Inhaled Nitric Oxide (INO) In Neonates

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).

**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 Inhaled Nitric Oxide (INO) **medically reasonable and necessary** as a component of the treatment of hypoxic respiratory failure when **ALL** of the following criteria are met:

1. Term and near term (> 34 weeks of gestation) neonate; and

2. Oxygenation Index (OI) of at least 25 recorded on 2 measurements made at least 15 minutes apart (hypoxic respiratory failure); and

3. 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); and

4. Neonates do not have pulmonary hypoplasia (e.g. congenital diaphragmatic hernia).

5. 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.
Note: 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.

CONTRAINDICATIONS / LIMITATIONS

1. Inhaled Nitric Oxide (INO) should NOT be used on treatment of neonates know to be dependent on right to left shunting of blood (Congenital Defect).

2. Is contraindicated in patients with congenital or acquired methemoglobinemia reductase deficiency.

3. 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 (Clinical Pharmacology, 2013).

Medical Card System, Inc. (MCS) considered the following indications Experimental, Investigational & NOT medically necessary for the treatment and use of Inhaled Nitric Oxide:

1. Adult Respiratory Distress Syndrome, and,

2. Premature neonates (<34 weeks of Gestation)

3. Prevention of Ischemia reperfusion injury/acute rejection following lung transplantation,

4. 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.

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).

WARNINGS

1. 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.

2. Nitric oxide may inhibit platelet aggregation and increase bleeding time in some patients.

3. 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 dioxide (NO₂) the limit is 5 ppm.
4. In patients with pre-existing left ventricular dysfunction (Heart Failure), Inhaled Nitric Oxide may increase pulmonary capillary wedge pressure leading to pulmonary edema.

5. 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.

6. Weaning of nitric oxide inhalation therapy should proceed slowly to prevent acute oxygen desaturation and rebound pulmonary hypertension. If signs of rebound pulmonary hypertension occur, restart inhaled nitric oxide immediately.

7. Monitor methemoglobin within 4—8 hours after beginning nitric oxide therapy and periodically throughout treatment.

8. Patients with thrombocytopenia or coagulopathy should be monitored closely during nitric oxide inhalation therapy.

9. 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.

CODING INFORMATION

CPT® Codes (List may not be all inclusive)

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>DESCRIPTION</th>
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<tr>
<td>93463</td>
<td>Pharmacologic agent administration (eg, 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>
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<tr>
<td>94799</td>
<td>Unlisted pulmonary service or procedure (Requires Pulmonary documentation)</td>
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ICD-9 CM® Diagnosis Codes (List may not be all inclusive)

<table>
<thead>
<tr>
<th>ICD-9 CM® CODES</th>
<th>DESCRIPTION</th>
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<tbody>
<tr>
<td>416.0</td>
<td>Primary Pulmonary Hypertension</td>
</tr>
<tr>
<td>416.8</td>
<td>Other chronic pulmonary heart diseases</td>
</tr>
<tr>
<td>518.82</td>
<td>Other Pulmonary insufficiency, not elsewhere classified</td>
</tr>
<tr>
<td>747.83</td>
<td>Persistent fetal circulation (i.e. Persistent Pulmonary Hypertension &amp; Primary Pulmonary Hypertension of Newborn)</td>
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### REFERENCES


POLICY HISTORY

<table>
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<tr>
<th>DATE</th>
<th>ACTION</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</td>
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<tr>
<td>August 27, 2009</td>
<td>Reviewed</td>
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acute lung injury, or vaso-occlusive crises in patients with sickle cell disease.

August 25, 2010  Yearly Review
August 15, 2011  Revised
Policy revised to add contraindications and precaution on the disruption of INO. Contraindicated for the prevention of progression to bronchopulmonary 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.

August 13, 2012  Revised
References updated.
New Indication # 5 was added.
New Off-Label† indications (1 – 4) Section was added.
Withdrawn 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.
Withdrawn from Contraindications: for the prevention of progression to bronchopulmonary dysplasia (BPD) in premature neonates with respiratory failure receiving mechanical ventilation, and labeled it as Experimental And Investigational and Not Medically Necessary.
New Contraindications #4 - #7 were added.

December 10, 2012  Revised
Withdrawn from Contraindications: for the management of post-operative pulmonary hypertension in pediatric patients with congenital heart disease.
Withdrawn from Contraindications: for the prevention of progression to bronchopulmonary 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 methemoglobinemia, 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 hypoxic 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 ventilation.
- 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.
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