Claims 1-19 of the '112 patent are unpatentable as obvious in view of *Bernasconi*, the *INOMAX label*, *Loh*, and *Goyal*

U.S. Pat. No. 8,846,112	*INOMAX label* (Ex. 1014), *Bernasconi* (Ex. 1004), *Loh* (Ex. 1006), and *Goyal* (Ex. 1007)
CLAIM 1	
A method of providing pharmaceutically acceptable nitric oxide gas, the method comprising:	*INOMAX label* teaches providing pharmaceutically acceptable nitric oxide gas for treatment: INOmax, 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. Ex. 1014 (*INOMAX label*) at 4.
obtaining a cylinder containing compressed nitric oxide gas in the form of a gaseous blend of nitric oxide and nitrogen;	*INOMAX label* teaches obtaining a cylinder containing compressed nitric oxide gas in the form of a gaseous blend of nitric oxide and nitrogen. INOmax™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax is a gaseous blend of nitric oxide (0.8%) and nitrogen (99.2%). INOmax is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]). Ex. 1014 (*INOMAX label*) at 1. **HOW SUPPLIED** INOmax™ (nitric oxide) is available in the following sizes: Size D Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01) Size D Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-001-01) Size 88 Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-002-02) Size 88 Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-001-02) Store at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Ex. 1014 (*INOMAX label*) at 6-7.
supplying the cylinder containing compressed nitric oxide gas to a medical provider responsible for treating neonates who have hypoxic respiratory failure,	*INOMAX label* teaches supplying compressed nitric oxide gas to treat neonates with hypoxic respiratory failure including some who do not have left ventricular dysfunction. INOmax™ (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax is a gaseous blend of nitric oxide (0.8%) and nitrogen (99.2%). INOmax is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]). Ex. 1014 (*INOMAX label*) at 1.

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including some who do not have left ventricular dysfunction;	**HOW SUPPLIED** INOmax™ (nitric oxide) is available in the following sizes: Size D Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01) Size D Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-001-01) Size 88 Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-002-02) Size 88 Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-001-02) Store at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F). [See USP Controlled Room Temperature.] Ex. 1014 (*INOMAX label*) at 6-7. The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (OI= mean airway pressure in cm H_2O x fraction of inspired oxygen concentration fF_iO_2] x 100 divided by systemic arterial concentration in mm Hg [P_aO_2]) and increases PaO_2 Ex. 1014 (*INOMAX label*) at 2. **INDICATIONS** INOmax, 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. Ex. 1014 (*INOMAX label*) at 4.
providing to the medical provider (i) information that a recommended dose of inhaled nitric oxide gas for treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide and (ii) information that, in patients with pre-existing left ventricular dysfunction, inhaled nitric oxide may increase pulmonary capillary wedge	The content of the *INOMAX label* is information provided to a medical provider. **CENTER FOR DRUG EVALUATION AND RESEARCH** **APPLICATION NUMBER: NDA 20845** **FINAL PRINTED LABELING** Ex. 1014 (*INOMAX label*) at i. *INOMAX label* teaches the recommended dose of inhaled nitric oxide gas for the treatment of neonates with hypoxic respiratory failure is 20 ppm nitric oxide.

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pressure (PCWP), leading to pulmonary edema, the information of (ii) being sufficient to cause a medical provider considering inhaled nitric oxide treatment for a plurality of neonatal patients who (a) are suffering from a condition for which inhaled nitric oxide is indicated, and (b) have pre-existing left ventricular dysfunction, to elect to avoid treating one or more of the plurality of patients with inhaled nitric oxide in order to avoid putting the one or more patients at risk of pulmonary edema.	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 INOmax therapy. Ex. 1014 (*INOMAX label*) at 6. The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (OI= mean airway pressure in cm H_2O x fraction of inspired oxygen concentration fF_iO_2] x 100 divided by systemic arterial concentration in mm Hg [P_aO_2]) and increases PaO_2 Ex. 1014 (*INOMAX label*) at 2. *INOMAX label* contains INDICATIONS and CONTRAINDICATIONS: **INDICATIONS** INOmax, 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. **CONTRAINDICATIONS** INOmax should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood. Ex. 1014 (*INOMAX label*) at 4. *Bernasconi* also teaches the recommended dose of inhaled nitric oxide gas for treating neonates with hypoxic respiratory failure is 20 ppm nitric oxide. The appropriate dose of iNO to assess pulmonary vascular resistance or treat pulmonary hypertension is not completely defined. Dose response studies have been performed in persistent pulmonary hypertension of the newborn (PPHN) and ARDS[41–46] and in congenital heart disease.[47,48] Inhaled NO doses required to treat pulmonary hypertension are higher than those required for improvement of ventilation The recommended dose by the FDA for the treatment of neonatal hypoxic respiratory failure is 20 ppm. Ex. 1004 (*Bernasconi*) at 3. **Neonates with hypoxaemic respiratory failure** Inhaled NO was targeted early to the newborn with persistent pulmonary hypertension of the newborn (PPHN). The first application of iNO in the newborn was described almost 10 years ago by Roberts et al. and Kinsella et al.[116,117] They used iNO in term neonates with hypoxaemic respiratory failure and found a rapid improvement in oxygenation without any lowering of the systemic pressure. Several studies have then confirmed its efficacy in this group of patients.[59,118–120] Ex. 1004 (*Bernasconi*) at 8. *Bernasconi* teaches the possibility of pulmonary edema upon administering inhaled nitric oxide to a patient with left ventricular dysfunction.

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There are several reports of the negative effects of inhaled NO in patients with left ventricular dysfunction and elevated pulmonary vascular resistance.[103–108] Inhaled NO produces selective pulmonary vasodilatation. However, in patients with elevated left atrial pressure due to left ventricular dysfunction, a decrease in pulmonary vascular resistance (induced by iNO) will lead to an increase in pulmonary venous return and hence to an increase in left atrial and left ventricular filling pressures; this may not be tolerated by a failing left ventricle working on the flat portion of the Frank-Starling curve.[108] This effect may lead to rapid left heart failure and pulmonary oedema, most marked if the right ventricular pressure is suprasystemic and the left cavity small.[103]

Ex. 1004 (*Bernasconi*) at 8.

Loh teaches measuring wedge pressure in patients in its study.

Background Pulmonary vascular resistance (PVR) is frequently elevated in patients with advanced heart failure. Nitric oxide (NO), which contributes to the activity of endothelium-derived relaxing factor, causes relaxation of pulmonary arteries and veins in vitro. Inhalation of NO gas causes pulmonary vasodilation in patients with primary and secondary forms of pulmonary hypertension.

Methods and Results To test the hypothesis that inhalation of NO gas lowers PVR in patients with heart failure, we studied the hemodynamic effects of a 10-minute inhalation of NO (80 ppm) in 19 patients with New York Heart Association class III (n=5) and class IV (n=14) heart failure due to left ventricular (LV) dysfunction. Although inhalation of NO had no effect on pulmonary artery pressures, the PVR decreased by 31±7% ($P<.001$) due to a 23±7% increase ($P<.001$) in pulmonary artery wedge pressure and despite a 4±2% ($P<.05$) decrease in cardiac index. The magnitude of the decrease in PVR with inhaled NO was inversely related ($r=-.713$; $P<.001$) to the baseline PVR. Inhaled NO had no effect on heart rate, systemic arterial pressure, systemic vascular resistance, or LV peak +dP/dt or −dP/dt.

Conclusions In patients with heart failure due to LV dysfunction, inhalation of NO causes a decrease in the PVR associated with an increase in LV filling pressure. These findings predict that inhaled NO, if used alone at this dose (80 ppm), may have adverse effects in patients with LV failure. (***Circulation*. 1994;90:2780-2785.**)

Key words • nitric oxide • lung • heart failure • endothelium-derived factors

Ex. 1006 (*Loh*) at Abstract.

Hemodynamic Measurements

Vasodilators, converting enzyme inhibitors, digitalis, and diuretics were withheld on the morning of the catheterization. A 7F Swan-Ganz catheter (Arrow International, Inc) was placed in the pulmonary artery. Femoral artery pressure was monitored via an 8F side-arm sheath (Cordis Laboratories). In 10 patients, a 7F micromanometer-tipped pigtail catheter (Millar Industries) was placed in the left ventricle (LV), allowing for simultaneous dP/dt and right heart pressure measurements. The ECG, femoral artery pressure, pulmonary artery pressure, and LV pressure were recorded on a strip chart recorder (Electronics for Medicine, PPG Biomedical Systems Division). Cardiac output was determined by the Fick method, based on the measured oxygen uptake (model MRM 2B, Waters Instruments, Inc) and oxygen content in the pulmonary and femoral arteries.[26] Oxygen content was calculated from the blood hemoglobin and oxygen saturation by standard methods.[26] Blood oxygen saturation was determined in duplicate samples on a Ciba-Corning model 270 Co-oximeter. LV peak +dP/dt (+dP/dt) and peak −dP/dt (−dP/dt) were computed on-line by an Electronics for Medicine amplifier (model 220A). Values for heart rate, arterial pressure, pulmonary arterial pressure, pulmonary artery wedge pressure, LV systolic pressure, LV end-diastolic pressure

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(LVEDP), and LV +dP/dt and −dP/dt were calculated by averaging at least 50 consecutive beats under each experimental condition.

Ex. 1006 (*Loh*) at 2780-81.

Loh teaches patients with left ventricular dysfunction show an increase in wedge pressure upon treatment with inhaled nitric oxide.

studied the hemodynamic effects of a 10-minute inhalation of NO (80 ppm) in 19 patients with moderate to severe heart failure secondary to LV dysfunction from idiopathic or ischemic dilated cardiomyopathy.

Ex. 1006 (*Loh*) at 2780.

To establish baseline conditions, patients inhaled room air (FIO_2, 21%; N_2, 79%) via the closed face mask system for 10 minutes before the baseline hemodynamic measurements. Patients then inhaled NO at 80 ppm (FIO_2, 21%; N_2, 79%)

Ex. 1006 (*Loh*) at 2781.

TABLE 1. Hemodynamic Effects of Inhaled NO in Patients With Congestive Heart Failure (n=19)

	Room Air	NO	*P*
HR, bpm	90±3	93±3	NS
MAP, mm Hg	79±3	81±3	NS
SVR, dyne · s · cm^{-5}	1102±104	1041±97	NS
PA, mm Hg	35±4	37±4	NS
PAWP, mm Hg	25±3	31±4	<.001
LVEDP, mm Hg; n=10	28±4	34±5	.02
PVR, dyne · s · cm^{-5}	226±30	119±13	<.001
PA−PAWP, mm Hg	11±1	6±0.5	<.001
SVI, mL/m^2	26±2	24±2	.03
CI, L · min^{-1} · m^{-2}	2.3±0.2	2.1±0.2	.03

HR indicates heart rate; bpm, beats per minute; MAP, mean arterial pressure; SVR, systemic vascular resistance; PA, mean pulmonary artery measure; PAWP, pulmonary artery wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary vascular resistance; SVI, stroke volume index; and CI, cardiac index.

Ex. 1006 (*Loh*) at 2781, Table 1.

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