a) Brand or Product Name
Leeden Medicinal Nitrous Oxide 100% v/v.

b) Name and Strength of Active Substance(s)
Nitrous Oxide 100% v/v.

c) Product Description
Medicinal gas, liquified.
Sweet smelling, colourless gas.

d) Pharmacodynamics (including clinical studies – clinical studies not applicable for generics)
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.

e) Pharmacokinetics
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.

f) Indication
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.

g) Recommended Dosage
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 Warnings and Precautions, section j).

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 Warnings and Precautions, section j).

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.

h) Route of Administration
Inhalation.

i) 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 B12 or folic acid deficiency or genetic perturbation in this system.

j) Warnings and Precautions

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 B12, 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 B12 levels in the normal range. In patients with undiagnosed subclinical deficiency of vitamin B12, neurological toxicity has occurred after single exposures to Nitrous Oxide during anaesthesia.

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.

k) Interactions with Other Medicaments

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 B12 (see Warnings and Precautions, section j).

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

l) 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 Warnings and Precautions and Side Effects).

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.

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.

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 Warnings and Precautions, section j).

m) Side 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 B12, 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 B12 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 B12/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://www.npra.gov.my/index.php/en/health-professionals/reporting-adr.html

n) Symptoms and Treatment of 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 04 6536 999

o) Effects on Ability to Drive and Use Machine

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.

p) Instruction for Use

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.

q) Storage Conditions

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 below 50°C.
• Precautions should be taken to prevent blows or falls.
• Cylinders containing different types of gases should 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.

r) Dosage forms and packaging available

Dosage: Liquified Medicinal Gases, Compressed
Packaging: Synthetic Medical air is packed in aluminium or steel cylinder with content between 1.85 to 30kg.

s) Name and address of manufacturer/ product registration holder

Manufacturer:
Leeden National Oxygen Ltd.
21 Tanjong Kling Road, Singapore 628047

Product registration holder:
Leeden Gases Sdn. Bhd.
Lot PT 5074 & 5075, Jalan Jangur 28/43, Seksyen 28,
40400 Shah Alam, Selangor Darul Ehsan, Malaysia

t) Date of revision of PI
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