guidelines on iNO for neonates with acute hypoxic respiratory failure include the following recommendations (DiBlasi et al. 2010):

- A trial of iNO is recommended in newborns (≥ 34 weeks gestational age and < 14 days of age) with a PaO2 < 100 mm Hg on FiO_2 100% and/or an 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 a CDH.
- The recommended starting dose for iNO is 20 ppm.
- 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 CHD.

SUPPLEMENTAL INFORMATION

Classification of prematurity based on gestational age (Kaneshiro 2022; Mandy 2022; Stewart et al. 2019; WHO 2023):

- Extremely preterm: less than 28 weeks
- Very preterm: 28 0/7 weeks through 31 6/7 weeks
- Moderate preterm: 32 0/7 weeks through 33 6/7 weeks
- Late preterm: 34 0/7 weeks through 36 6/7 weeks
- Early term: 37 0/7 weeks through 38 6/7 weeks
- Full term: 39 0/7 weeks through 40 6/7 weeks
- Late term: 41 0/7 weeks through 41 6/7 weeks
- Post term: greater than or equal to 42 weeks

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
94799	Unlisted pulmonary service or procedure [when specified as iNO Therapy]

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

10/09/2024	Policy reviewed, no changes to criteria.
10/12/2023	Policy reviewed, changes to criteria include clarification of gestational age ≥ 34 weeks, addition of HFJV, and removal of OI requirement. Updated Overview, Summary of Medical Evidence, and References sections. IRO Peer Review on September 26, 2023 by a practicing, board-certified physician with a specialty in Neonatal-Perinatal Medicine.
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. IRO Peer Review on September 14, 2021, by a practicing, board-certified physician with specialties in Pediatrics, Neonatal-Perinatal Medicine.
09/16/2020	Policy reviewed, no changes, updated references.
09/18/2019	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.
03/08/2018	Policy reviewed, no changes.
06/22/2017	Policy reviewed, no changes.
07/21/2016	Policy reviewed by staff from the NICU program and neonatologists. 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. No changes to criteria.
10/30/2013	Policy reviewed, no changes.
10/04/2012	New policy.

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