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Mallinckrodt and Novoteris Receive Clearance from Health Canada to Start Pilot Trial of High-Dose Inhaled Nitric Oxide Therapy for COVID-19 Infection and Associated Lung Complications

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-- Study to investigate antiviral activity and improvement in oxygenation and pulmonary arterial pressure in patients suffering from COVID-19 --

STAINES-UPON-THAMES, United Kingdom and GARDEN GROVE, Calif., April 1, 2020 /PRNewswire/ -- Mallinckrodt plc (NYSE: MNK), a global biopharmaceutical company, and Novoteris, LLC, a clinical stage medical device and pharmaceutical developer focused on innovative nitric oxide gas applications, today announced that the Therapeutic Products Directorate of Health Canada has cleared the companies' joint pilot clinical trial, entitled "Inhaled Gaseous Nitric Oxide (gNO) Antimicrobial Treatment of Difficult Bacterial and Viral Lung (COVID-19) Infections" application to investigate the use of Thiolanox®, a high-dose inhaled nitric oxide therapy for the treatment of patients infected with novel coronavirus (SARS-CoV-2) at Vancouver Coastal Health Authority facilities. The investigative therapy employs Novoteris' Inhaled Nitric Oxide Delivery Device (INODD) and Mallinckrodt's high-concentration, 5000 PPM nitric oxide gas for inhalation canisters. The study will investigate the therapy's safety and effectiveness in treating COVID-19 and its associated lung complications. The companies expect to begin recruiting patients in the coming days.

"Inhaled nitric oxide may have an antiviral effect, as well as improve oxygenation and pulmonary arterial pressure in patients suffering from COVID-19," said **Steven Romano, M.D., Executive Vice President and Chief Scientific Officer at Mallinckrodt.** "We're proud to be partnering with Novoteris on this pilot trial and are committed to increasing understanding of this potentially important therapeutic option for healthcare providers on the front lines of this unprecedented health emergency."

COVID-19 is a contagious respiratory illness caused by a novel coronavirus. Patients with COVID-19 have mild to severe respiratory illness that can include symptoms such as cough, fever and shortness of breath.[1] In severe cases, COVID-19 can cause acute respiratory distress syndrome (ARDS) – a disorder in which fluid leaks into the lungs, making breathing difficult or impossible – and can lead to multi-organ failure and sometimes death.[1,2]

"Our collaboration with Mallinckrodt to study high-dose inhaled nitric oxide to treat patients with COVID-19 and associated lung complications is an exciting step in both companies' commitment to helping the world battle this global pandemic," said **Alex Stenzler, Founder and President at Novoteris.**

Inhaled nitric oxide (iNO) has been evaluated in randomized controlled trials, both in pediatric and adult patients with ARDS,[3,4,5,6,7] and demonstrated partially dose-dependent improvement in blood oxygenation and decreased pulmonary artery pressure[3] and, in one trial, improvements in the composite measure of days alive or free of ventilator support at day 28 of the trial (the last day evaluated).[8] There have been other trials evaluating iNO in the context of ARDS, which have demonstrated mixed results.[6,7,9] In an *in vitro* study, inhaled nitric oxide has demonstrated an inhibitory effect on the replication cycle of severe acute respiratory syndrome-related coronavirus (SARS-CoV).[10] Furthermore, a small clinical trial in SARS-CoV patients demonstrated improvements in blood oxygenation, a reduction in supplemental oxygen and a reduction in the amount of ventilator support.[11]

"This is an important day for patients and healthcare providers," said **Chris Miller, Ph.D., Assistant Professor, Faculty of Medicine at University of British Columbia and Founder and Scientific Advisor at Novoteris.** Dr. Miller, team lead for the study at Vancouver Coastal Health Research Institute, and an expert in nitric oxide therapies, with a research career spanning more than 25 years studying the antimicrobial effect of high-dose nitric oxide to treat lung infections, said, "I am very pleased to be working with Mallinckrodt and Novoteris on this study using high-dose inhaled nitric oxide for patients with COVID-19."

Mallinckrodt is currently working with the U.S. Food and Drug Administration on the possibility of making the company's INOmax® (nitric oxide) gas, for inhalation product available to U.S. patients with pulmonary complications of COVID-19 as quickly as possible through the appropriate regulatory mechanism. INOmax has been on the market in the U.S. since 2000, and is indicated for the treatment of term and near-term neonates with hypoxic respiratory failure associated with pulmonary hypertension. Please see Important Safety Information below. The safety and efficacy of INOmax and iNO for pulmonary complications associated with COVID-19 have not been established.

For more information, please visit clinicaltrials.gov.

Canada – Indications and Important Safety Information

INDICATIONS & CLINICAL USE

- 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.
- The safety and effectiveness of INOmax have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation.
- In clinical trials, no efficacy has been demonstrated with the use of INOmax in patients with congenital diaphragmatic hernia.

CONTRAINDICATIONS

- In patients where systemic oxygenation is wholly dependent on extra-pulmonary right-to-left shunting, use of INOmax has the potential to decrease right-to-left blood flow, which, in this condition, is potentially fatal.

MOST SERIOUS WARNINGS & PRECAUTIONS

- **Left-to-Right Shunting:** Treatment might aggravate cardiac insufficiency due to unwanted pulmonary vasodilation caused by inhaled nitric oxide, resulting in a further increase of already existing pulmonary hyperperfusion. It is recommended to perform pulmonary artery catheterization or echocardiographic examination of central hemodynamics prior to administration.

OTHER RELEVANT WARNINGS & PRECAUTIONS

- If clinical response is inadequate at 4-6 hours after starting INOmax: availability of nitric oxide on transport to another hospital should be assured to prevent worsening of condition on acute discontinuation of INOmax. Rescue, such as ECMO, should be considered on continued deterioration or failure to improve, defined by local hospital criteria.
- INOmax should not be discontinued abruptly as it may result in rebound pulmonary hypertension. If rebound pulmonary hypertension occurs, reinstate therapy immediately.
- Neonates are known to have diminished methemoglobin reductase activity and could be at greater risk of developing methemoglobinemia.
- NO2 rapidly forms in gas mixtures containing nitric oxide and O2, and nitric oxide may in this way cause airway inflammation and damage.
- Patients with left ventricular dysfunction treated with inhaled nitric oxide, experienced serious adverse events. Discontinue INOmax while providing symptomatic care.
- Animal models have shown that nitric oxide may interact with homeostasis, resulting in an increased bleeding time. Data in adult humans are conflicting.

For more information please consult the product monograph at https://www.mallinckrodt.ca/wp-content/uploads/2017/11/INOMAX-Product-Monograph.pdf for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The product monograph is also available by calling us at 1-855-399-6742.

U.S. – Indications and Important Safety Information

INDICATION

INOmax® (nitric oxide) gas, for inhalation, is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term (>34 weeks gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension in conjunction with ventilatory support and other appropriate agents.

IMPORTANT SAFETY INFORMATION

- INOmax is contraindicated in the treatment of neonates dependent on right-to-left shunting of blood.
- Abrupt discontinuation of INOmax may lead to increasing pulmonary artery pressure and worsening oxygenation.
- Methemoglobinemia and NO_2 levels are dose dependent. Nitric oxide donor compounds may have an additive effect with INOmax on the risk of developing methemoglobinemia. Nitrogen dioxide may cause airway inflammation and damage to lung tissues.
- In patients with pre-existing left ventricular dysfunction, INOmax may increase pulmonary capillary wedge pressure leading to pulmonary edema.
- Monitor for PaO_2, inspired NO_2, and methemoglobin during INOmax administration.
- INOmax must be administered using a calibrated FDA-cleared Nitric Oxide Delivery System.

Please see Full Prescribing Information.

ABOUT MALLINCKRODT
Mallinckrodt is a global business consisting of multiple wholly owned subsidiaries that develop, manufacture, market and distribute specialty pharmaceutical products and therapies. The company's Specialty Brands reportable segment's areas of focus include autoimmune and rare diseases in specialty areas like neurology, rheumatology, nephrology, pulmonology and ophthalmology; immunotherapy and neonatal respiratory critical care therapies; analgesics and gastrointestinal products. Its Specialty Generics reportable segment includes specialty generic drugs and active pharmaceutical ingredients. To learn more about Mallinckrodt, visit

www.mallinckrodt.com.

Mallinckrodt uses its website as a channel of distribution of important company information, such as press releases, investor presentations and other financial information. It also uses its website to expedite public access to time-critical information regarding the company in advance of or in lieu of distributing a press release or a filing with the U.S. Securities and Exchange Commission (SEC) disclosing the same information. Therefore, investors should look to the Investor Relations page of the website for important and time-critical information. Visitors to the website can also register to receive automatic e-mail and other notifications alerting them when new information is made available on the Investor Relations page of the website.

ABOUT NOVOTERIS, LLC

Novoteris, LLC is a privately held limited liability company managed by a group of international industry veterans and clinicians involved in developing and producing innovative, cutting-edge medical products. The company was formed in 2013 to consolidate the nitric oxide assets and other resources from 12th Man Technologies, Inc. (Garden Grove, CA) and Nitric Solutions, Inc. (Vancouver, Canada) for the completion of inhaled nitric oxide trials for the treatment of patients with cystic fibrosis. The company received Orphan Drug designations for the treatment of cystic fibrosis from both the FDA and EMA in 2013. Novoteris is headquartered in Garden Grove, California with an EU entity in Belgium (Novoteris GVC). For additional information, please visit www.novoteris.com.

CAUTIONARY STATEMENTS RELATED TO FORWARD-LOOKING STATEMENTS

This release includes forward-looking statements concerning inhaled nitric oxide ("iNO") and Mallinckrodt's INOmax product, including statements with regard to potential regulatory developments, the potential impact of iNO on patients and anticipated benefits associated with its use, as well as statements related to COVID-19. The statements are based on assumptions about many important factors, including the following, which could cause actual results to differ materially from those in the forward-looking statements: clinical trial results; the impact of the outbreak of the COVID-19 coronavirus; satisfaction of regulatory and other requirements; actions of regulatory bodies and other governmental authorities; changes in laws and regulations; issues with product quality, manufacturing or supply, or patient safety issues; and other risks identified and described in more detail in the "Risk Factors" section of Mallinckrodt's most recent Annual Report on Form 10-K and other filings with the SEC, all of which are available on its website. The forward-looking statements made herein speak only as of the date hereof and Mallinckrodt does not assume any obligation to update or revise any forward-looking statement, whether as a result of new information, future events and developments or otherwise, except as required by law.

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