NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ENTONOX ®, 50% Oxygen, 50% Nitrous Oxide medicinal gas, compressed.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each cylinder contains:

Nitrous oxide	50% mol/mol
Oxygen	50% mol/mol
Filling pressure	125 bar measured at 15°C

A cylinder of 2.8 litres filled to 125bar contains 0.46 m3 of gas at a pressure of 1 bar at 15 °C.
A cylinder of 10 litres filled to 125 bar contains 1.8 m3 of gas at a pressure of 1 bar at 15 °C.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Medicinal gas, compressed.

Colourless, odourless gas

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ENTONOX is indicated for the treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are wanted.

It may be used in patients of all ages except children below one month.

4.2 Dose and method of administration

ENTONOX should only be administered by competent personnel with access to adequate resuscitation equipment. Special precautions should be taken when working with nitrous oxide mixture. Nitrous oxide should be administered according to local guidelines.

Posology

Administration of ENTONOX should commence shortly before the desired analgesic effect is required. The analgesic effect is seen after 4-5 breaths and reaches its maximum within 2- 3 minutes. Administration of ENTONOX should continue throughout the painful procedure, or for as long as the analgesic effect is desired. Following discontinuation of the administration/inhalation, the effects wear off quickly within a few minutes.

Paediatric population

There is no difference in dose recommendations in the paediatric population.

Method of administration

ENTONOX is administered via inhalation in spontaneously breathing patients via a face mask.

Administration of ENTONOX is governed by the patient's breathing. By holding the mask securely around the mouth and nose and breathing via the mask, a so-called "demand valve" is opened and ENTONOX flows out of the equipment and is administered to the patient via the airways. Uptake occurs from the lungs.

In dentistry, the use of a double mask is recommended, alternatively, a nasal mask or nasobuccal mask with adequate scavenging/ventilation should be used.

ENTONOX should only be administered by personnel with knowledge of its use. Administration of ENTONOX should only occur under supervision of, and with instruction from, personnel familiar with the equipment and its effects. ENTONOX should only be administered when the possibility of oxygen supplementation and equipment for resuscitation are readily available.

Ideally, the patient should hold the mask through which ENTONOX is administered.

The patient should be instructed to hold the mask to his/her face and breathe normally. This is an additional safety measure to minimise the risk of overdose. If for any reason the patient receives more ENTONOX than is necessary, and wakefulness becomes affected, the patient will drop the mask and administration will cease. By breathing ambient air, the effect of ENTONOX rapidly wears off and the patient will regain consciousness.

ENTONOX should preferably be used in patients capable of understanding and following instructions about how the equipment and the mask should be used.

Due to the increased risk of the patient becoming markedly sedated and unconscious, this form of administration, should, however, only take place under controlled conditions. Continuous gas flow should only be used in the presence of competent personnel and with equipment available to manage the effects of more pronounced sedation/decreased level of consciousness. The potential risk of possible inhibition of protective airway reflexes should be acknowledged and preparedness to secure the airway and assist ventilation available whenever constant flow is used.

When administration is ended, the patient should initially be allowed to recover under calm and a controlled condition for around 5 minutes or until the patient's degree of alertness/consciousness has recovered satisfactorily.

ENTONOX can be administered for up to 6 hours without haematological monitoring in patients with no risk factors (see Section 4.4).

Paediatric population
In children that are not capable to understand and follow the instructions, ENTONOX might be administered under the supervision of competent medical personnel who can help them keep the mask in place, and actively monitor the administration. In such cases, ENTONOX may be administered with a constant gas flow.

4.3 Contraindications

During inhalation of ENTONOX, gas bubbles (gas emboli) and enclosed gas filled spaces may expand due to the enhanced diffusivity of nitrous oxide. Consequently, the use of ENTONOX is contraindicated:

- In patients presenting with the symptoms of pneumothorax, pneumopericardium, severe bullous emphysema, gas embolus, or severe head trauma.
- After a recent dive (risk of decompression sickness).
- After recent cardiopulmonary bypass with heart–lung machine or coronary bypass without heart lung machine.
- In patients with a recent intra ocular injection of gas (e.g. SF_6, C_3F_8) until said gas has been completely reabsorbed, due to the risk of further expansion of the gas bubble possibly leading to blindness.
- In patients with gross abdominal gaseous distension.

ENTONOX is also contraindicated:

- In patients with heart failure or severely impaired cardiac function (e.g. after cardiac surgery), since the mild myocardio depressive effect may cause further deterioration in cardiac function.
- In patients presenting persistent signs of confusion, changed cognitive function or other signs that could be related to increased intra-cranial pressure, as nitrous oxide may further increase the intra-cranial pressure.
- In patients presenting decreased consciousness and/or co-operability because of the risk for loss of protecting reflexes.
- In patients presenting with a vitamin B_{12} or folic acid deficiency or genetic perturbation in this system.
- In patients with facial injury where use of a face mask may present difficulties or risks.

4.4 Special warnings and precautions for use

Special precautions for use
The effects of nitrous oxide on the cardiovascular system are negligible in healthy patients with good cardiovascular function. Nitrous oxide has been shown to have a slight depressant effect on the contractility of heart muscle, but this is offset by a slight increase in the sympathetic stimulation of the heart, such that there is normally no significant net effect on the circulation. However, due to the potential for myocardial depression, nitrous oxide should be used with caution in patients with mild to moderate cardiac dysfunction and is contraindicated in patients with severe cardiac dysfunction or pronounced cardiac failure.

ENTONOX should only be administered by competent personnel with access to adequate resuscitation equipment (see 4.2).

In patients that are not capable to follow instructions, the use of constant gas flow may be required. When a constant flow of the gas mixture is used, the risk of pronounced sedation, unconsciousness and effects on protective reflexes, e.g. regurgitation and aspiration, should be acknowledged.

Nitrous oxide may already in concentration of 50% lead to the loss of laryngeal reflexes and reduce consciousness.

Nitrous oxide may diffuse into air filled spaces. ENTONOX can, by diffusion of nitrous oxide, induce increase in middle ear pressure.

- ENTONOX should be used with caution in patients presenting with facial trauma interfering with the use of the facial mask or mouthpiece.

In patients taking other centrally acting depressant medicinal products, e.g. morphine derivatives and/or benzodiazepines, concomitant administration of ENTONOX may result in increased sedation, and consequently have effects on respiration, circulation and protective reflexes. If ENTONOX is to be used in such patients, this should take place under the supervision of appropriately trained personnel (see 4.5).

ENTONOX should be used with caution in patients with compromised chemoreceptor sensitivity/function (e.g. Chronic Obstructive Pulmonary Disease - COPD) due to the relative high content (50 vol.%) of oxygen. Inhalation of high doses of oxygen may in such patients cause respiratory depression and increase in PaCO2.

After cessation of ENTONOX administration, nitrous oxide rapidly diffuses from blood to the alveoli. Due to the rapid wash-out dilution, a decrease of the alveolar oxygen concentration, diffusion hypoxia might occur. This can be prevented by oxygen supplementation.

Following discontinuation of administration of ENTONOX, the patient should be advised to recover under proper supervision until these potential risks resulting from use of ENTONOX have subsided and the patient has recovered satisfactorily. Recovery of the patient should be assessed by healthcare professional.

<u>Occupational exposure, pollution of surrounding ambient air</u>

Efforts should be made to keep nitrous oxide concentrations in the working environment as low as possible and according to local regulations.

At present, it is not possible to document a clear causal relationship between exposure to trace concentrations of nitrous oxide and any negative health effects. The risk for impaired fertility that has been reported in medical or paramedical personnel during chronic exposure and in rooms not properly ventilated cannot be entirely ruled out.

Rooms where nitrous oxide is frequently used should have appropriate ventilation or scavenging system allowing the maintenance of nitrous oxide concentration in the ambient air below national set guidelines, occupational exposure limit (OEL), commonly assessed by time weighted average (TWA). Also see the environmental risk assessment in section 5.3.

<u>Abuse use and risk for addiction</u>

The potential of abuse should be acknowledged. Repeated administration or exposure to nitrous oxide may lead to addiction. Caution should be exercised in patients with a known history of substance abuse or in healthcare professionals with occupational exposure to nitrous oxide.

Nitrous oxide causes inactivation of vitamin B_{12}, which is a co-factor of methionine synthase. Folate metabolism is consequently interfered with and DNA synthesis is impaired following prolonged administration of Nitrous Oxide. Prolonged or frequent use of Nitrous oxide may result in megaloblastic marrow changes, myeloneuropathy and subacute combined degeneration of the spinal cord. Nitrous oxide should not be used without close clinical supervision and haematological monitoring. Specialist advice should be sought from a haematologist in such cases.

Haematological assessment should include assessment for megaloblastic change in red cells and hypersegmentation of neutrophils. Neurological toxicity can occur without anaemia or macrocytosis and with vitamin B_{12} levels in the normal range. In patients with undiagnosed subclinical deficiency of vitamin B_{12}, neurological toxicity has occurred after single exposures to Nitrous Oxide during anaesthesia.

Nitrous oxide interferes with vitamin B_{12}/folic acid metabolism. ENTONOX should subsequently be used with caution in patients at risk of vitamin B_{12} or folic acid deficiency, i.e. those with deficient intake or absorption of vitamin B_{12}/folic acid or genetic perturbations in this system, and in immunocompromised patients. The possibility of vitamin B_{12}/folic acid replacement or substitution therapy should be considered.

The mixture should be stored in and administered at a temperature higher than -5°C: at temperatures lower than -5°C, component gases may separate, leading to risk for potential inhalation of a hypoxic gas mixture.

<u>Paediatric population</u>
ENTONOX can be used in children that are able to follow instructions on how to use the equipment.

In the treatment of younger children that are not capable to follow instructions, the use of constant gas flow may be required. Constant gas flow should only be provided by healthcare personnel trained in use of the gas with equipment available to secure the airway and for provision of assisted ventilation (see also 4.2).

Paediatric neurotoxicity:
Published juvenile animal studies demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive defects when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans.

Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anaesthetic agents early in life and may result in adverse cognitive or behavioural effects. These studies have substantial limitations and it is not clear if the observed effects are due to the anaesthetic/sedative agent administration or other factors such as the surgery or underlying illness.

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks (see also section 4.6).

4.5 Interaction with other medicines and other forms of interaction

Combination with other medicinal products

The nitrous oxide component of ENTONOX interacts in an additive manner with other active substances with effect on the central nervous system (e.g. opiates, benzodiazepines and other psychomimetics).

The use of nitrous oxide potentiates the effect of methotrexate on folate metabolism, yielding increased toxicity such as severe, unpredictable myelosuppression, and stomatitis. Whilst this effect can be reduced by administering calcium folinate, the concomitant use of nitrous oxide and methotrexate should be avoided.

The pulmonary toxicity associated with drugs such as bleomycin, amiodarone, (paraquat), furadantin and similar antibiotics may be exacerbated by inhalation of increased concentration of oxygen.

Other interactions

Medicinal nitrous oxide interacts with Vitamin B_{12} (see special warnings and precautions for use, section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

A large amount of data on pregnant women exposed to a single administration of nitrous oxide during the 1st trimester (more than 1000 exposed outcomes) indicate no malformative toxicity. Moreover, no fetal nor neonatal toxicity has been specifically associated with nitrous oxide exposure during pregnancy. Therefore, nitrous oxide can be used during pregnancy if clinically needed.

When nitrous oxide is used close to delivery, new-borns should be supervised for possible adverse effects (see sections 4.4 and 4.8).

Risk summary statement:

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

Preclinical data

Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (see also section 5.3).

No risk for adverse foetal effects has been observed for women occupationally exposed to chronic inhalation of nitrous oxide during pregnancy when an appropriate scavenging or ventilation system is in place. In the absence of appropriate scavenging or ventilation system, an increase in spontaneous abortions and malformations has been reported. These findings are questionable due to methodological biases and exposure conditions, and no risk was observed in subsequent studies when an appropriate scavenging or ventilation system had been implemented (see section 4.4 regarding need for satisfactory scavenging or ventilation system).

Breastfeeding
ENTONOX can be used during the breast-feeding period but should not be used during breast-feeding itself.

Fertility
The potential effect of clinical doses of ENTONOX on fertility in patients, are unknown. No data are available.

The potential risk associated to chronic workplace exposure cannot be ruled out (see section 4.4).

4.7 Effects on ability to drive and use machines

Nitrous oxide has effects on cognitive and psychomotor functions. The Nitrous oxide component of ENTONOX is rapidly eliminated from the body after brief inhalation and adverse psychometric effects are rarely evident 20 minutes after the administration has stopped while its influence on the cognitive capabilities can persist for several hours.

When used as the sole analgesic/sedative agent, driving and use of complex machinery is not recommended for at least 30 minutes after cessation of the administration of ENTONOX and until the patient has returned to their initial mental status as judged by the attending healthcare professional.

4.8 Undesirable effects

Due to the effects of nitrous oxide on vitamin B_{12}, in cases of prolonged or frequently repeated administration of ENTONOX, megaloblastic anaemia and leucopoenia have been reported. With exceptionally heavy or frequent administration, neurological disorders such as myelopathy or polyneuropathy have been reported. In suspected or confirmed vitamin B_{12} deficiency, or where symptoms compatible with affected methionine synthetase occur, vitamin B substitution therapy should be given in order to minimize the risk for adverse signs/symptoms associated to methionine synthetase inhibition such as leukopenia, megaloblastic anaemia, myelopathy and polyneuropathy.

Other analgesic therapies should be considered in patients showing signs of vitamin B_{12}/folate deficiency.

Tabulated summary of adverse reactions

The undesirable effects listed are derived from public domain scientific medical literature and post marketing safety surveillance.

System organ class	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1 000 to 1/100)	Rare (≥1/ 10 000 to 1/1 000)	Very rare (<1/ 10 000)	Not known (cannot be estimated from the available data)
Blood and lymphatic system disorders	—	—	—	—	—	Leukopenia, megaloblastic anaemia
Psychiatric disorders	—	Euphoria	—	—	—	Psychosis, confusion, anxiety, addiction
Nervous system disorders	—	Dizziness, light-headedness	Somnolence	—	Paraparesis	Headache, Myelopathy, neuropathy, subacute degeneration of the spinal cord, Generalised seizures*
Ear and labyrinth disorders	—	—	Feeling of pressure in the middle ear	—	—	
Gastrointestinal disorders	—	Nausea, vomiting,	Bloating, increased gas volume in the intestines	—	—	
General disorders and administration site conditions	—	sense of intoxication	—	—	—	
Respiratory, thoracic and mediastinal disorders	—	—	—	—	—	Respiratory depression

** Only reported in connection with pain management*

<u>Paediatric population</u>

There are no known additional undesirable effects in the paediatric population than in adults.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/}

4.9 Overdose

Since participation of the patient is required to administer the gas mixture, the risk of overdose is very small.

If during use of ENTONOX the patient shows signs of decreased alertness, does not respond or does not respond adequately to command, or in some other way shows signs of pronounced sedation, administration should be stopped immediately. The patient should not receive any further ENTONOX until full consciousness has been restored.

If cyanosis appears any time during the administration, it is imperative to immediately stop the treatment, and, if the cyanosis does not disappear rapidly, to administer supplementary oxygen and in case of respiratory depression assist ventilation.

Reversible neurological toxicity and megaloblastic bone marrow change have also been observed following exceptionally prolonged inhalation.

Overdose can arise as the result of inappropriate storage of the gas cylinders at temperatures below -5°C. At temperatures lower than -5°C, the component gases may separate, leading to risk for potential inhalation of a hypoxic gas mixture.

Paediatric population
The risk for overdose in the paediatric populations is the same as in the adult population.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Other general anaesthetics; ATC code: NO1AX63

Nitrous oxide at a concentration of 50% has an analgesic effect of increasing the threshold of diverse painful stimuli and decreasing the perception of pain.

The exact pharmacological mechanism of action of nitrous oxide analgesia has not been fully elucidated, but it is known to involve modulation of several CNS neurotransmitter systems including the endogenous opioids and noradrenergic transmission within the spinal cord and also has effects on the GABA and NMDA receptor systems.

The intensity of the analgesic effect depends on the psychological state of the patient. At 50% concentration, nitrous oxide does not have major anaesthetic effects. It leads to analgesia and a conscious sedation: the patient is relaxed, with a detached attitude.

The 50% oxygen concentration, over two times that of ambient air, will support proper haemoglobin oxygen saturation.

5.2 Pharmacokinetic properties

The uptake as well as the elimination of the nitrous oxide via the pulmonary route is fast and equilibration between inhaled and blood concentration is rapidly reached due to its low solubility in the blood and tissues. These properties explain the fast onset of the analgesic effect as well as the fast offset of analgesia and return to initial mental status of the patient when inhalation is stopped.

Nitrous oxide is not metabolised, it is eliminated by pulmonary ventilation only.

The very high diffusion rate of nitrous oxide into air- or gas-filled spaces explains some of its contra indications and special warnings.

There are no essential observations about the pharmacokinetics of oxygen at this concentration.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Prolonged continual exposure to 15 – 50% nitrous oxide has been shown to induce neuropathy in fruit bats, pigs and monkeys.

Teratogenic effects of nitrous oxide have been observed in rats after chronic exposure to levels higher than 500 ppm.

Pregnant rats exposed to 50 – 75% nitrous oxide for 24 hours on each of days 6 to12 of gestation show higher incidence of foetal wastage and malformations of the ribs and vertebrae.

Animal toxicology and/or pharmacology

Published studies in animals demonstrate that the use of anaesthetic and sedative agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on Gestation Day 122 increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on Gestation Day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear; however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

Environmental Risk Assessment (ERA)
The environmental risk shall be considered from two perspectives: The risks linked to the components of the product individually and the risk related to the packaging and its disposal.

Potential environmental risk
Nitrous oxide contributes to the greenhouse effect. The amount of nitrous oxide derived from medical practice is, however, small, about 1% of the global production of the agent and this accounts for 0.01% of the greenhouse effect (water vapour included).

Potential occupational risk
Studies are not completely conclusive in the relationship between safety hazard and nitrous oxide exposure. In order to minimize the potential risks, efforts should be made to keep working environment concentrations as low as possible. Also see, special warnings and precautions for use, section 4.4.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Not listed.

6.4 Special precautions for storage

Storage of ENTONOX cylinders
The product is sensitive to low temperatures. The mixture can separate at temperatures below - 5°C. A liquid nitrous oxide rich phase can condense from the mixture leading to inhalation of gas containing too much oxygen at the beginning of the treatment (mixture less analgesic) and too much nitrous oxide at the end (risk for hypoxic mixture). Do not expose cylinders to a temperature below -5°C.

If it is suspected that the cylinders have been exposed to lower temperatures, the cylinders shall be stored in HORIZONTAL POSITION for at least 48 hours at a temperature between +10 and + 30°C before use.

For all other situations, the storage position does not matter.

Attention of the emergency units should be brought on the necessity to protect cylinders against low temperatures, in the vehicles and during the use outdoors.

Storage of the medicinal gas cylinders

- Cylinders should be stored in a well-ventilated and lockable area reserved for the storage of medicinal gases.
- The cylinders should be stored under cover, protected against weather and wind, kept dry and clean, free from inflammable material and not subjected to extreme temperatures.
- Precautions should be taken to prevent blows or falls.
- Cylinders containing different types of gases should be kept segregated.
- Full and empty cylinders should be stored separately.
- When delivered from the manufacturer, the cylinder should have an intact tamper evident seal.

6.5 Nature and contents of container <and special equipment for use, administration or implantation.

The cylinders are made of high tensile steel or aluminium equipped with pin-index valves.

The cylinder body is painted white and the cylinder shoulder is painted White and Royal Blue in 4 of 90° Sectors (Quadrants)

Packs (incl. material and valves):

Cylinder size (L water capacity)	Valve type	Cylinder material	Filling pressure at 15C (125bar)	Content (m^3 ENTONOX at 15°C, 125 bar)
A 2.9L	Pin index	Aluminium	125	0.46
D2 10L	Pin index	Aluminium	125	1.8
E 15L	Pin index	Aluminium	125	2.7
G 46.6L	Pin index	Steel	125	8.4

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

General

- Do not smoke or use flame in areas where medicinal gases are stored or administered.
- Never use oil or grease, even if the cylinder valve sticks or if the regulator is difficult to connect.
- Handle valves and devices belonging to them with clean and grease-free (hand-cream etc.) hands.
- In case of cleaning of cylinder or attached equipment, do not use combustible products and especially oil-based material. In case of doubt, check compatibility.

- Do not use any cylinder suspected to have been exposed to temperature below minus 5°C unless stored during 48 hours at least in horizontal position, at a temperature between + 10 and + 30°C.
- Prior to any use, ensure the sufficient quantity of product remains to allow completion of the planned administration. During use, ensure that sufficient quantity of product remains to allow sufficient necessary flow.
- Use only standard devices that are designed for nitrous oxide – oxygen mixture administration.

Preparation for use

- Remove the seal from the valve before use.

The instructions below are applicable for ENTONOX cylinders where a separate pressure regulator shall be connected before use.

- Use only regulators designed for medicinal nitrous oxide – oxygen mixture.
- Check that the connection on the coupling or regulator is clean and that the connections are in good condition.
- Never use pliers to force pressure/flow regulators that are designed to be connected manually, as this can damage the joint.
- Check that the pressure regulator is properly attached before opening the valve.
- Open the cylinder valve gently – at least half turn.
- Check for leakage according to instructions that accompany the regulator. Do not attempt to remedy leakage from the valve or device in any way other than by changing the pack or O-ring.
- In the event of leakage, close the valve and uncouple the regulator. Label defective cylinders, put them aside, and return them to the supplier.

Use of the gas cylinder

- Ensure ENTONOX cylinders are secured to a suitable cylinder support in vertical position when in use, to prevent them from falling.
- For cylinders equipped with integrated valves, the user should be prepared to change the cylinder when the pressure gauge is in the yellow zone and change it when it enters the red zone to keep sufficient flow.
- For cylinders that are not equipped with integrated valves, when a small amount of gas remains in the cylinder (approx. 2 bar), the cylinder valve should be closed. It is important to leave a slight residual pressure in the cylinder in order to protect it from contamination.
- After use, the cylinder valve should be closed with normal force. Depressurise the regulator or connection.

Transportation of cylinders

Large cylinders should be transported with appropriate type of trolley. Particular attention should be paid to ensuring that connected devices are not accidentally loosened.

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

BOC Limited
988 Great South Road
Penrose
AUCKLAND, New Zealand
Telephone: 0800 656 334

BOC Limited, a Linde Company
Linde AG
Klosterhofstrasse 1
80331 Munich
Germany

9. DATE OF FIRST APPROVAL

27 Feb 1986

10. DATE OF REVISION OF THE TEXT

27 Nov 2024

SUMMARY TABLE OF CHANGES

Version	Date	Changes
1	27 Nov 1986	Original issue.
2	5 Jun 2017	Revision to SmPC format; Inclusion of additional warnings raised by US FDA per Medsafe request; Alignment to Linde Group content
3	27 Nov 2024	Adapted from Linde Global Core Company Data Sheet for Entonox (NITROUS OXIDE- OXYGEN 50%-50% MIXTURE) Version 14. Effective date: 12 Oct 2022. Inclusion of additional warnings raised by US FDA per Medsafe request April 2017