NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Nitrous Oxide 100%, medicinal gas, compressed.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitrous oxide
There are no excipients.

3. PHARMACEUTICAL FORM

Medicinal gas, liquefied.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- As an anaesthetic agent, for use in combination with any other anaesthetic agent administered intravenously or by inhalation.
- For the treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are wanted.

Medicinal nitrous oxide is indicated in all age groups.

4.2 Dose and method of administration

Posology

General anaesthesia
When used in general anaesthesia, nitrous oxide is commonly used in doses ranging from 35 to 75%, in a mixture with oxygen.

- Nitrous oxide is usually not sufficient to create an adequate anaesthetic effect on its own and should therefore be used in combination with appropriate dose of another anaesthetic when used for general anaesthesia. Nitrous oxide has an additive interaction with most other anaesthetics (also see interaction with other medicinal products and other forms of interaction, section 4.5).
- Nitrous oxide in combination with oxygen in a composition such as one part of oxygen and two parts of nitrous oxide, creating a mixture of about 33% oxygen and 66% nitrous oxide is commonly used, providing an equivalent to about 63% of one MAC (Minimal Alveolar Concentration).

The effects of nitrous oxide are not age dependent but the interaction with other anaesthetics does however differ with age. A more pronounced effect can be seen in older age groups with the relative MAC reducing-effect increasing after the age of about 40-45 years.

Analgesia, conscious sedation
Nitrous oxide exhibits analgesic and sedative properties.

When used as a sole agent, concentrations of 30-60% nitrous oxide possess dose dependent analgesia and sedative effects.

Medicinal nitrous oxide should be used during the entire duration of the procedure or for as long as the analgesic effect is desired.

Breathing, circulation, and protecting reflexes are usually safely preserved at these concentrations (also see overdose, section 4.9).

Medicinal nitrous oxide should not be administered in higher concentrations than 70%-75% to ensure a safe oxygen fraction can be guaranteed. In patients with compromised oxygenation, oxygen fraction >30% may be required.

Medicinal nitrous oxide can be administered for up to 6 h without haematological monitoring in patients with no risk factors (see special warnings and precautions for use, section 4.4).

Paediatric population
There is no difference in the dosage recommendations for the paediatric population.

Method of administration
Precautions to be taken before handling or administering the medicinal product, see special precautions for disposal and other handling (section 6.6).

Nitrous oxide should be administered via inhalation via specific equipment, either during spontaneous or controlled ventilation.

Nitrous oxide should be administered in combination with oxygen via specific equipment providing a mixture of nitrous oxide and medicinal oxygen. The equipment should include monitoring of the content of oxygen, with alarms not allowing a concentration of oxygen below 21%.

When used in anaesthesia, nitrous oxide is administered via special equipment where the exhaled gas is recirculated and can be rebreathed (i.e. a circular system with rebreathing).

Nitrous oxide should be administered only in rooms with proper ventilation and/or scavenging equipment in order to avoid excessive ambient air concentrations according to local regulations (see special warnings, section 4.4).

Paediatric population
When used for short term pain conditions in children that are not capable to understand and follow the instructions, nitrous oxide might be administered under the supervision of competent medical personnel who can help them keep the mask in place, and actively monitor the administration.

4.3 Contraindications

During inhalation of nitrous oxide, gas bubbles (gas emboli) and enclosed gas filled spaces may expand due to the enhanced diffusivity of nitrous oxide. Consequently, the use of Medicinal nitrous oxide 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.
- In patients with a recent intra ocular injection of gas (e.g. SF6, C3F8) until the 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.

Medicinal nitrous oxide is also contraindicated:

- In patients with cardiac 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 intracranial pressure.
- In patients presenting decreased consciousness and/or co-operability, when used in analgesia, 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.

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.

Nitrous oxide when used for procedural pain management as sole agent may in high concentration (>50%) lead to the loss of laryngeal reflexes and reduce consciousness. In concentrations higher than 60-70% it often causes unconsciousness and the risk for impairment of the laryngeal reflexes increases.

Nitrous oxide should only be used where supplemental oxygen can be administered and in the presence of personnel trained in emergency procedures.

Nitrous oxide may diffuse into air filled spaces. Nitrous oxide may thus increase middle ear pressure as well as the pressure in other gas filled areas. Nitrous oxide administration may increase the pressure in catheter balloons e.g. in tracheal intubation.

Nitrous oxide should not be used during laser surgery in the airways due to the relative risk for explosive fire.

After general anaesthesia consisting of a high percentage of nitrous oxide the risk for hypoxaemia (diffusion hypoxaemia) is a well-recognised clinical problem dependent on not only the alveolar gas composition but also the compromised responses to hypoxia, hypercapnia and hypoventilation. After general anaesthesia supplementary oxygen and monitoring of oxygen saturation with pulse oximetry is recommended.

Occupational exposure, pollution of surrounding ambient air

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.

Abuse use and risk for addiction

The potential for 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. Nitrous oxide 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.

Paediatric population

The special warnings and precautions for use in the paediatric population is the same as in the adult populations in addition to the following;

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

There are additive effects when nitrous oxide is used in combination with other inhaled anaesthetics or drugs having a central depressant action (e.g. opiates, benzodiazepines and other psychotropics).

These interactions have clear effects in clinical practice, decreasing the dose needed for the other agents combined with nitrous oxide, causing less cardiovascular and respiratory depression and increasing speed of emergence.

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.

Other interactions

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

Paediatric population

No other interactions are known, than those in the adult population.

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, newborns 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

Nitrous oxide can be used during the breast-feeding period, but should not be used during breastfeeding itself.

Fertility

No data are available. The potential effect of clinical doses of nitrous oxide on fertility is unknown.

The potential risk associated to chronic work place exposure cannot be ruled out (see special warnings and precautions for use, section 4.4).

4.7 Effects on ability to drive and use machines

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

When used as sole agent, driving and use of complex machinery is not recommended for at least 30 min after cessation of administration of nitrous oxide and until the patients have returned to their initial mental status as judged by attending healthcare professional.

4.8 Undesirable effects

Summary of the safety profile

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

Due to the effects of nitrous oxide on vitamin B_{12}, in cases of prolonged or frequently repeated administration of nitrous oxide, 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

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*

Paediatric population

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

Reporting of suspected adverse reactions

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

Medicinal nitrous oxide should always be used in combination with sufficient oxygen in order to guarantee adequate oxygenation/oxygen saturation. Administration equipment should not allow concentration of oxygen below 21%.

Excess inhalation of nitrous oxide will result in hypoxaemia and unconsciousness.

In case of accidental overdose (i.e. concentrations jeopardising adequate oxygen delivery), hypoxia and ischaemia may develop. In that case, the nitrous oxide concentration should be lowered or the administration discontinued. The oxygen fraction should be increased and adjusted until the patient fulfils criteria for adequate oxygenation.

When used for pain release, administration should be stopped immediately if 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, during the use of medicinal nitrous oxide in analgesic concentrations. The patient should not receive any further medicinal nitrous oxide until full consciousness has been restored.

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

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

Pharmacotherapeutic group: General anaesthetics, ATC code: NO1AX13.

The exact pharmacological mechanism of action of nitrous oxide analgesia/anaesthesia 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. Nitrous oxide also has effects on GABA and NMDA receptor systems.

The intensity of the analgesic effect depends on the psychological state of the patient. Nitrous oxide exhibits dose-dependent analgesic and cognitive effects.

At inhaled concentrations of up to about 50 to 60% nitrous oxide exhibits increasing analgesic and cognitive effects. It leads to analgesia and a conscious sedation: the patient is relaxed, with a detached attitude.

At concentration of about 60 to 70% nitrous oxide causes light anaesthesia characterized by unconsciousness, loss of response to verbal command and mild tactile stimulation.

When combined with other anaesthetics/analgesics, nitrous oxide creates more profound anaesthesia.

5.2 Pharmacokinetic properties

Absorption

Nitrous oxide is administered by inhalation and its uptake is dependent on the pressure gradient between inhaled air and the blood passing through the ventilated alveoli.

Distribution

Distribution in the body tissues is dependent on blood perfusion and the nitrous oxide saturation of the blood. The equilibration in other tissues is dependent on the solubility, which is governed by the partition (distribution) coefficient for individual tissues. Nitrous oxide has low solubility in blood as well as other compartments leading to a fast equilibration between inspired and end-tidal gas concentration, i.e. nitrous oxide has a fast "wash-in" and equilibrates more rapidly than other inhaled anaesthetics.

Elimination

Nitrous oxide is inert and is not metabolised; it is excreted through alveolar ventilation and exhaled. Elimination is solely dependent on alveolar excretion and ventilation. The required time for elimination of nitrous oxide after discontinuation of administration is similar to that of saturation with the gas.

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, or carcinogenic potential.

Prolonged continual exposure to 15-50% nitrous oxide has been showed 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 h 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 minimise 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

- Do not smoke or use a naked flame in areas where medicinal gases are stored or administered (used).
- Cylinders should be stored in a well-ventilated area reserved for the storage of medicinal gases.
- Cylinders should be stored under cover, kept dry and clean, kept free from oil and grease, free from flammable material.
- Cylinders should be stored at temperatures from -40°C to +65°C.
- Precautions should be taken to prevent blows or falls.
- Cylinders containing different types of gases should be must be stored separately.
- Full and empty cylinders should be stored separately.

- Cylinders should be stored and transported with valves closed.
- After delivery from the manufacturer a cylinder must have an undamaged plastic valve cover.

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

The cylinders are made of either high tensile steel or aluminium, equipped with pin index valves. They may be supplied as a single cylinder or as bundled, pack of cylinders.

The cylinder body is painted white and the cylinder shoulder is painted royal blue

Cylinder size (L water capacity)	Valve type	Cylinder material	Content (kg Nitrous Oxide)
A – 2.9L	Pin index	Aluminium	1.99kg
D2 – 10L	Pin index	Aluminium	6.6kg
E – 15L	Pin index	Steel/Aluminium	9.89kg
GS – 38.5L	Pin index	Steel	28.8kg
G – 47L	Pin index	Steel	33.9kg
G15- 699L	Pin index	Steel	501.98kg

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

The cylinder package must not be disposed but returned to the supplier.

General precautions

- Medicinal gases must only be used for medicinal purposes.
- Never use grease, oil or similar substances, 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 cylinders or attached equipment, do not use combustible products and especially not oil-based material. In case of doubt, verify compatibility.
- Prior to any use, ensure sufficient quantity of product remains to allow completion of the planned administration.
- Only use standard devices designed for administration of medicinal product.

- When delivered from the manufacturer, the cylinders should have an intact tamper evident seal.

Preparation for use

- Remove the plastic cover from the valve before use.
- The instructions below are applicable for cylinders where a separate pressure regulator shall be connected before use:
- Use only regulators designed for product.
- Check that the connection on the coupling or regulator is clean and that the connections are in good condition.
- Never use pliers to force regulators that are designed to be connected manually, as this can damage the connection.
- Check that the regulator is properly attached before opening the valve.
- Open the cylinder valve gently, at least half a turn.
- Check for leakage according to instructions that accompany the regulator
- In the event of leakage, close the valve and disconnect the regulator. Mark the defective cylinder, keep it separate and return it to your supplier.

Use

- Close the cylinder in the event of fire or when not in use.
- Ensure 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.
- For cylinders that are not equipped with residual pressure valves, the cylinder valve should be closed when a small amount of gas remains in the cylinder (approx. 2 bars). 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 and the regulator or connection depressurised.

Transportation of cylinders

- When being transported, the cylinders must be secured to prevent them from falling.
- Larger cylinders should be transported with appropriate type of trolley. Particular attention should be paid to ensuring 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 is a member of the Linde Group
Linde AG
Klosterhofstrasse 1
80331 Munich, Germany

9. DATE OF FIRST APPROVAL

27 Nov 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 Nitrous Oxide Version 14. Effective date: 12 Oct 2022. Inclusion of additional warnings raised by US FDA per Medsafe request April 2017