Inhaled Nitric Oxide (INO) in Neonates

[For the list of services and procedures that need preauthorization, please refer to www.mcs.com.pr. Go to “Comunicados a Proveedores”, and click “Cartas Circulares”.]

This medical policy applies to MCS-Life Commercial Line of Business (LOB) only.

Medical Policy: MP-ME-01-08
Original Effective Date: August 25, 2008
Revised: October 18, 2016
Next Revision: October 2017

This policy applies to products subscribed by the following corporations, MCS Life Insurance Company (Commercial), and Medical Card System, Inc., provider’s contract; unless specific contract limitations, exclusions or exceptions apply. Please refer to the member’s benefit certification language for benefit availability. Managed care guidelines related to referral authorization, and precertification of inpatient hospitalization, home health, home infusion and hospice services apply subject to the aforementioned exceptions.

DESCRIPTION

Inhaled Nitric Oxide (INO) (i.e., Inomax®) is a drug considered as a pulmonary vasodilator, which in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO) (FDA, 2013).

Extracorporeal membrane oxygenation (ECMO) is a more invasive treatment that uses a pump to circulate blood through an artificial lung back into the bloodstream of a very ill neonate, by providing a heart-lung bypass support outside of the neonate’s body (MedlinePlus, 2016).

Inhaled nitric oxide has been widely studied for its selective pulmonary vasodilation effects in adults and pediatric patients. It is currently the gold standard therapy in neonates with persistent pulmonary hypertension (PPHN) and has been shown to decrease the extent to which extracorporeal membrane oxygenation (ECMO) is needed for hypoxemic respiratory failure. However, nitric oxide has not improved overall mortality in newborns affected by PPHN. Although doses up to 80 ppm have been administered in neonates, doses over 20 ppm have not been shown to be superior and increase the risk of methemoglobinemia. Inhaled nitric oxide is FDA-approved for use in neonates, it is not FDA-approved for use in other pediatric populations (Clinical Pharmacology, 2014).

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate member certificate and subscriber agreement contract for applicable diagnostic imaging, DME, laboratory, machine tests, benefits and coverage.
INDICATIONS

Medical Card System, Inc. (MCS) considers the use of Inhaled Nitric Oxide (INO) as medically necessary, for the Commercial Line of Business (LOB) ONLY, when used as a component for the treatment of hypoxic respiratory failure that meets ALL of the following criteria:

1. Term and near term (> 34 weeks of gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension; and

2. INO is utilized in conjunction with ventilatory support and other appropriate agents (e.g., vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation).

LIMITATIONS

1. The manufacturer states that use in neonates older than 14 days, or younger than 34 weeks of gestational age, currently are NOT indicated uses.

2. Available data suggest the INO is least effective in neonates with pulmonary hypoplasia (e.g., congenital diaphragmatic hernia), and therefore should not be used in neonates with this condition.

3. A trial of INO is recommended in newborns (i.e., >34 weeks) with a partial pressure of arterial oxygen in the blood (PaO₂) < 100 mm Hg, on a fraction of inspired oxygen (FiO₂) of 1.0, and/or an oxygenation index (OI) > 25.

4. It is recommended that response to a short trial (30–60 min.) of INO should be judged by an improvement in PaO₂ or oxygenation index (OI); if there is no response, INO should be discontinued.

5. The recommended dose of INO is 20 parts per million (ppm), maintained for up to 14 days or, until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned.

6. Monitoring of nitric oxide inhalation therapy should also include periodic measurement of methemoglobin and continuous monitoring of nitrogen dioxide, nitric oxide and oxygen concentrations.

CONTRAINDICATIONS / WARNINGS

1. Inhaled Nitric Oxide (INO) is contraindicated in the treatment of neonates known to be dependent upon right-to-left shunting of blood (i.e., Patent Ductus Arteriosus (PDA)-dependent congenital heart disease).

2. Patients with severe left ventricular dysfunction (New York Heart Association [NYHA] Class III-IV) should receive diagnostic or therapeutic exposure to nitric oxide only in combination with other agents known to maintain or improve left ventricular function.
3. Patients with congenital or acquired methemoglobin reductase deficiency should not receive nitric oxide inhalation therapy as they may develop significant methemoglobinemia.

4. The use of nitric oxide requires an experienced clinician. Health care professionals that administer nitric oxide must complete a comprehensive training program that is provided by the delivery system and drug manufacturers.

5. Do not abruptly discontinue Nitric Oxide (NO); however, an optimal weaning regimen has not yet been described. Abrupt discontinuation of Nitric Oxide could result in worsening pulmonary artery pressure and/or blood oxygenation (PaO$_2$), even in neonates with no apparent response to NO.

**EXPERIMENTAL/INVESTIGATIONAL/UNPROVEN COVERAGE**

Medical Card System, Inc. (MCS) considers the use of Inhaled Nitric Oxide (INO) for neonates as Experimental, Investigational or Unproven for ALL of the following indications:

1. Premature neonates (<34 weeks of gestation).
3. For the prevention of progression to Chronic Lung Disease (CLD), also known as Broncopulmonary Dysplasia (BPD), in premature neonates with respiratory failure receiving mechanical ventilation.
4. For the treatment of acute lung injury (ALI) or acute distress syndrome (ARDS).
5. Administration of inhaled nitric oxide for indications other than those approved by the FDA or in other neonatal populations, including compassionate use (AAP, 2010).

**CODING INFORMATION**

**CPT® Codes (List may not be all inclusive)**

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>+93463</td>
<td>Pharmacologic agent administration (e.g., inhaled nitric oxide, intravenous infusion of nitroprusside, dobutamine, milrinone, or other agent) including assessing hemodynamic measurements before, during, after and repeat pharmacologic agent administration, when performed (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>94002</td>
<td>Ventilation assist and management, initiation of pressure, or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, initial day</td>
</tr>
<tr>
<td>94003</td>
<td>Ventilation assist and management, initiation of pressure, or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, each subsequent day</td>
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**HCPCS CODES (List may not be all inclusive)**

<table>
<thead>
<tr>
<th>HCPCS® CODES</th>
<th>DESCRIPTION</th>
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<tr>
<td>J3490</td>
<td>Unclassified drugs</td>
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**ICD-10-CM Procedure Codes (List may not be all inclusive)**

<table>
<thead>
<tr>
<th>ICD-10 PCS CODES</th>
<th>DESCRIPTION</th>
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</thead>
<tbody>
<tr>
<td>3E0F7SD</td>
<td>Introduction of nitric oxide gas into respiratory tract, via natural or artificial opening</td>
</tr>
</tbody>
</table>

**ICD-10 Codes (List may not be all inclusive)**

<table>
<thead>
<tr>
<th>ICD-10-Codes</th>
<th>DESCRIPTION</th>
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</thead>
<tbody>
<tr>
<td>I27.0</td>
<td>Primary pulmonary hypertension</td>
</tr>
<tr>
<td>I27.2</td>
<td>Other secondary pulmonary hypertension</td>
</tr>
<tr>
<td>I27.89</td>
<td>Other specified pulmonary heart diseases</td>
</tr>
<tr>
<td>J80</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>P22.0</td>
<td>Respiratory distress syndrome of newborn</td>
</tr>
<tr>
<td>P24.01</td>
<td>Meconium aspiration with respiratory symptoms</td>
</tr>
<tr>
<td>P24.11</td>
<td>Neonatal aspiration of (clear) amniotic fluid and mucus with respiratory symptoms</td>
</tr>
<tr>
<td>P24.21</td>
<td>Neonatal aspiration of blood with respiratory symptoms</td>
</tr>
<tr>
<td>P24.81</td>
<td>Other neonatal aspiration with respiratory symptoms</td>
</tr>
<tr>
<td>P24.9</td>
<td>Neonatal aspiration, unspecified</td>
</tr>
<tr>
<td>P28.5</td>
<td>Respiratory failure of newborn</td>
</tr>
<tr>
<td>P28.9</td>
<td>Respiratory condition of newborn, unspecified</td>
</tr>
<tr>
<td>P29.3</td>
<td>Persistent fetal circulation</td>
</tr>
<tr>
<td>P84</td>
<td>Other problems with newborn</td>
</tr>
<tr>
<td>Q33.1</td>
<td>Accessory lobe of lung</td>
</tr>
<tr>
<td>Q33.4</td>
<td>Congenital bronchiectasis</td>
</tr>
</tbody>
</table>
Q33.5  Ectopic tissue in lung

Q33.8  Other congenital malformations of lung

Q33.9  Congenital malformation of lung, unspecified

REFERENCES


POLICY HISTORY

<table>
<thead>
<tr>
<th>DATE</th>
<th>ACTION</th>
<th>COMMENT</th>
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<tr>
<td>August 26, 2008</td>
<td>Origination of Policy</td>
<td>Policy revised to add investigational and experimental indications and precaution on the disruption of INO. Also added information on insufficient evidence to support INO for Prevention of Ischemia reperfusion injury/acute rejection following lung transplantation, or the treatment of acute lung injury, or vaso-occlusive crises in patients with sickle cell disease.</td>
</tr>
<tr>
<td>August 27, 2009</td>
<td>Revised</td>
<td></td>
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<tr>
<td>August 25, 2010</td>
<td>Yearly Revision</td>
<td></td>
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<tr>
<td>August 15, 2011</td>
<td>Revised</td>
<td>Policy revised to add contraindications and precaution on the disruption of INO. Contraindicated for the prevention of progression to broncopulmonary dysplasia (BPD) in premature neonates with respiratory failure receiving mechanical ventilation and in patients with congenital or acquired methemoglobinemia reductase deficiency. Code 93463 added to policy.</td>
</tr>
<tr>
<td>August 13, 2012</td>
<td>Revised</td>
<td>References updated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New Indication # 5 was added.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New Off-Label† indications (1 – 4) Section was added.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrew from Contraindications: for the management of post-operative pulmonary hypertension in pediatric patients with congenital heart disease, and put in the Off Label Use Indications.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrew from Contraindications: for the prevention of progression to</td>
</tr>
</tbody>
</table>

This document is designated for informational purposes only and is not an authorization, or an explanation of benefits (EOB), or a contract. Medical technology is constantly changing and we reserve the right to review and update our policies periodically.
December 10, 2012  
Revised  
Withdraw from Contraindications: for the management of post-operative pulmonary hypertension in pediatric patients with congenital heart disease.  
Withdraw from Contraindications: for the prevention of progression to broncopulmonary dysplasia (BPD) in premature neonates with respiratory failure receiving mechanical ventilation, and labeled it as Experimental And Investigational and Not Medically Necessary.  
New Warnings Section was added.  
Note: ALL changes from August 13, 2012 were reviewed by the Medical Card System (MCS) Medical Advisory Committee (MAC) on December 10, 2012. Final changes that were approved are documented under December 10, 2012.

September 26, 2013  
Revised  
References updated. Added new references, numbers 1-6, 8-9, 11, 13, 16, 19-21, 23-24, 27-30.  
To the Descriptions Section:  
• Deleted: Inhaled Nitric Oxide (INO) is a pulmonary vasodilator approved by the FDA, works in conjunction with ventilator support and other appropriate agents, for the treatment of term or near term neonates ( >34 weeks of gestation) experiencing hypoxic respiratory failure associated with pulmonary hypertension. Hypoxic respiratory failure is a potentially fatal condition in which newborn infants, for a variety of reasons cannot breathe in enough oxygen to survive. Among the causes of hypoxic respiratory failure are respiratory distress syndromes, meconium aspiration, pulmonary hypertension (high blood pressure in the lungs); and congenital diaphragmatic hernia. Management of infants with respiratory failure may include one or more of the following treatments: administration of high concentrations of oxygen; hyperventilation; high frequency ventilation; the induction of alkalosis; neuromuscular blockade; use of post-natal steroids for the prevention of chronic lung disease; and, inhalation of nitric oxide therapy. An alternative treatment for hypoxic respiratory failure is an invasive procedure called extracorporeal membrane oxygenation (ECMO), in which blood is removed from a large vein that empties into the infant's heart, pumped into a system that oxygenates the blood, and then returned to a large vessel in the infant’s neck. As a result of this procedure, one of the carotid arteries, which carry blood to the right side of the brain, is often permanently lost. ECMO is expensive, requires constant monitoring, and is associated with nearly 20 percent rate of neurologic abnormalities. Of the 1,000 newborns in the U.S. who are treated with ECMO each year, approximately 82 percent survive. Because of the risks and costs associated with ECMO, a non-invasive alternative treatment such as nitric oxide therapy represents a major advance.INO therapy improves oxygenation and ventilation, reduces the need for extracorporeal membrane oxygenation (ECMO), and lowers the incidence of chronic lung disease and death among term and near term neonates with respiratory failure. The duration of therapy is normally less than five days, but may be maintained for up to 14 days, or until the underlying oxygen desaturation has been resolved. Inhalation of Nitric Oxide involves a series of toxic effects in the neonate one of the most important is
methylene, a condition in which the iron within hemoglobin is oxidized from the ferrous (Fe2+) state to the ferric (Fe3+) state, resulting in the inability to transport oxygen and carbon dioxide. Maximum methemoglobin levels are usually reached at approximately 8 hours after initiation. Therefore, reduction or discontinuation of the dose of INOmax is based on the monitoring of the methemoglobin level so it can minimize this risk.

Added: Inhaled Nitric Oxide (INO) (i.e. Inomax®) is a drug considered as a pulmonary vasodilator, which in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for Extracorporeal Membrane Oxygenation (ECMO) (FDA, 2013). Extracorporeal membrane oxygenation (ECMO) is a more invasive treatment that uses a pump to circulate blood through an artificial lung back into the bloodstream of a very ill neonate, by providing a heart-lung bypass support outside of the neonate’s body. Since neonates who are considered for ECMO are already very ill, they are also at high risk for long-term problems, including death. Once the neonate is placed on ECMO, additional risks arise which include: bleeding, blood clot formation, infection & transfusion problems (MedlinePlus, 2012). Inhaled nitric oxide has been widely studied for its selective pulmonary vasodilation effects in adults and pediatric patients. It is currently the gold standard therapy in neonates with Persistent Pulmonary Hypertension (PPHN) and has been shown to decrease the extent to which Extracorporeal Membrane Oxygenation (ECMO) is needed for hypoxemic respiratory failure. However, nitric oxide has not improved overall mortality in newborns affected by PPHN. Although doses up to 80 ppm have been administered in neonates, doses over 20 ppm have not been shown to be superior and increase the risk of methemoglobinemia. Inhaled nitric oxide is FDA-approved for use in neonates, it is not FDA-approved for use in other pediatric populations, and is recommended by professional societies, such as the American Academy of Pediatrics (Clinical Pharmacology, 2013). INOmax® must be administered using the INOmax DSIR®, INOmax® DS, or INOvent® Nitric Oxide Delivery Systems, which deliver operator-determined concentrations of nitric oxide in conjunction with a ventilator or breathing gas administration system after dilution with an oxygen/air mixture. A Nitric Oxide Delivery System includes a nitric oxide administration apparatus, a nitric oxide gas analyzer and a nitrogen dioxide gas analyzer. Failure to calibrate the Nitric Oxide Delivery System could result in under- or over-dosing of nitric oxide (FDA, 2013). The U.S. Company Ikaria also markets the following registered trademarks of INO Therapeutics LLC: INOtherapy®, INOcal®, and INOmeter®. These products, as well as the previously mentioned, are involved in the delivery of Inomax. The Inomax DS delivery system was cleared by the FDA for marketing in 2006 and is intended for use in neonatal intensive care and neonate transfer settings (ECRI, 2013). Current evidence supports the use of INO for infants ≥35 weeks' gestational age at birth with hypoxemic respiratory failure who fail to respond to appropriate respiratory management. For infants with pulmonary disease, treatment may include optimizing tidal volume/pressure and the use of manoeuvres to recruit lung units such as surfactant, high-frequency oscillatory ventilation and/or jet ventilation. Ideally, all newborn candidates for INO therapy should undergo
Echocardiographic evaluation to rule out cyanotic congenital heart disease, and to assess for pulmonary hypertension and cardiac function (NIH, 2012). The recommended dose of INOmax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from the INO therapy (FDA, 2013).

To the Indications Section:
- Revised Indication 1 so it would be in concordance to the FDA, and rewrote it: 1. Term and near term (> 34 weeks of gestation) neonate.
- Deleted: Indication #2: Oxygenation Index (OI) of at least 25 recorded on 2 measurements made at least 15 minutes apart (hypoxic respiratory failure).
- To indication #3, updated the list of conventional therapies, and added: vasodilators, IV fluids, bicarbonate therapy & mechanical information.
- To indication #4: updated information by adding the phrase: pulmonary hypoplasia.
- Added New Indication: Partial Pressure of arterial Oxygen in the blood (PaO2) < 100 mm Hg, on a Fraction of Inspired Oxygen (FiO2) of 1.0, and/or an Oxygenation Index (OI) > 25.
- Added: New Note 1: It is recommended that response to a short trial (30–60 min.) of INO should be judged by an improvement in PaO2 or Oxygenation Index (OI); if there is no response, INO should be discontinued.

To the Contraindications / Limitations Section: Added #3.

To the Experimental, Investigational and NOT medically necessary Coverage statement, added #5: Administration of inhaled Nitric Oxide for indications other than those approved by the FDA or in other neonatal populations, including compassionate use (AAP, 2010).

To the Warnings Section: Added #5-9.

To the Coding Information: Added new ICD-9 Code 747.83.

February 21, 2014 Revised
To the Coding section: A new ICD-10 Codes (Preview Draft) section was added to the policy.

September 29, 2014 Revised
References updated. Added new references, numbers 23-25.

Added the following statement to heading of medical policy: This medical policy applies to MCS-Life Commercial Line of Business (LOB) only.

To the Description Section:
- Deleted: Since neonates who are considered for ECMO are already very ill, they are also at high risk for long-term problems, including death. Once the neonate is placed on ECMO, additional risks arise which include: bleeding, blood clot formation, infection & transfusion problems.
- Deleted phrase: and is recommended by professional societies, such as the American Academy of Pediatrics.
- Deleted: INOmax® must be administered using the INOmax DSIR®, INOmax® DS, or INOvent® Nitric Oxide Delivery Systems, which deliver operator-determined concentrations of nitric oxide in conjunction with a ventilator or breathing gas administration system after dilution with an oxygen/air mixture. A Nitric Oxide Delivery System includes a nitric oxide administration apparatus, a nitric oxide gas analyzer and a nitrogen dioxide gas analyzer. Failure to calibrate the Nitric
Oxide Delivery System could result in under- or over-dosing of nitric oxide (FDA, 2013). The U.S. Company Ikaria also markets the following registered trademarks of INO Therapeutics LLC: INOtherapy®, INOcal®, and INometer®. These products, as well as the previously mentioned, are involved in the delivery of Inomax. The Inomax DS delivery system was cleared by the FDA for marketing in 2006 and is intended for use in neonatal intensive care and neonate transfer settings (ECRI, 2013).

- Deleted: Current evidence supports the use of INO for infants ≥35 weeks’ gestational age at birth with hypoxemic respiratory failure who fail to respond to appropriate respiratory management. For infants with pulmonary disease, treatment may include optimizing tidal volume/pressure and the use of maneuvers to recruit lung units such as surfactant, high-frequency oscillatory ventilation and/or jet ventilation. Ideally, all newborn candidates for INO therapy should undergo echocardiographic evaluation to rule out cyanotic congenital heart disease, and to assess for pulmonary hypertension and cardiac function (NIH, 2012).

- Deleted: The recommended dose of INOmax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from the INO therapy (FDA, 2013).

To the Indications Section:

- Revised and modified opening coverage statement to read as it follows: Medical Card System, Inc., (MCS) considers the use of Inhaled Nitric Oxide (INO) as medically necessary, for the Commercial Line of Business (LOB) ONLY, when used as a component for the treatment of hypoxic respiratory failure, that meets ALL of the following criteria.

- Deleted the following indication: Oxygenation Index (OI) of at least 25 recorded on 2 measurements made at least 15 minutes apart (hypoxic respiratory failure).

- Deleted the following indication: Conventional therapies have failed or are expected to fail (e.g. administration of high concentration of oxygen, hyperventilation, high frequency ventilation, the induction of alkalosis, neuromuscular blockage and sedation, vasodilators, IV fluids, bicarbonate therapy & mechanical information).

- Moved to New Limitations Section, the following indication: Neonates do not have pulmonary hypoplasia (e.g. congenital diaphragmatic hernia).

- Moved to New Limitations Section, the following indication: Partial Pressure of arterial Oxygen in the blood (PaO2) < 100 mm Hg, on a Fraction of Inspired Oxygen (FiO2) of 1.0, and/or an Oxygenation Index (OI) > 25.

- Moved previous Note 1 to the New Limitations Section: It is recommended that response to a short trial (30–60 min.) of INO should be judged by an improvement in PaO2 or Oxygenation Index (OI); if there is no response, INO should be discontinued.

To the Limitations Section:

- Created new section separately from the Contraindications, and added the following Limitations:
  1. The manufacturer states that use in neonates older than 14 days, or younger than 34 weeks of gestational age, currently are NOT indicated uses.
  2. Available data suggest the INO is least effective in neonates with pulmonary hypoplasia (e.g., congenital diaphragmatic hernia), and therefore should not be used in neonates with this condition.
3. A trial of INO is recommended in newborns (i.e., >34 weeks) with a Partial Pressure of arterial Oxygen in the blood (PaO2) < 100 mm Hg, on a Fraction of Inspired Oxygen (FiO2) of 1.0, and/or an Oxygenation Index (OI) > 25.

4. It is recommended that response to a short trial (30–60 min.) of INO should be judged by an improvement in PaO2 or Oxygenation Index (OI); if there is no response, INO should be discontinued.

5. The recommended dose of INO is 20 parts per million (ppm), maintained for up to 14 days or, until the underlying oxygen desaturation has resolved.

To the Contraindications/Warnings Section:

- Added to title of Section: Warnings.
- Deleted: Nitric oxide should not be abruptly discontinued as it may result in worsening Pulmonary Artery Pressure (PaO2) and/or blood oxygenation. Inhalation rates should be decreased slowly in a stepwise fashion. An optimal regimen for withdrawal has not been determined.
- Deleted: Nitric oxide may inhibit platelet aggregation and increase bleeding time in some patients.
- Deleted: Accidental exposure should be avoided. The 8-hour weighted average exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm and for nitric dioxides (NO2) the limit is 5 ppm.
- Deleted: In patients with pre-existing left ventricular dysfunction (Heart Failure), Inhaled Nitric Oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- Deleted: Patients with severe left ventricular dysfunction should receive diagnostic or therapeutic exposure to nitric oxide only in combination with other agents known to maintain or improve left ventricular function.
- Deleted: Weaning of nitric oxide inhalation therapy should proceed slowly to prevent acute oxygen desaturation and return pulmonary hypertension. If signs of rebound pulmonary hypertension occur, restart inhaled nitric oxide immediately.
- Deleted: Monitor methemoglobin within 4—8 hours after beginning nitric oxide therapy and periodically throughout treatment.
- Deleted: Patients with thrombocytopenia or coagulopathy should be monitored closely during nitric oxide inhalation therapy.
- Deleted: The most important requirements for safe administration of inhalation nitric oxide are continuous analysis of nitric oxide and NO2 concentrations, frequent calibration of the monitoring equipment, frequent analysis of blood methemoglobin levels, use of certified tanks, and administration of the lowest nitric oxide concentration required.
- To #1 revised and modified content to read as it follows: Inhaled Nitric Oxide (INO) is contraindicated in the treatment of neonates known to be dependent upon right-to-left shunting of blood (i.e., Patent Ductus Arteriosus (PDA)-dependent congenital heart disease).
- Added new #2: Patients with severe left ventricular dysfunction (New York Heart Association [NYHA] Class III-IV) should receive diagnostic or therapeutic exposure to nitric oxide only in combination with other agents known to maintain or improve left ventricular function.
- To #3 revised and modified content to read as it follows: Patients with congenital or acquired methemoglobin reductase
deficiency should not receive nitric oxide inhalation therapy as they may develop significant methemoglobinemia.

- Added new #5: Do not abruptly discontinue Nitric Oxide (NO); however, an optimal weaning regimen has not yet been described. Abrupt discontinuation of Nitric Oxide could result in worsening pulmonary artery pressure and/or blood oxygenation (PaO2), even in neonates with no apparent response to NO.

To the Experimental/Investigational/Unproven Coverage Section:
- Created heading for this section.
- Revised and modified Experimental Coverage Statement to read as it follows: Medical Card System, Inc. (MCS) considers as Experimental, Investigational or Unproven, the use of Inhaled Nitric Oxide (INO) for neonates, for the **ALL** of the following indications.
- Deleted the following Experimental Indication: Adult Respiratory Distress Syndrome.

To the Coding Information Section:
- Added new CPT Codes: 94002 & 94003.
- Deleted CPT Code: 94799.

<table>
<thead>
<tr>
<th>November 23, 2015</th>
<th>Revised</th>
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<tr>
<td>To the coding section:</td>
<td>References updated. Deleted #9, 10, 11, 12, 13, 14, 15 &amp; 27. Added #4 and #11.</td>
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</tbody>
</table>

To the Indications Section:
- Merged indications #1 and #2.

To the Limitations Section:
- To # 5 added to sentence: and the neonate is ready to be weaned.
- Added #6: Monitoring of nitric oxide inhalation therapy should also include periodic measurement of methemoglobin and continuous monitoring of nitrogen dioxide, nitric oxide and oxygen concentrations.

To the Experimental/Investigational/Unproven Coverage Section:
- Rephrased opening statement as follows: Medical Card System, Inc. (MCS) considers the use of Inhaled Nitric Oxide (INO) for neonates as Experimental, Investigational or Unproven for **ALL** of the following indications:
- Added #4: For the treatment of acute lung injury (ALI) or acute distress syndrome (ARDS).

To the Coding Section:
- Added HCPCS code J3490
- Added ICD-10-PCS code 3E0F7SD
This document is for informational purposes only. It is not an authorization, certification, explanation of benefits, or contract. Receipt of benefits is subject to satisfaction of all terms and conditions of coverage. Eligibility and benefit coverage are determined in accordance with the terms of the member’s plan in effect as of the date services are rendered. Medical Card System, Inc. (MCS) medical policies are developed with the assistance of medical professionals and are based upon a review of published and unpublished information including, but not limited to, current medical literature, guidelines published by public health and health research agencies, and community medical practices in the treatment and diagnosis of disease. Because medical practice, information, and technology are constantly changing, Medical Card System, Inc. (MCS) reserves the right to review and update its medical policies at its discretion. Medical Card System, Inc. (MCS) medical policies are intended to serve as a resource to the plan. They are not intended to limit the plan’s ability to interpret plan language as deemed appropriate. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment they choose to provide.