New Zealand Data sheet
Medical nitrous oxide.

1 Product name
Medical nitrous oxide

2 Qualitative and quantitative composition
Medical nitrous oxide cylinders are supplied to the following specification:
Medical nitrous oxide purity 98.0% v/v

The Medical nitrous oxide cylinder specification complies with the current European Pharmacopeia (0416)

3 Pharmaceutical form
Medicinal gas, compressed

4 Clinical particulars
4.1 Therapeutic indications

Nitrous oxide is used:

- When an inhalation anaesthetic is required, the administration of nitrous oxide is usually accompanied by simultaneous administration of a volatile agent such as isoflurane, sevoflurane and desflurane etc.
- In the relief of severe pain, usually in emergency situations, by inhalation with 50% oxygen
- In short-term procedures which inevitably involve pain, such as wound and burn dressing, wound debridement and suturing. Administered usually with 50% oxygen
- In dental work to provide short-term analgesia for tooth extraction and other brief procedure, administered with 50% oxygen
- Occasionally as an insufflating agent in laparoscopy
- In cryosurgery as a refrigerant

4.2 Dose and method of administration

Nitrous oxide is administered through a face mask or tracheal tube by means of an anaesthetic apparatus. The gas is breathed in by the patient and absorbed through the lungs.

Where the clinical indication is the production of general anaesthesia, it should be noted that:
- In the average adult, nitrous oxide is administered by inhalation through a suitable anaesthetic apparatus in concentrations up to 70% with oxygen as the balance.

Concentrations of nitrous oxide above 70% should be administered with caution due to the risk of hypoxemia
- As people age, there is a steady reduction in the indices of cardiac and respiratory function evinced by a lowering of cardiac output and in lung ventilation and perfusion. In addition, there is an increase in dead space in the lung which increases minute ventilation. Cerebral blood flow is reduced by up to 30%. The result of these changes means that susceptibility to anaesthesia is increased. Nitrous oxide is, therefore, more useful in the elderly and the depressant effects of added agents are reduced
- There are no essential differences in clinical indications between the adult and child
- In obstetrical anaesthesia, the nitrous oxide level is kept below 70% to allow a substantial oxygen level to be provided. Nitrous oxide plays a major role because injected agents depress the breathing of the infant and volatile agents depress uterine contraction
- As a general rule, the more ill the patient, the more susceptible is the patient to other anaesthetic agents and the more nitrous oxide is relied upon

The possibility of vitamin B12/folic acid replacement or substitution therapy should be considered after a prolonged use exceeding 6 hours or recurrent use, and haematological monitoring should be instituted to minimise risk of potential side effects.

Nitrous oxide is usually not sufficient to create an adequate anaesthetic effect on its own, and should therefore be used in combination with appropriate doses of another anaesthetic when used for general anaesthesia. Nitrous oxide has additive interaction with most other anaesthetics (see interactions 4.5).

4.3 Contraindications

Nitrous oxide should not be used with any condition where gas is entrapped within a body and where its expansion might be dangerous, such as:
- Head injuries with impairment of consciousness
- Artificial, traumatic or spontaneous pneumothorax
- Air embolism
- Decompression sickness
- Following a recent underwater dive
- Following air encephalography
- Severe bullous emphysema
- During myringoplasty
- Gross abdominal distension
- Intoxication
- Maxillofacial injuries
- In patients having received recent intraocular injection of gas (such as SF6)

4.4 Special warnings and precautions for use

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.

The possibility of vitamin B_{12}/folic acid replacement or substitution therapy should be considered after a prolonged continuous use exceeding 6 h or recurrent use and haematological monitoring should be instituted to minimise risk of potential side effects.

Haematological assessment should include an assessment for megaloblastic change in red cells and hypersegmentation of neutrophils. Neurological toxicity can occur without anaemia or macrocytosis and with 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 general anaesthesia.

Assessment of vitamin B12 levels should be considered in people with risk factors for vitamin B12 deficiency prior to using nitrous oxide anaesthesia. Risk factors include the elderly, those with poor or vegetarian diet, and previous history of anaemia.

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.

Reduced fertility in healthcare personnel has been reported where they have been repeatedly exposed to high levels of nitrous oxide above the specified occupational exposure limits in inadequately ventilated rooms. There is no documented evidence to confirm or exclude the existence of any causal connection between these cases and exposure to nitrous oxide. Scavenging of waste nitrous oxide gas should be used to reduce operating theatre and equivalent treatment room levels to a level below 100 ppm of ambient nitrous oxide.

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

At the end of a nitrous oxide/oxygen anaesthesia, withdrawal of the mask leads to an outpouring of nitrous oxide from the lung and consequent dilution of oxygen in incoming air. This results in "diffusion hypoxia" and is counteracted by giving 100% oxygen for a few minutes when the flow of nitrous oxide is stopped.

Nitrous oxide is non-flammable but strongly supports combustion and should not be used near sources of ignition.

Smoking should be prohibited when using nitrous oxide.

Under no circumstances should oils or grease be used to lubricate any part of the nitrous oxide cylinder or the associated equipment used to deliver the gas to the patient.

Where moisturising preparations are required for use with a facemask, oil based creams should not be used.

Check that hands are clean and free from any oils or grease.

Where alcohol gels are used to control microbiological cross-contamination ensure that all alcohol has evaporated before handling nitrous oxide cylinders or equipment nitrous oxide is stored in high pressure gas cylinders as a liquid under pressure.

Rapid opening of the valve can cause the discharged gas to re-liquefy. This liquid can cause cold bums if in contact with the skin. Cylinders should only be used in the vertical position with the valve uppermost. If not, liquid may be discharged when the valve is opened.

Paediatric population:

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

Nitrous oxide inactivates vitamin B12 and potentiates the effects of methotrexate on folate metabolism.

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 practise, decreasing the dose needed for the other agents combined with nitrous oxide, causing less cardiovascular and respiratory depression and increasing speed of emergence.

4.6 Fertility, pregnancy and lactation

Pregnancy:

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 primates corresponding to periods prior to the third trimester in humans (see also section 5.3).

Mild skeletal teratogenic changes have been observed on pregnant rat embryos when the dam has been exposed to high concentrations of nitrous oxide during the period of organogenesis. However,

no increased incidence of foetal malformation has been discovered in 8 epidemiological studies and case reports in human beings.

There is no published material which shows that nitrous oxide is toxic to the human foetus.

Therefore, there is no absolute contraindication to its use in the first 16 weeks of pregnancy.

Lactation:

There are no known adverse effects to using nitrous oxide during the breast-feeding period.

4.7 Effects on ability to drive and use machines

Nitrous oxide is rapidly eliminated but driving, use of machinery and other psycho-motor activities should not be undertaken until 12 hours have elapsed after nitrous oxide anaesthesia.

4.8 Undesirable effects

Events such as euphoria, disorientation, sedation, nausea, vomiting, dizziness and generalised tingling are commonly described. These events are generally minor and rapidly reversible.

Prolonged or frequent use of nitrous oxide, including heavy occupational exposure and addiction, may result in megaloblastic anaemia. Agranulocytosis has been reported following prolonged nitrous oxide administration (see section 4.4).

Myeloneuropathy and sub-acute combined degeneration have also been reported following prolonged or frequent use. However, in patients with undiagnosed subclinical deficiency of vitamin B12, neurological toxicity has occurred after a single exposure to nitrous oxide for anaesthesia (see section 4.4).

Addiction may occur.

Nitrous oxide passes into all gas containing spaces in the body faster than nitrogen passes out.

Prolonged exposure may result in bowel distension, middle ear damage and rupture of ear drums.

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Inappropriate, unwitting or deliberate inhalation of nitrous oxide will ultimately result in unconsciousness, passing through stages of increasing light-headedness and intoxication, and, if the victim were to be within a confined space, death from anoxia could result. The treatment is removal to fresh air, mouth-to-mouth resuscitation and, if necessary, the use of an oxygen resuscitator.

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 – N01AX13

The characteristics of nitrous oxide are:

- Sweet smelling, colourless gas
- Molecular weight 44.01
- Boiling point -88.6oC (at 1 bar)
- Density 1.875 kg/m^3 (at 15°C)

Nitrous oxide is not very soluble in water but is fifteen times more soluble than oxygen. Water dissolves nitrous oxide, taking 100 vol %, and blood plasma 45 vol %.

Nitrous oxide is eliminated unchanged from the body mostly by the lungs.

Nitrous oxide is a potent analgesic and a weak anaesthetic. Induction with nitrous oxide is relatively rapid, but a concentration of about 70% is needed to produce unconsciousness.

Endorphins are probably involved in the analgesic effect; a concentration of 25% nitrous oxide is usually adequate to provide a marked reduction in pain.

5.2 Pharmacokinetic properties

Nitrous oxide is a low potency inhalation anaesthetic and only slightly soluble. The advantage of this is that concentrations not greater than 70% are used and induction of anaesthesia and recovery occur quickly.

At a constant inspired concentration, the rise time of alveolar concentrations is faster than that of any other anaesthetic agent. The elimination of nitrous oxide is faster than that of any other anaesthetic.

The blood/gas partition coefficient of nitrous oxide at 37°C is 0.46 compared with that of Nitrogen of 0.015, causing nitrous oxide to expand into internal gas spaces.
Under normal anaesthesia, the adult body contains about 25 litres of gaseous nitrous oxide (this gives some notion of its essential safety and lack of acute toxicity).

The flow of nitrous oxide out from the tissues through the lungs at the end of anaesthesia may lead to a degree of transient hypoxia.

5.3 Preclinical safety data

The current published toxico-pharmacological data indicates that medical nitrous oxide will not be harmful to humans.

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.

6 Pharmaceutical particulars

6.1 List of excipients

None

6.2 Incompatibilities

Nitrous oxide is chemically inactive and will not react with other compounds at normal temperatures.

Medical nitrous oxide strongly supports combustion and will cause substances to burn vigorously, including some materials that do not normally burn in air. It is highly dangerous in the presence of oils, greases, tarry substances and many plastics due to the risk of spontaneous combustion in the presence of nitrous oxide in relatively high concentrations.

6.3 Shelf life

Not listed

6.4 Special precautions for storage

Medical nitrous oxide cylinders should be:

- Stored under cover, preferably inside, kept dry and clean, not subjected to extremes of heat or cold and stored away from stocks of material
- Not stored near stocks of combustible materials or near sources of heat
- Stored separately from industrial and other non-medical cylinders
- Stored to maintain separation between full and empty cylinders
- Used in strict rotation so that cylinders with the earliest filling date are used first
- Stored separately from other medical cylinders within the store
- Stored vertically

Warning notices prohibiting smoking and naked lights must be posted clearly in the cylinder storage area and the Emergency Services should be advised of the location of the cylinder store.

Precautions should be taken to protect the cylinders from theft.

Care is needed when handling and using medical nitrous oxide cylinders

6.5 Nature and contents of container

Medical nitrous oxide is supplied in cylinders manufactured from either high tensile steel or aluminium, fitted with pin indexed valves.
May be supplied as a single gas cylinder or as a bundled pack.

6.6 Special precautions for disposal and other handling

All personnel handling medical nitrous oxide gas cylinders should have adequate knowledge of:

- Properties of the gas
- Correct operating procedures for the cylinder
- Precautions and actions to be taken in the event of an emergency

Preparation for use:

To prepare the cylinder for use:

- Remove the tamper evident seal and the valve outlet protection. Do not remove and discard batch labels fitted to the cylinder
- Ensure that an appropriate medical nitrous oxide regulator is selected for connection to the cylinder
- Ensure the connecting face on the regulator is clean and the sealing washer fitted is in good condition
- Connect the regulator, using moderate force only and connect the tubing to the regulator / flowmeter outlet. Only the appropriate regulator should be used for the particular gas concerned
- Open the cylinder valve slowly and check for any leaks
- If using with a mixing apparatus, check operability of oxygen mixing apparatus and availability of oxygen

Leaks:

Having connected the regulator or manifold yoke to the cylinder check the connections for leaks using the following procedure:

- Should leaks occur this will usually be evident by a hissing noise
- Should a leak occur between the valve outlet and the regulator or manifold yoke, depressurise and remove the fitting and fit an approved sealing washer. Reconnect the fitting to the valve with moderate force only, fitting a replacement regulator or manifold tailpipe as required
- Sealing or jointing compounds must never be used to cure a leak
- Never use excessive force when connecting equipment to cylinders
- If leak persists. label cylinder and return to BOC

Use of cylinders:

When medical nitrous oxide cylinders are in use ensure that they are:

- Only used for medicinal purposes
- Turned off, when not in use, using moderate force to close the valve
- Only moved with the appropriate size and type of trolley or handling device
- Handled with care and not knocked violently or allowed to fall

- Firmly secured to a suitable cylinder support when in use
- Not allowed to have any markings, labels or batch labels obscured or removed
- Not used in the vicinity of persons smoking or near naked lights
- Used vertically with the valve uppermost
- Used in a well ventilated area with waste gas scavenging systems in place to maintain the average occupational exposure level of the healthcare professional to less than 100ppm (over an 8 hour period)
- Cylinder pressure is not an indicator of quantity remaining in the cylinder until all liquid has vapourised. Measure contents by weight

When the medical nitrous oxide cylinder is empty ensure that:
- The cylinder valve is closed using moderate force only and the pressure in the regulator is released
- The empty cylinders are immediately returned to the empty cylinder store for return to BOC

7 Medicine schedule
Prescription

8 Sponsor
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10 Date of revision of the text
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Summary table of changes
5 Jun 2017 - Revision to SmPC format; Inclusion of additional warnings raised by US FDA per Medsafe request; alignment to Linde Group content