

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. 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 (Hu et al. 2026). 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]) (Hu et al. 2026; Stark & Eichenwald 2026). 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, where it may improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) (Hu et al. 2026; Stark & Eichenwald 2026).

According to Stark & Eichenwald (2026), “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 conventional respiratory support, including high-frequency ventilation (Hu et al. 2026; Stark & Eichenwald 2026; Chojnacka et al. 2025). 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 2026). An $OI < 15$ is considered mild hypoxemia, an $OI \geq 15$ and < 25 is considered moderate hypoxemia, an $OI \geq 25$ and < 40 is considered severe hypoxemia, and an $OI \geq 40$ is considered very severe hypoxemia (Stark & Eichenwald 2026; Chojnacka et al. 2025). 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 2026).

PPHN may be associated with an underlying cause, such as meconium aspiration syndrome or respiratory distress syndrome (Chojnacka et al. 2025). Treating the underlying cause of PPHN is necessary for the overall treatment of PPHN and can reduce the amount of time a neonate requires iNO or eliminate the need for iNO. In infants requiring respiratory support, it is recommended to optimize ventilation and lung inflation, including the use of high-frequency ventilation (HFOV or HFJV) and surfactant administration, prior to the initiation of iNO (Hu et al. 2026; Chojnacka et al. 2025). 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 the administration of oxygen at 100% FiO_2 and optimized lung inflation (Stark & Eichenwald 2026; Chojnacka et al. 2025). Implementing optimal ventilation and lung inflation strategies can improve hypoxemia while the underlying cause of hypoxemia is treated (Chojnacka et al. 2025). Additionally, optimizing ventilation and lung inflation can improve the delivery of iNO as **iNO is absorbed into the pulmonary capillary bed through recruited alveoli** (Hu et al. 2026).

Additionally, iNO may be beneficial in the pre-operative, perioperative, and post-operative management of neonatal and pediatric patients with pulmonary hypertension due to certain congenital heart defects (Hu et al. 2026; Ollosu et

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



al. 2026). According to Ollosu et al. (2026), “postoperative pulmonary arterial hypertension is often exacerbated by increased pulmonary vascular reactivity, where vasospastic triggers cause abrupt increases in pulmonary arterial pressure and resistance.” The use of cardiopulmonary bypass during congenital heart defect surgical repair can activate inflammatory cascades and platelet activation which in turn “promote endothelial dysfunction and vasoconstriction in the pulmonary bed, acutely raising pulmonary vascular resistance and predisposing susceptible patients to right ventricular failure and pulmonary hypertensive crises (Hu et al. 2026).” Another common occurrence related to cardiopulmonary bypass is the development of low cardiac output syndrome, with a reported incidence between 17% and 67% in the pediatric population (Abouzid et al. 2023). The postoperative administration of iNO can relax the pulmonary vascular smooth muscle and counteract an increased pulmonary vascular resistance. Studies suggest that nitric oxide delivered directly into the cardiopulmonary bypass oxygenator sweep gas during congenital heart surgery leads to decreased ventilator and intensive care length of stay, less development of low cardiac output syndrome, and lower usage of ECMO; however, “heterogeneity and limited long-term endpoints preclude firm conclusions” on efficacy (Hu et al. 2026).

The initial recommended starting dose of iNO is 20 parts per million (ppm) (Stark & Eichenwald 2026; Mitra et al. 2023). The individual 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 (PaO₂) on an arterial blood gas or a 20% increase in oxygen saturation (SpO₂) within the first 15 minutes from initiation of therapy (Stark & Eichenwald 2026). 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) (Mitra et al. 2023). 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 gradually decreased to at least 60% (Stark & Eichenwald 2026). 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 facilitate weaning and discontinue administration of iNO (Mazepa et al. 2026; McGlothlin et al. 2022; Stark & Eichenwald 2026).

Overall data suggests that routine usage of iNO in infants born with a congenital diaphragmatic hernia is not recommended based on a lack of long-term benefits noted in most studies (Hedrick & Adzick 2026). Additionally, early usage of iNO in infants born with a congenital diaphragmatic hernia has been associated with increased mortality and use of ECMO (Noh et al. 2023). However, researchers note that infants with a congenital diaphragmatic hernia that also have normal left ventricular function and significant right-to-left shunting (preductal SpO₂ < 85% or pre- to postductal SpO₂ difference of > 10%) may benefit from iNO (Hedrick & Adzick 2026).

Regulatory Status

In 1999, the U.S. Food and Drug Administration (FDA) approved INOmax (nitric oxide) gas for inhalation (INO Therapeutics, Inc.) in conjunction with ventilatory support and other appropriate agents in the treatment of term and near-term (>34 weeks) neonates with hypoxemic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for ECMO. 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.

Multiple iNO delivery devices have received FDA clearance. The Datex-Ohmeda Inovent Delivery System (DATEX OHMEDA), the AeroNOx Universal, AeroNOx Bedside, and AeroNOx Transport systems (Pulmonox Medical Corp) received initial FDA clearance in 2000. The NOxBOXi Nitric Oxide Delivery System (Praxair Distribution, Inc.) received initial FDA clearance in 2018. A class I recall was issued for the NOxBOXi by the FDA on October 6, 2025 due to potential fluctuations in drug delivery if total ventilator flow is less than the minimum device requirement (FDA 2025). NOxBOXi will install updated software to correct the issue. The AeroNOx 2.0 Nitric Oxide Titration & Monitoring System (International Biomedical) received FDA clearance in 2020. The Ulspira TS Nitric Oxide Therapy System (Airgas Therapeutics) received FDA clearance in 2023 and the Evolve Nitric Oxide Delivery System (Mallinckrodt Manufacturing LLC) received FDA clearance in 2024. All devices are cleared for the delivery and monitoring of iNO, and typically for use in the neonatal intensive care unit, and some for neonatal transport settings. Additional FDA regulatory decisions for

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



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 associated with 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, including ALL the following:
 - 1) Advanced cardiovascular support
 - 2) Attempts to correct acid-base balance
 - 3) High-frequency ventilation (high-frequency oscillatory or high-frequency jet) to optimize lung recruitment*
 - *NOTE: Optimizing ventilation and lung inflation can improve the delivery of iNO due to iNO being absorbed into the pulmonary capillary bed through recruited alveoli. High-frequency ventilation is recommended as a ventilatory strategy to optimize lung recruitment and thereby maximize iNO therapy (Hu et al. 2026; Kinsella et al. 1997)
 - 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 members 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 **neonates ≥ 34 weeks gestational age at birth and pediatric members** 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 or pediatric member 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

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



3. Following a 4- to 6-hour period of clinical stability and improved oxygenation, the FiO₂ should be gradually reduced to 60% to 80% before initiating weaning of the iNO dose.
 - a. **For members with difficulty weaning iNO or refractory pulmonary hypertension despite administration of iNO therapy:** Consider the administration of sildenafil and / or other vasodilators to facilitate weaning from iNO (Hu et al. 2026; Kim et al. 2026; Mazepa et al. 2026)
4. Neonates and pediatric members who cannot be weaned from iNO after 7 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 the treatment of preterm infants < 34 weeks gestation at birth, acute bronchiolitis, bronchopulmonary dysplasia, congenital diaphragmatic hernia (except as noted above), , and vaso-occlusive crises in members with sickle cell disease is considered **experimental, investigational, and unproven** due to insufficient evidence in the peer-reviewed medical literature to establish long-term safety, efficacy, and effect on net health outcomes.
3. iNO therapy is considered **not medically necessary** as a salvage therapy for the treatment of life-threatening conditions deemed by the neonatologist / medical team as likely to result in death or significant neurological impairment despite the administration of iNO therapy (e.g., 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 inhaled nitric oxide (iNO) improved systemic oxygenation and that fewer term and near-term infants with birth age greater than 34 weeks gestation required extracorporeal membrane oxygenation (ECMO) and/or developed chronic lung disease due to the administration of iNO. A summary of the most relevant studies is outlined below.

Persistent Pulmonary Hypertension (PPHN) and Neonatal Respiratory Failure

Randomized Controlled Trials

Clark et al. (2000) conducted an RCT to evaluate if low dose nitric oxide reduced the need for ECMO in neonates with PPHN born after 34 weeks' gestation who required assisted ventilation due to hypoxemic respiratory failure. A total of 248 neonates were enrolled and randomized 1:1, creating the nitric oxide group (n=126) and the control group (n=122). Inclusion criteria were neonates (> 34 weeks gestation), four days or older, requiring assisted ventilation, had an oxygenation index of 25 or higher, echocardiographic evidence of pulmonary hypertension without structural heart disease. Pre-enrollment treatment with high-frequency ventilation and/or surfactant was encouraged. Treating physicians and nurses were blinded to the treatment group, as the respiratory therapists directed treatment and made adjustments to keep the concentration of nitric oxide within the prescribed range. The administration of the study gas (nitrogen or nitric oxide) was started at 20 ppm for four hours, at which time arterial-blood gases and methemoglobin were measured and directed whether the dose could be decreased or remain the same. The goal was to reduce the gas to 5 ppm when the neonate's condition was stable. Neonates that were unable to have a reduce gas dose were re-evaluated every four hours until criteria were met or treatment failure was assigned. Treatment was considered a failure if the neonate could not tolerate the decreased dose at 24 hours or if at 96 hours the study gas could not be discontinued. The results refuted the primary hypothesis that there would be no difference in ECMO rates between the

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



two groups, as ECMO was less common in the nitric oxide group vs the control group (38 percent vs. 64 percent, $P=0.001$). Additionally, chronic lung disease incidence was significantly lower in the nitric oxide group vs control group (7 percent vs. 20 percent, $P=0.02$). However, there was not a significant difference between the groups in all other secondary outcomes such as death rate, age at discharge, age at extubation, duration of extracorporeal membrane oxygenation, and neurologic abnormalities. The authors concluded that the administration of low dose nitric oxide independently affected ECMO use rates and chronic lung disease incidence.

Kinsella et al. (1997) conducted an RCT to evaluate the roles of iNO and high frequency oscillatory ventilation (HFOV). A total of 205 neonates were enrolled, with inclusion criteria being > 34 week gestation at birth, severe hypoxemia despite mechanical ventilation, echocardiographic evidence of PPHN. Initially, the neonates were randomly placed into either the iNO + conventional mechanical ventilation group ($n=107$) or HFOV alone group ($n=98$). Non-responders from either group were crossed over to receive combined HFOV + iNO therapy. Of the 98 HFOV neonates, 75 were non-responders and crossed over to combination therapy. Of the 107 iNO neonates, 77 were non-responders and crossed over to combination therapy. In those that crossed over to the combination therapy group, while there was little change in PaO₂ during iNO or HFOV alone treatment, there was a significant improvement in PaO₂ occurred when iNO was combined with HFOV. When stratified by disease category, meconium aspiration syndrome, respiratory distress syndrome, and idiopathic PPHN neonates had better response rates for combination therapy than either therapy alone ($p < 0.05$). Response rates were low for all treatment categories in neonates with congenital diaphragmatic hernia. This led the researchers to conclude that combination HFOV + iNO therapy is more effective than either therapy alone.

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 iNO would reduce the occurrence of death and/or initiation of 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 iNO 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 iNO or control gas. While the incidence of death by 120 days of age was similar in both groups (iNO, 14%; control, 17%), significantly fewer infants in the iNO 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 iNO treated group (46% vs. 64%, $p = 0.006$). The iNO 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 iNO group (66%) than the control group (26%, $p < 0.001$). Of the 125 infants who did not respond to 20 ppm iNO or control, similar percentages of iNO-treated (18%) and control (20%) patients had at least a partial response to 80 ppm iNO or control drug, suggesting a lack of additional benefit for the higher dose of iNO. No infant that had the study drug discontinued for toxicity. iNO 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, audiological, or neurologic evaluations.

Systematic Reviews and Meta-Analyses

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 PaO₂). 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 congenital diaphragmatic hernia 2) gestational age < 34 weeks, 3) infants with

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



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 discharge 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 congenital diaphragmatic hernia and a subgroup comparing infants with a congenital diaphragmatic hernia. Analysis of the subgroup without a congenital diaphragmatic hernia showed that iNO significantly improved PaO₂ compared to the control group. Analysis of the subgroup with a congenital diaphragmatic hernia showed that iNO tended to increase PaO₂ compared to the control group but there was no overall significant difference between either group.

Refractory Persistent Pulmonary Hypertension Following iNO Therapy

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Kim et al. (2026) conducted a single-center, retrospective cohort analysis of infants with PPHN refractory to iNO (non-responders). Infants were excluded if they had not received iNO or had major congenital anomalies (e.g., congenital diaphragmatic hernia, atrioventricular septal defect, etc.). A total of 114 infants were included for analysis. "The etiologies of PPHN included meconium aspiration syndrome (47.4%), respiratory distress syndrome (23.7%), idiopathic causes (16.7%), and early-onset sepsis (8.8%)." The infants were classified as fast (n = 23), slow (n = 59), or non-responders (n = 32) based on changes in the OI within the first 24 hours of iNO administration. A total of 16 of the non-responders received adjunctive intravenous Treprostinil. Infants were enrolled into two groups: Treprostinil-exposed group (n = 16) and Treprostinil-unexposed group (n = 98). Infants in the Treprostinil-exposed group were noted to have a lower mean gestational age (35.5±4.6 weeks vs. 38.5±3.0 weeks, p = 0.021), higher initial OI at time of iNO administration (33.3±4.8 vs. 29.6±5.6, p = 0.017), and more frequent inotropic support (100% vs. 70.4%, p = 0.011). Infants in the Treprostinil-exposed group showed improvements in OI at approximately 36 hours (with Treprostinil being initiated at 24 hours). The Treprostinil-exposed group was noted to have a significantly earlier time to iNO wean to 10ppm compared to the Treprostinil-unexposed group (p = 0.005). Additionally, the Treprostinil-unexposed group "showed a slower and more delayed improvement in oxygenation, with a more gradual decline in the OI over time" compared to the Treprostinil-exposed group. Mortality and ECMO use were not significantly different between groups despite greater illness severity in those receiving Treprostinil. Treprostinil exposure was the only variable independently associated with earlier clinical stabilization in a multivariable Cox model (HR = 4.99, 95% CI 1.47-16.98, p = 0.010). No significant differences were noted for other clinical characteristics, such as gestational age or etiology. No major adverse events were noted. Researchers noted the results suggest Treprostinil administration may be beneficial in improving oxygenation in infants; however, additional studies focused on long-term outcomes are needed.

Mazepa et al. (2026) conducted a retrospective, descriptive study of data from four hospitals to assess the profile and evolution of newborns ≥ 34 weeks gestational age at birth and ≤ 28 days of life with refractory PPHN following administration of iNO. A total of 70 infants were included. All received either epoprostenol via intravenous infusion or Treprostinil via intravenous infusion or subcutaneous administration. Median gestational age was 39 3/7 weeks. Median birth weight was 3200g. A total of 43 infants were treated with Treprostinil alone, 22 were treated with epoprostenol alone, and 5 were treated with both epoprostenol and Treprostinil. Congenital diaphragmatic hernia was the primary etiology for refractory PPHN, though each of the 4 centers had different proportions of patients with congenital diaphragmatic hernias (center 1: 45.8%, center 2: 52.4%, center 3: 57.1%, center 4: 91%). Treprostinil was initiated at a median age of 5 days of life in the congenital diaphragmatic hernia group and 1 day of life in the non-congenital diaphragmatic hernia group with a median treatment duration of 23 days in the congenital diaphragmatic hernia group and 4 days in the non-congenital diaphragmatic hernia group. Epoprostenol was initiated at a median age of 2 days of life in the congenital diaphragmatic hernia group and 1 day of life in the non-congenital diaphragmatic hernia group with a median treatment duration of 13.5 days in the congenital diaphragmatic hernia group and 4 days in the non-congenital diaphragmatic hernia group. Researchers noted that "an improvement in pH appears to occur from the third day following the initiation of prostacyclin analogue" and "the pre-ductal SpO₂ does not appear to change significantly after initiation of prostacyclin analogues, while post-ductal SpO₂ shows an upward trend." Echocardiographic improvements were also noted from the third day following initiation of prostacyclin analogue treatment with the improvement occurring more rapidly in the non-congenital diaphragmatic hernia group. Arterial

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



hypotension was a frequent event (n= 40 patients). A total of 69/70 infants required norepinephrine. Dopamine was required for 17 patients with a median treatment duration of 2 days. Epoprostenol and/or Treprostinil were discontinued in four patients due to poor hemodynamic intolerance. The median duration of iNO administration was 22.5 days in the congenital diaphragmatic hernia group and 8 days in non-congenital diaphragmatic hernia group. Approximately 33/70 infants required at least one other treatment for PPHN (e.g., bosentan, sildenafil, or inhaled prostacyclin analogue). ECMO was required in 17/70 infants (10 in congenital diaphragmatic hernia and 7 in non-congenital diaphragmatic hernia). A total of 8/17 receiving ECMO died. ECMO was initiated at a median age of 3 days of life and the median duration of ECMO was 5 days for venoarterial and 11.5 days for venovenous. Overall mortality at discharge was 45.7% (32/70). Mortality rates were 46.5% (n = 20) for the Treprostinil only group, 45.5% (n = 10) in the epoprostenol only group, and 40% (n = 2) in the group treated with both. The mortality rate in the congenital diaphragmatic hernia group was 57.5% (n = 23) vs. 30% (n = 9) in the non-congenital diaphragmatic hernia group. Two ECMO-related deaths were attributed to bleeding. Researchers concluded that “initiation of prostacyclin analogues appears to be associated with favorable outcomes in iNO refractory PPHN. The results indicate that the favorable evolution of [pulmonary hypertension] appears to be slower in the [congenital diaphragmatic hernia] group.” Additionally, higher doses and longer treatment duration were required for the congenital diaphragmatic hernia group.

Congenital Diaphragmatic Hernia

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Dang et al. (2025) conducted a retrospective, observational study at the Vietnam Children’s Hospital to determine mortality rates and associated factors in neonates with a congenital diaphragmatic hernia. The study included 74 neonates born between November 2021 and September 2023. The median gestational age was 38 weeks. Approximately 83.8% of neonates required immediate postnatal intubation. HFOV was the initial mode of ventilation in 52.7% (39/74) of cases. Approximately 13.5% (10/74) of neonates received iNO and 29.7% (19/64) received ilomedin. Approximately 6.8% (5/74) of neonates required ECMO. Milrinone was used as a pulmonary vasodilator in cases where iNO and ECMO were unavailable. The hospital mortality rate was 50% (37/74). Immediate postnatal intubation was associated with a higher risk of hospital mortality (OR 6.481, 95% CI 1.310-32.072). The use of HFOV as the initial mode of ventilation was associated with significantly increased risk of hospital mortality (OR 18.729, 95% CI 5.793-60.549) with 31/39 dying. All infants receiving iNO or ECMO died. Fifteen out of 19 receiving ilomedin died. Researchers noted that all neonates in the study were referred from other hospitals and generally had more severe clinical presentations necessitating transfer, likely leading to disproportionate representation of outcomes.

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 congenital diaphragmatic hernia. 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 congenital diaphragmatic hernia 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.

Congenital Heart Defects in Neonates and Pediatrics

Randomized Controlled Trials

Kolcz et al. (2022) conducted an RCT to assess the influence of nitric oxide administration during cardiopulmonary bypass for congenital heart defect repair. A total of 115 patients undergoing Fontan surgery were randomized to receive nitric oxide (Fontan-NO group, n = 48) or control (Fontan-only, n = 49) with 18 patients being excluded due to participation refusal, infection, severe extracardiac abnormalities, or procedure changes. The Fontan-NO group received nitric oxide administered directly into the oxygenator during cardiopulmonary bypass. Participant ages ranged from 1.8 years to 3.3 years. Cardiac defects included hypoplastic left heart syndrome variants (n = 55), tricuspid atresia (n = 29), hypoplasia of the right ventricle (n = 8), double inlet left ventricle (n = 7), double outlet right ventricle (n = 6), pulmonary atresia and intact ventricular septum (n = 5), and heterotaxy syndrome (n = 5). Those receiving nitric oxide had significantly shorter respiratory support time (median duration 9.3 hours Fontan-NO vs 13.9 hours Fontan-only, p = 0.03), intensive care length of stay (median duration 3.4 days Fontan-NO vs 4.3 days Fontan-only, p = 0.04), and lower pulmonary artery pressures immediately following separation from cardiopulmonary bypass until 8 hours after separation from cardiopulmonary bypass. Additionally, those receiving nitric oxide had lower concentration of lactates and glucose after separation from cardiopulmonary bypass and lower catecholamine index.

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026
Next Review Due By: October 2027



Systematic Reviews and Meta-Analyses

Ollosu et al. (2026) conducted a systematic review with network meta-analysis with goal of identifying the most effective vasodilator or inodilator in reducing perioperative mortality and morbidity in pediatric patients undergoing surgery for a congenital heart defect. A total of 28 studies were included, with 15 of the included studies enrolling patients at high risk of developing post-operative pulmonary hypertension. A total of 3118 patients were included across all studies. Analysis for perioperative mortality included 15 trials with a total of 2255 patients with no statistically or clinically significant difference noted in mortality between those treated with iNO and those in the control group. Intravenous levosimendan ranked highest in decreasing post-operative mortality, although the effect was not statistically significant. Intravenous sildenafil and iNO significantly reduced the duration of mechanical ventilation (MD = -15.10, 95% CI -24.53 to -5.67 and MD = -6.34, 95% CI -12.16 to -0.53 respectively), though none of the effects were clinically relevant. Inhaled levosimendan, intravenous levosimendan, and intravenous milrinone were associated with longer duration of mechanical ventilation. iNO significantly shortened intensive care length of stay (MD = -0.68, 95% CI -1.30 to -0.06), although the effect was not statistically or clinically significant. Inhaled iloprost, iNO, and enteral sildenafil significantly reduced mean pulmonary artery pressure while intravenous iloprost was associated with an increase in mean pulmonary artery pressure. The most common adverse events were cardiac complications observed in 142/1651 (8.6%) patients followed by respiratory, thoracic, and mediastinal complications occurring in a combined total of 62/1635 (3.8%) patients. General cardiovascular events occurred in 52/679 (7.7%) receiving iNO compared to 43/685 (6.3%) in the placebo group. Postoperative arrhythmias occurred in 34/245 (13.9%) patients, with 9 occurring in the intravenous aminophylline group (9/72, 12.5%), 9 in the levosimendan group (9/47, 19.1%), 7 in the milrinone group (7/39, 17.9%), and 9 in the control group (9/87, 10.3%). Low cardiac output syndrome was observed in 3/144 (2.1%) patients. Adverse respiratory events and thoracic or mediastinal complications occurred in 38/1448 (2.6%) patients, with 16 of those being in the iNO group (16/679, 2.4%), 1 in the tadalafil group (1/21, 4.8%), 3 in the sildenafil group (3/41, 7.3%), and 18 in the control group (18/707, 2.5%). Pneumonia occurred in 24/229 (10.5%) patients with 13 being in the placebo group (13/115, 11.5%), 10 in the levosimendan group (10/94, 10.6%), and 1 in the sildenafil group (1/20, 5.0%). Researchers noted that “consistent association between specific treatments and adverse events could not be established.” Regarding outcomes, it was noted that “intravenous sildenafil and iNO are associated with a statistically significant reduction in the duration of mechanical ventilation, with iNO also showing a reduction in intensive care unit length of stay and mean pulmonary artery pressure. Vasodilators and inodilators did not significantly decrease perioperative mortality in pediatric congenital heart disease.” However, all studies “were judged to have some concerns regarding risk of bias...undermin[ing] confidence in these findings.”

Abouzid et al. (2023) conducted a systematic review and meta-analysis to determine the effects of nitric oxide administered during cardiopulmonary bypass on mortality rates, mechanical ventilation and cardiopulmonary bypass duration, and intensive care length of stay. A total of 17 studies were included with 10 studies involving adults and 7 studies including children, infants, and neonates. A total of 2897 patients were included across all studies and populations. No significant differences between groups (nitric oxide vs. control) were noted for mortality or cardiopulmonary bypass duration. Intensive care length of stay was significantly lower for those receiving nitric oxide (MD = -0.80, 95% CI -1.31 to -0.29, $p = 0.002$). Hospital length of stay was significantly lower without sensitivity analysis (MD = -0.41, 95% CI -0.79 to -0.02, $p = 0.04$). However, there was no significant difference between groups when sensitivity analysis was applied (MD = -0.31, 95% CI -0.69 to 0.07, $p = 0.11$). The duration of mechanical ventilation was significantly different between groups for the total population (MD = -3.04, 95% CI -5.42 to -0.67, $p = 0.01$). A subgroup analysis for duration of mechanical ventilation showed no significant difference between groups for adults; however, a significant difference was observed between groups for children (MD = -4.58, 95% CI -5.63 to -3.53, $p < 0.001$). Researchers noted that administering nitric oxide during cardiopulmonary bypass “is associated with overall lower intensive care unit and hospital stay and lower duration of mechanical ventilation, especially in children.” However, “sensitivity analysis showed insignificant results for the influence of nitric oxide on reducing intensive care unit time for children and overall hospital stay...[indicating] further studies on a larger sample size for more robust evidence” are needed. Additionally, there was moderate-to-high heterogeneity present in most analyses, likely limiting the generalizability of findings.

Extremely, Very, and Moderate Preterm (< 34 Weeks) Neonates

Randomized Controlled Trials

King et al. (2026) conducted a single-center, double-blind RCT to assess if iNO for early echocardiographic pulmonary hypertension decreases the risk of death or BPD in extremely preterm infants (≤ 29 weeks GA) receiving positive pressure ventilation at 72 $\pm$ 24 hours after birth. Screening echocardiograms were obtained at 72 $\pm$ 24 hours post-birth. Exclusion criteria included flow-associated pulmonary hypertension from large left-to-right patent ductus arteriosus,

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



severe left ventricular dysfunction (ejection fraction < 40%), and/or the presence of a complex cardiac defect. Those with genetic conditions, major anomalies, or maternal COVID history were also excluded. Enrolled infants were categorized as having moderate (estimated pulmonary artery pressure > 0.5 to < systemic systolic blood pressure or flat end-systolic interventricular septum) or severe (estimated pulmonary artery pressure $\geq$ systemic systolic blood pressure or end-systolic septal bowing into the left ventricle) pulmonary hypertension. Infants were randomized to 20ppm iNO or placebo with randomization stratified by gestational age and pulmonary hypertension severity. The intervention response was defined as changes in pulmonary artery pressure on echocardiogram and/or respiratory response through respiratory severity score, SpO₂/FiO₂ ratio, or OI. Non-responders were defined as having a lack of improvement in pulmonary artery pressures on serial echocardiograms and/or < 10% improvement from baseline in respiratory severity scores, SpO₂/FiO₂ ratio, or OI. Initially, 180 neonates were enrolled with 148 excluded, leaving 32 for randomization. All but one infant received invasive ventilation and surfactant. Two neonates had severe pulmonary hypertension with the remaining neonates having moderate pulmonary hypertension. There were no significant differences in maternal or neonatal characteristics. There was no difference in mortality or BPD and treatment response within 72 hours did not differ between groups. Treatment duration also did not differ between groups. Of the excluded infants, 51 had received iNO before enrollment and were more likely to have lower gestational age, less antenatal steroids, lower 5-minute APGAR, higher O₂ requirement to maintain SpO₂ > 85%, severe pulmonary hypertension, IVH, and death. Authors concluded that iNO for early pulmonary hypertension may be futile in extremely preterm infants.

Systematic Reviews and Meta-Analyses

Zhou et al. (2025) performed a systematic review and meta-analysis to evaluate the safety and efficacy of iNO in preterm infants with respiratory disease such as respiratory failure, RDS, pulmonary hypoplasia, and PPHN. The review included 31 studies, including 20 RCTs and 11 cohort studies, for a total of 20,080 preterm infants (mostly < 34 weeks gestation). Key findings of the meta-analysis indicated that iNO was associated with a statistically significant reduction in the composite outcome of death or bronchopulmonary dysplasia (BPD) (risk ratio [RR] 0.94, 95% CI 0.88 to 0.99, 6 studies, n = 1954), and in BPD alone among RCTs (RR 0.91, 95% CI 0.84 to 0.99, 8 studies, n = 2196). However, iNO had no significant effect on death before discharge or at 36 weeks postmenstrual age. GRADE certainty of evidence for mortality outcomes was rated as very low due to imprecision and risk of bias, whereas evidence for BPD reduction was rated as moderate in RCTs and very low in cohort studies. The composite outcome of death or BPD in RCTs was supported by high-quality evidence, though the effect size did not reach strong statistical significance (RR 0.94, 95% CI 0.89 to 1.00). In two RCT (n = 441), iNO significantly improved pulmonary oxygenation parameters within 30 minutes of administration at 5 ppm, as evidenced by an improved oxygenation index (standard mean difference [SMD] -0.62) and increased PaO₂ (SMD 0.68). Additionally, iNO reduced the need for supplemental oxygen at 1-year corrected age (RR 0.79, 95% CI 0.65 to 0.96, 3 studies, n = 1259). For adverse effects, iNO was associated with a modest but statistically significant increase in the risk of retinopathy of prematurity (ROP) (RR 1.08, 95% CI 1.01 to 1.16, 17 studies, n = 7220), although no increase in severe ROP (stage III and above) or ROP requiring treatment was observed. iNO was also associated with a slight reduction in head circumference at 1-year corrected age (SMD -0.17), but no significant difference was found in other long-term neurodevelopmental outcomes. Additionally, no significant differences were observed between iNO and control groups for other neonatal complications, such as intraventricular hemorrhage, necrotizing enterocolitis, pulmonary hemorrhage, patent ductus arteriosus, vasopressor use, or length of hospital stay. The authors concluded that iNO may reduce the incidence of death or BPD and BPD alone in preterm infants with respiratory disease. Currently, the use of iNO in preterm infants < 34 weeks gestation is off-label and mostly limited to emergency rescue. Data indicates that the safety and efficacy of iNO for treating respiratory disease in these patients remains unclear and controversial. While iNO may reduce the incidence of the composite outcome of death or BPD and BPD alone, it shows no significant effect on other morbidities or adverse events.

Zheng et al. (2023) completed a meta-analysis to determine “the significance of iNO on the potential occurrence and outcomes of BPD in premature infants” $\leq$ 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, BPD, grade 3 or 4 IVH, 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 BPD and found a statistically significant difference in favor of the iNO group (p = 0.006), particularly when the iNO dose was $\geq$ 10 ppm (p = 0.03). Eight of the studies evaluated the rate of IVH 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

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



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 BPD 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.”

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, 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 $\geq$ 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 because 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.

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 congenital diaphragmatic hernia* (Puligandla et al. 2024). The update states the following regarding the use of iNO in infants with a congenital diaphragmatic hernia: “The use of targeted pulmonary vasodilator therapy is recommended in the context of congenital diaphragmatic hernia-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 (Mitra et al. 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 $PaO_2 < 100$ mmHg 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.

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



- 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 congenital diaphragmatic hernia 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 PaO_2 is < 100 mmHg while receiving oxygen at 100% FiO_2 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 for *neonatal respiratory care for babies born preterm* 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 a clinical report in 2014 on the *use of iNO in preterm infants*. The report was reaffirmed in August 2025, with 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.

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



- 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 $\text{PaO}_2 < 100$ mm Hg on FiO_2 100% and/or an $\text{OI} > 25$.
- iNO therapy can 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 congenital diaphragmatic hernia.
- 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 congenital heart disease.

SUPPLEMENTAL INFORMATION

Classification of prematurity based on gestational age (Kaneshiro 2022; Mandy 2025; 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

10/14/2026	Policy revised. Changes to criteria include addition of note for use of HFV to improve lung recruitment/iNO therapy, addition of "pediatric members" and sildenafil/other vasodilators for refractory pulmonary hypertension/difficulty weaning in continuation criteria section, and removal of adult-specific limitations. Policy title updated to "Neonatal and Pediatric Inhaled Nitric Oxide." IRO Peer Review on September 16, 2026 by a board-certified physician with a specialty in Neonatal-Perinatal Medicine.
10/08/2025	Policy reviewed. No changes to coverage criteria.
10/09/2024	Policy reviewed. No changes to coverage criteria.
10/12/2023	Policy revised. Changes to criteria include clarification of gestational age ≥ 34 weeks, addition of HFJV, and removal of OI requirement. 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 coverage criteria. IRO Peer Review on September 14, 2021, by a practicing, board-certified

Molina Clinical Policy

Neonatal and Pediatric Inhaled Nitric Oxide (iNO)

Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



09/16/2020	physician with specialties in Pediatrics, Neonatal-Perinatal Medicine.
09/18/2019	Policy reviewed. No changes to coverage criteria.
03/08/2018	Policy reviewed. Added criteria for congenital heart defects causing PAH and pulmonary hypertensive crisis associated with heart or lung surgery.
06/22/2017	Policy reviewed. No changes to coverage criteria.
07/21/2016	Policy revised 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 to coverage criteria.
10/04/2012	New policy.

REFERENCES

- 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/CIR.0000000000000329. Epub 2015 Nov 3. Erratum in: *Circulation*. 2016 Jan 26;133(4):e368. PMID: 26534956.
- Abouzid M, Roshdy Y, Daniel JM, et al. The beneficial use of nitric oxide during cardiopulmonary bypass on postoperative outcomes in children and adult patients: a systematic review and meta-analysis of 2897 patients. *Eur J Clin Pharmacol*. 2023 Nov;79(11):1425-1442. doi: 10.1007/s00228-023-03554-9. Epub 2023 Aug 31. PMID: 37650923; PMCID: PMC10618325.
- Barrington KJ, Finer N, Pennaforte T. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev*. 2017 Jan 3;1(1):CD000509. doi: 10.1002/14651858.CD000509.pub5. PMID: 28045472; PMCID: PMC6464861.
- Chojnacka K, Singh Y, Gahlaut S, et al. Persistent pulmonary hypertension of the newborn: a pragmatic review of pathophysiology, diagnosis, and advances in management. *Biomedicine*. 2025 Sep 24;13(10):2332. doi: 10.3390/biomedicine13102332. PMID: 41153619; PMCID: PMC12561312.
- Clark RH, Kueser TJ, Walker MW, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *Clinical Inhaled Nitric Oxide Research Group*. *N Engl J Med*. 2000 Feb 17;342(7):469-74. doi: 10.1056/NEJM200002173420704. PMID: 10675427.
- Dang DA, Van Nguyen T, Nguyen DTT, et al. Clinical characteristics and outcomes of neonates with congenital diaphragmatic hernia at the Vietnam National Children's Hospital: a retrospective observational study. *BMC Pediatr*. 2025 Oct 2;25(1):729. doi: 10.1186/s12887-025-06108-3. PMID: 41039287; PMCID: PMC12492845.
- DiBlasi RM, Myers TR, Hess DR. Evidence-based clinical practice guideline: Inhaled nitric oxide for neonates with acute hypoxic respiratory failure. *Respir Care*. 2010 Dec;55(12):1717-45. PMID: 21122181.
- Hansmann G, Koestenberger M, Alastalo TP, et al. 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension: The European Pediatric Pulmonary Vascular Disease Network (EPPVDN), endorsed by AEPC, ESPR and ISHLT. *J Heart Lung Transplant*. 2019 Sep;38(9):879-901. doi: 10.1016/j.healun.2019.06.022. Epub 2019 Jun 21. PMID: 31495407.
- Hedrick HL, Adzick NS. Congenital diaphragmatic hernia (CDH) in the neonate: Management and outcome. Updated May 1, 2026. Literature review current through July 2026. Accessed August 12, 2026. <https://www.uptodate.com>.
- Hu C, Chen Z, Lv L, et al. Clinical application of inhaled nitric oxide in conditions of excessive right heart load: a review from neonatal pulmonary hypertension to perioperative cardiac surgery management. *J Cardiovasc Dev Dis*. 2026 Feb 8;13(2):81. doi: 10.3390/jcdd13020081. PMID: 41745329; PMCID: PMC12940944.
- Kaneshiro NK. Premature infant. Updated October 20, 2024. Accessed August 12, 2026. <https://medlineplus.gov/ency/article/001562.htm>
- Kim TH, Youn SE, Chung SH. Clinical impact of treprostinil in neonates with persistent pulmonary hypertension refractory to inhaled nitric oxide: A retrospective cohort study. *Medicine (Baltimore)*. 2026 Jan 2;105(1):e46984. doi: 10.1097/MD.00000000000046984. PMID: 41496061; PMCID: PMC12778240.
- King TL, McNamara PJ, Bischoff AR. Does inhaled nitric oxide treatment of pulmonary hypertension in extremely premature infants improve patient outcomes? *J Perinatol*. 2026 Apr;46(4):678-680. doi: 10.1038/s41372-026-02666-1. Epub 2026 Apr 9. PMID: 41957165; PMCID: PMC13120996.
- Kinsella JP, Truog WE, Walsh WF, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. *J Pediatr*. 1997 Jul;131(1 Pt 1):55-62. doi: 10.1016/s0022-3476(97)70124-0. PMID: 9255192.
- Kolcz J, Karnas E, Madeja Z, et al. The cardioprotective and anti-inflammatory effect of inhaled nitric oxide during Fontan surgery in patients with single ventricle congenital heart defects: a prospective randomized study. *J Intensive Care*. 2022 Oct 13;10(1):48. doi: 10.1186/s40560-022-00639-y. PMID: 36229863; PMCID: PMC9558421.
- Kumar P; Committee on Fetus and Newborn; American Academy of Pediatrics. Use of inhaled nitric oxide in preterm infants. *Pediatrics*. 2014 Jan;133(1):164-70. doi: 10.1542/peds.2013-3444. Epub 2013 Dec 30. PMID: 24379225.
- Mandy GT. Preterm birth: Definitions of prematurity, epidemiology, and risk factors for infant mortality. Updated August 22, 2025. Literature review current through July 2026. Accessed August 12, 2026. <https://www.uptodate.com>
- Mazepa C, Mur S, Gascoin G, et al. Descriptive study of the effects of treprostinil and/or epoprostenol in newborn infants with inhaled NO refractory persistent pulmonary hypertension of the newborn (PPHN). *Therapie*. 2026 Mar 18:S0040-5957(26)00047-8. doi: 10.1016/j.therap.2026.03.001. Epub ahead of print. PMID: 42128749.
- McGlothlin DP, Granton J, Klepetko W, et al. ISHLT consensus statement: Perioperative management of patients with pulmonary hypertension and right heart failure undergoing surgery. *J Heart Lung Transplant*. 2022 Sep;41(9):1135-1194. doi: 10.1016/j.healun.2022.06.013. Epub 2022 Jun 23. PMID: 36123001.
- Mitra S, Altit G, Canadian Pediatric Society (CPS). Inhaled nitric oxide use in newborns. Published February 10, 2023. Accessed August 12, 2026. <https://cps.ca/en/documents/position/inhaled-nitric-oxide>.
- National Institute for Health and Care Excellence (NICE). Specialist neonatal respiratory care for babies born preterm. NICE guideline [NG124]. Published April 3, 2019. Accessed August 14, 2026. <https://www.nice.org.uk/guidance>

Molina Clinical Policy
Neonatal and Pediatric Inhaled Nitric Oxide (iNO)
Policy No. 121

Last Approval: 10/14/2026

Next Review Due By: October 2027



22. Neonatal Inhaled Nitric Oxide Study Group (NINOS). Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med*. 1997 Feb 27;336(9):597-604. doi: 10.1056/NEJM199702273360901. Erratum in: *N Engl J Med* 1997 Aug 7;337(6):434. PMID: 9036320.
23. Noh CY, Chock VY, Bhombal S, et al. Early nitric oxide is not associated with improved outcomes in congenital diaphragmatic hernia. *Pediatr Res*. 2023 Jun;93(7):1899-1906. doi: 10.1038/s41390-023-02491-8. Epub 2023 Feb 1. Erratum in: *Pediatr Res*. 2023 Apr 12; PMID: 36725908.
24. Ollosu M, Tripodi VF, Aresu C, et al. Efficacy and safety of pulmonary vasodilator and inodilator drugs in congenital heart disease surgery: a systematic review and network meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth*. 2026 Jan;40(1):333-346. doi: 10.1053/j.jvca.2025.08.053. Epub 2025 Aug 27. PMID: 40968005.
25. Puligandla P, Skarsgard E, Baird R, et al. Diagnosis and management of congenital diaphragmatic hernia: a 2023 update from the Canadian Congenital Diaphragmatic Hernia Collaborative. *Arch Dis Child Fetal Neonatal Ed*. 2024 Apr 18;109(3):239-252. doi: 10.1136/archdischild-2023-325865. PMID: 37879884.
26. Stark AR, Eichenwald EC. Persistent pulmonary hypertension of the newborn (PPHN): Management and outcome. Updated March 27, 2026. Literature review current through July 2026. Accessed August 12, 2026. <https://www.uptodate.com>.
27. Stewart DL, Barfield WD; Committee on fetus and newborn. Updates on an at-risk population: Late-preterm and early-term infants. *Pediatrics*. 2019 Nov;144(5):e20192760. doi: 10.1542/peds.2019-2760. Epub 2019 Oct 21. PMID: 31636141.
28. Theodore AC. Measures of oxygenation and mechanisms of hypoxemia. Updated July 22, 2026. Literature review current through July 2026. Accessed August 12, 2026. <https://www.uptodate.com>.
29. United States Food and Drug Administration (FDA). 510(k) premarket notification. EVOLVE nitric oxide delivery system. Product code MRN. 510(k): K240410. Accessed September 15, 2025. <https://www.fda.gov>
30. United States Food and Drug Administration (FDA). 510(k) premarket notification. ULSPIRA TS nitric oxide therapy system. Product code MRN. 510(k): K212409. Accessed September 15, 2025. <https://www.fda.gov>
31. United States Food and Drug Administration (FDA). 510(k) premarket notification. INOmax DSIR Plus. Product code MRN. 510(k): K200389. Accessed September 15, 2025. <https://www.fda.gov>
32. United States Food and Drug Administration (FDA). 510(k) premarket notification. AeroNOx 2.0 nitric oxide titration & monitoring system. Product code MRN. 510(k): K193481. Accessed September 15, 2025. <https://www.fda.gov>
33. United States Food and Drug Administration (FDA). 510(k) premarket notification. AeroNOx universal, model p/n 360000, aeronox bedside, model p/n 360001, aeronox transport, model p/n 360002. Product code MRN. 510(k): K000653. Accessed September 15, 2025. <https://www.fda.gov>
34. United States Food and Drug Administration (FDA). Class 1 device recall NOxBOXi nitric oxide delivery system. Issued October 6, 2025. Accessed August 21, 2026. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=215844>
35. United States Food and Drug Administration (FDA). New Drug Application (NDA). INOmax (nitric oxide). NDA: 20-845. Accessed September 23, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20845_INOmax.cfm
36. Wang X, Li C, Wang S, et al. Utility of inhaled nitric oxide for pulmonary hypertension in cyanotic congenital heart disease: a cohort study with propensity score matching. *Med Gas Res*. 2026 Jun 1;16(2):93-97. doi: 10.4103/mgr.MEDGASRES-D-25-00062. Epub 2025 Aug 18. PMID: 40826929; PMCID: PMC12413876.
37. Wang X, Li B, Ma Y, Zhang H. Effect of NO inhalation on ECMO use rate and mortality in infants born at or near term with respiratory failure. *Medicine (Baltimore)*. 2019 Oct;98(41):e17139. doi: 10.1097/MD.00000000000017139. PMID: 31593077; PMCID: PMC6799754.
38. World Health Organization (WHO). Preterm birth. Updated May 10, 2023. Accessed August 12, 2026. <https://www.who.int/news-room/fact-sheets/detail/preterm-birth>
39. Zheng Y, Wu Q, Han S. Inhaled nitric oxide in premature infants for preventing bronchopulmonary dysplasia: a meta-analysis. *BMC Pediatr*. 2023 Mar 29;23(1):139. doi: 10.1186/s12887-023-03923-4. PMID: 36991371; PMCID: PMC10053486.
40. Zhou K, Xu W, Li D, Lao C, Zou S, Liu S, et al. Inhaled nitric oxide in preterm infants with respiratory disease: a systematic review and meta-analysis. *Eur J Med Res*. 2025 Aug 29;30(1):821. doi: 10.1186/s40001-025-03008-1. PMID: 40877918; PMCID: PMC12395824.