21st May 2021

Direct Healthcare Professional Communication

This letter is intended for hospital pharmacists, nursing staff and physicians using INOmax in intensive care units and refers to the following products :

- INOmax 400 ppm mol/mol medicinal gas, compressed, aluminium cylinders 2 & 10 litre
- INOmax 800 ppm mol/mol medicinal gas, compressed, aluminium cylinders 2 & 10 litre

INOmax (nitric oxide): Difficulties in closing the cylinder valves after use if the cylinder is not empty: precautions for use when disconnecting the cylinders from pressure regulators.

BOC Limited, in agreement with the Medicines and Healthcare products Regulatory Agency (MHRA), is providing you with the following important user information:

- There have been reports of users not being able to properly close the INOmax® cylinder after opening, when the cylinder is not yet empty (as indicated by the pressure still showing on the regulator).
- This can result in the user not being able to purge the pressure regulator hose according to the instructions in the user manual of the administration device for nitric oxide (NO) and can prevent removal of the pressure regulator from the cylinder valve. The removal of nitrogen dioxide (NO_2) in the hose between uses is not impacted.
- The correct administration of INOmax to the patient is not affected by the reported malfunction. No adverse effects in patients have been reported.

If faced with a defective cylinder valve, follow the steps outlined below:

1. Do not interrupt a treatment in progress and continue to use the cylinder until the end of the treatment or until the cylinder is empty (empty cylinders can be closed without any problems).
2. If this defect occurs during the initiation of a therapy, you can still start the therapy. However, it is recommended to use the back-up administration system.
3. Never try to remove the pressure regulator from the valve forcibly or use any tools, such as a screwdriver, to pry off the regulator.
4. When ready, try to close the INOmax cylinder valve via the INOmeter with extra force using your hand.
5. If this does not help to close the cylinder valve, contact your BOC representative for further support, BOC will manage the next steps to proceed further with this cylinder connected to the pressure regulator.
6. Mark the affected cylinder as defective, add the cap to the cylinder outlet, place in a safe location and issue a complaint to BOC via the standard complaint process – as detailed at the bottom of this letter.
7. Use a back-up administration system as necessary.

Further information
INOmax, in conjunction with ventilatory support and other appropriate active substances, is indicated:

- for the treatment of newborn infants ≥ 34 weeks gestation with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, in order to improve oxygenation and to reduce the need for extracorporeal membrane oxygenation.
- as part of the treatment of peri- and post-operative pulmonary hypertension in adults and newborn infants, infants and toddlers, children and adolescents, ages 0-17 years in conjunction to heart surgery, in order to selectively decrease pulmonary arterial pressure and improve right ventricular function and oxygenation.

BOC has received reports of a total of 24 faulty valves from 17 reporters, in which the valve does not fully close after opening when the cylinder is not empty. The manufacturer of the valve has identified the cause for this defect and actions to solve this defect have been implemented, meaning that all INOmax cylinders filled at the cylinder manufacturing site from 1st May 2021 will not have this defect.

In the meantime, there may be INOmax cylinders on the market that may have this defect, so we advise users to please follow the advice outlined in this letter

There is no additional risk that nitric oxide can leak from cylinders with a defective valve into the atmosphere or room while connected to the INOmax DSIR device, or to the INOmax regulator. If it is possible to safely remove the INOmax regulator from the cylinder, add the cap to the valve outlet as usual.

Call for reporting

Please continue to report suspected adverse drug reactions (ADRs) and medical device related problems to the MHRA through the Yellow Card Scheme.

Please report:

- All suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- All suspected ADRs associated with new drugs and vaccines identified by the black triangle ▼
- All problems with medical devices which have or could have resulted in injury to the patient or user

It is easiest and quickest to report online via the Yellow Card website or via the Yellow Card app available from the Apple App Store or Google Play Store. Alternatively, you can report to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm. You can leave a message outside of these hours.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

Please continue to report any suspected defective cylinder valves to your local BOC Account Manager or our freephone line **0800 917 4024.**

Company contact point

If you require any further information relating to the above, please contact your local BOC Account Manager or our freephone line **0800 917 4024**, or at ukcsc@linde.com

Your Sincerely,

John Hennigan

Head of Quality & Regulatory Affairs

INO Therapeutics

BOC Healthcare