INOMAX® Overview

Mallinckrodt Pharmaceuticals

U.S. Indications

- INOMAX (nitric oxide) for inhalation is a 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 (HRF) associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

International Indications

- Canada: INOMAX, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and late pre-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.
- Japan: INOMAX is marketed as INOflo®, and is approved for use in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.
  - Pulmonary hypertension associated with cardiac surgery indication - new 2015: INOflo is a vasodilator, which, in conjunction with ventilator support and other appropriate agents, is indicated for the improvement of peri-operative pulmonary hypertension associated with heart surgery. INOflo selectively decreases pulmonary arterial pressure and improves right ventricular function and oxygenation.
- Australia: INOMAX is a selective 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, in order to improve oxygenation and reduce the need for extracorporeal membrane oxygenation.
  - Pulmonary hypertension associated with cardiac surgery indication - new 2015: INOmax, in conjunction with ventilator support and other appropriate agents, is indicated as part of the treatment of peri- and post-operative pulmonary hypertension in newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction with heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

By Unique Indication:

- U.S.
  - Total HRF patients = 25,000
  - Average duration of treatment = 3 days
  - Average cost per hour = $85
  - Totaling = $150 million market size
- O.U.S. Markets
  - ~10% the size of U.S. market by $ for HRF
  - 2016 CV market = 3.5 million Japan & 500,000 Australia



INOmax (nitric oxide) FOR INHALATION



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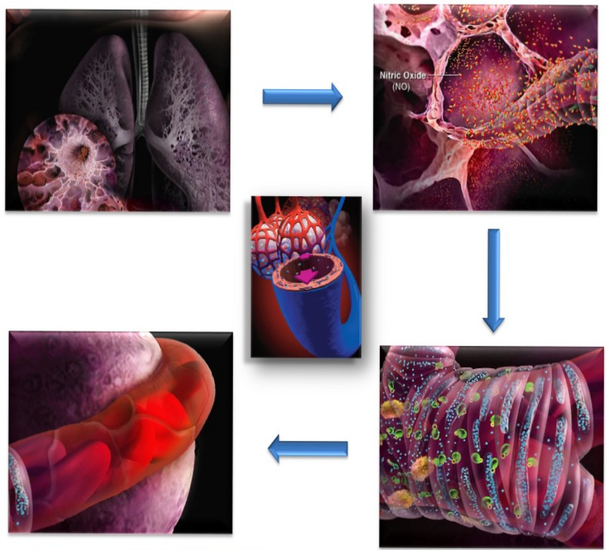
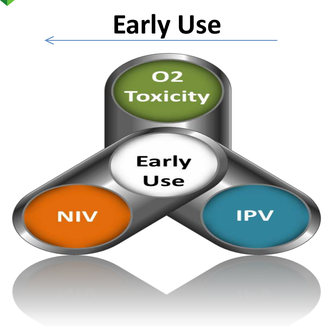
INOMAX-Mechanism of Action

- INOMAX selectively dilates pulmonary vasculature thus Increasing pulmonary blood flow and Improving oxygenation.
- When inhaled, INOMAX travels through the trachea and bronchioles to the alveoli into the epithelial cells, it diffuse into the vascular smooth muscle cells adjacent to the pulmonary arterioles.
- In the muscle cells, nitric oxide activates soluble guanylate cyclase (sGC) which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) which inhibits the influx of calcium ions (Ca++) into the smooth muscle fibers, this decreased concentration of calcium prevents smooth muscle contraction resulting in smooth muscle relaxation and arteriolar dilation.



Vasodilation



Term & Near Term

Ventilated Patients

- INOMAX® is nitric oxide for inhalation, a vasodilator which, in conjunction with ventilator support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure.
- Non-invasive ventilation (NIV) and O2 toxicity initiatives are designed to generate data and to educate clinicians on the early use and non-invasive approach to delivering INOMAX.

Hemodynamic

- The known hemodynamic effects of INOMAX have been used OUS to gain indications for use in pulmonary hypertension associated with cardiac surgery

CT Surgery

- Post-Op risk of pulmonary HTN
- Procedural risk: Hypolastic left heart surgery
- ASD closure in left to right shunt

PAH

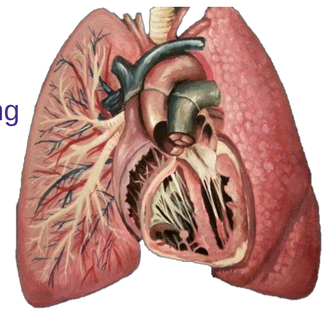
- IPAH / HPAH: CCB Therapy
- IC/SC Prostacyclin: IV weaning

CHF/LVAD

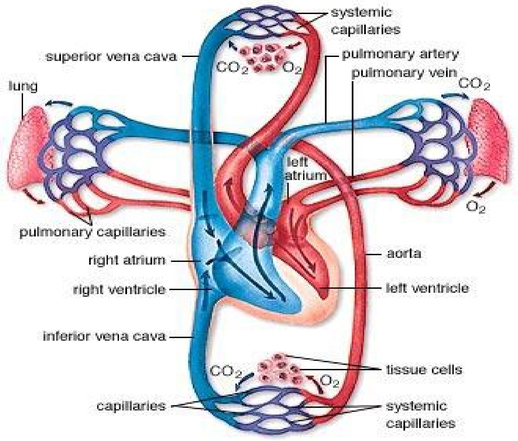
- LVAD: Pre- & Post-Op
- Management & weaning

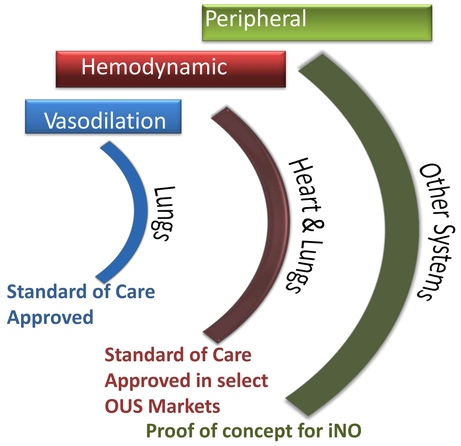
Transplant

- Heart and lung transplant in heart & lung disease



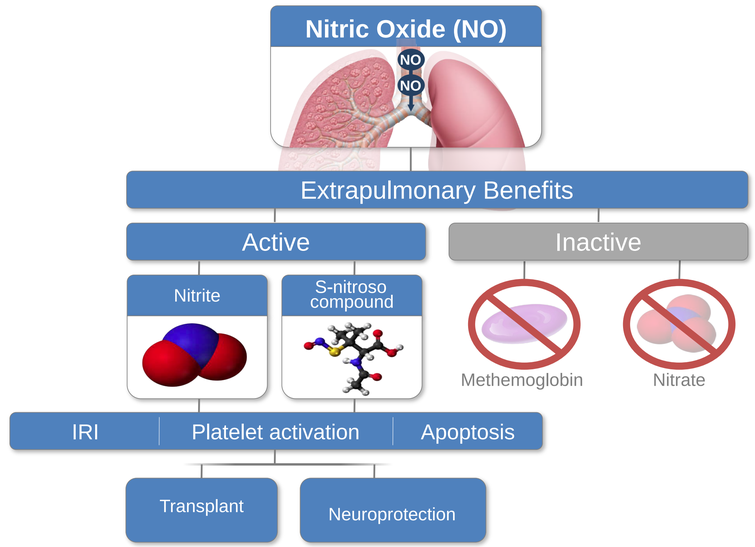
Potential of INOMAX





- Our current US indication is based on the vasodilatory effect of INOMAX in neonates and is the standard of care in this patient population.
- The hemodynamic effects of INOMAX have allowed expansion into pulmonary hypertension associated with the cardiovascular surgery OUS.
- The peripheral effects of INOMAX may support exploration of opportunities in transplantation and neuroprotection.

Scientific Rationale: Extrapulmonary Benefits



References: 1. McMahon TJ, Doctor A. Extrapulmonary effects of inhaled nitric oxide: role of reversible S-nitrosylation of erythrocytic hemoglobin. Proc Am Thorac Soc. 2006;3(2):153-160. 2. Duranski MR, Greer JJM, Dejam A, et al. Cytoprotective effects of nitrite during in vivo ischemia-reperfusion of the heart and liver. J Clin Invest. 2005;115(5):1232-1240. 3. Roberts BW, Mitchell J, Kilgannon JH, et al. Nitric oxide donor agents for the treatment of ischemia/reperfusion injury in human subject: a systematic review. SHOCK. 2013;39(3):229-239

INVESTOR DAY 2015 DECEMBER 7 NEW YORK, NY



INOmax (nitric oxide) FOR INHALATION



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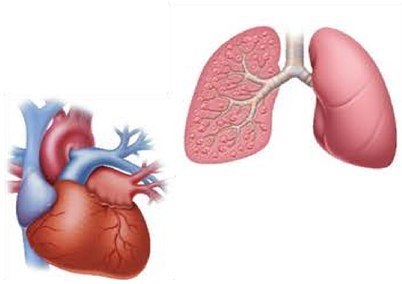
Scientific Rationale for Potential Future Application

▶ 80% of donor lungs are discarded and not used for transplant

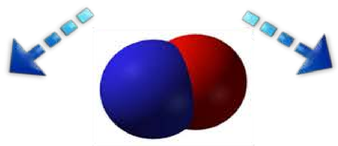
Current Use

TRANSPLANT SURGERY

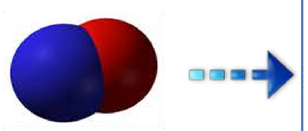
- Inhaled NO is used per ISHLT Guidelines for prevention of Primary Graft Dysfunction (PGD)



Inhaled Nitric Oxide (NO) in patients



Nitric Oxide (NO) delivered in devices



Potential Future Uses

TRANSPLANT SURGERY

- Support **evidence of longer duration of NO (48-72hrs) post-surgery** for improved outcomes in PGD

ORGAN PERFUSION

"Marginal"-condition transplant organ

Viable transplant organ

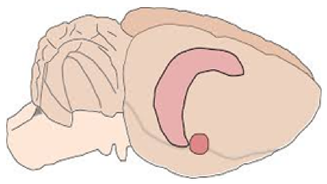
References: 1. Takashima S Koukoulis G Inokawa H et al. Inhaled nitric oxide reduces ischemia-reperfusion injury in rate lungs from non-heart-beating donors. *J Thorasc Cardiovasc Surg.* 2006;132:132-139. **2.** Srinivasan P, Yagi S, Doorschodt B et al. Impact of venous systemic oxygen persufflation supplemented with nitric oxide gas in cold-stored, warm ischemia-damaged experimental liver grafts. *Liver Transplantation*. 2012;18:219-225. **3.** Kageyama S, Yagi S, Tanaka H et al. Graft reconditioning with nitric oxide gas in rat liver transplantation from cardiac death donors. *Transplantation*. 2014;97:618-625. Shagrall Y Huenther G, Ahya V et al., Report of ISJLT Working Group of Primary Graft Dysfunction Part IV: Treatment, *J Heart Lung Transplant* 2005;24:1489-1500. Dong B, Abano J, Egan T, Nitric Oxide Ventilation of Rat Lings from Non-Heart Beating Donors Improves Post transplant Function, *Am J Tran* 2009; 9:2707-2715. Kobashigawa J, Zuckerman A, Macdonald P, Report from a consensus conference on primary graft dysfunction after cardiac transplantation, J Heart Lung Trans 2014; 33:327-340.

Scientific Rationale for Potential Future Application

▶ 60% of myocardial infarction survivors will have moderate to severe cognitive deficits 3 months after resuscitation

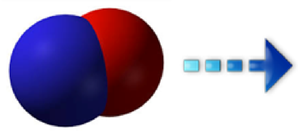
Completed Animal Studies

POST CARDIAC ARREST/CPR



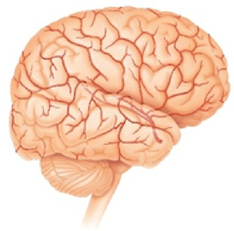
Global ischemia and reperfusion brain damage occurs *over time (hours to days) in patients* Post CA/CPR

Inhaled Nitric Oxide (NO) in patients



Potential Future Uses

POST CARDIAC ARREST/CPR



NO administration for 24 hours may mitigate global ischemia and reperfusion brain damage delivered 1-2 hours post CA/CPR

References: 1. Minamishima S, Kida K, Tokuda K et al. Inhaled nitric oxide improves outcomes after successful cardiopulmonary resuscitation in mice. *Circulation*. 2011;124:1645-1653. **2.** Kida K, Shirozu K, Yu B et al. Beneficial effects of nitric oxide on outcomes after cardiac arrest and cardiopulmonary resuscitation in hypothermia-treated mice. *Anesthesiology*. 2014;120:1-10.