New Zealand data sheet

ENTONOX®.

1 Product name.

Entonox®

2 Qualitative and quantitative composition.

Entonox cylinders are supplied to the following specification:
Oxygen 50.0 % +/- 2.0 %
Nitrous oxide 50.0 % +/- 2.0 %

The medical oxygen specification complies with the current European Pharmacopeia monograph (0417).

The nitrous oxide specification complies with the current European Pharmacopeia monograph (0416).

3 Pharmaceutical form.

Medicinal gas, compressed

4 Clinical particulars.

4.1 Therapeutic indications

ENTONOX is used exclusively for the relief of pain. Common examples of the use of ENTONOX are:

- Acute trauma
- Short-term relief in dental work
- Short-term relief for procedures inevitably involving pain, such as wound and burn dressing, wound debridement and suturing
- Normal labour
- Acute surgical or medical conditions in which the pain is relieved, only to return on cessation of the analgesia so allowing an unfettered assessment to be made

4.2 Dose and method of administration

ENTONOX is administered through a facemask or mouthpiece. The facemask or mouthpiece is connected to an ENTONOX supply through a demand valve system which allows the ENTONOX to be self-regulated by the patient. The demand valve is operated by the act of inhalation of the patient and closes down when the patient ceases to inhale.

In nearly all cases, ENTONOX is self-administered, but it may be administered by attendant medical personnel. Since pain is usually relieved by a concentration of 25% nitrous oxide, continued inhalation does not occur. However, should inhalation continue, light anaesthesia occurs and the

mask or mouthpiece drops away as the patient relaxes, or is removed if administration has been by attendant personnel.

4.3 Contraindications

ENTONOX should not be used in any condition where gas is entrapped within a body and where its expansion might be dangerous, such as with:

- Artificial, traumatic or spontaneous pneumothorax
- Air embolism
- Decompression sickness
- Following a recent dive
- Following air encephelography
- Severe bullous emphysema
- Use during myringoplasty
- Gross abdominal distension
- In patients having received recent intraocular injection of gas (such as SF6)

4.4 Special warnings and precautions for use

The nitrous oxide constituent of ENTONOX 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 sub-acute combined degeneration of the spinal cord.

Continuous administration for periods of more than 6 hours should be applied with caution because of the potential risk for clinical manifestations from the inhibitory effects on the methionine synthase. Prolonged continuous use or recurrent use should be accompanied by haematological monitoring to minimise risk of potential side effects. Thus intermittent ENTONOX inhalations should not be used for more than a total of 24 hours, or more frequently than every 4 days, without close clinical supervision and haematological monitoring. Specialist advice should be sought from a haematologist in such cases.

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.

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. Thorough ventilation or scavenging of waste gases should reduce operating theatre and equivalent treatment room levels of ambient nitrous oxide to a level below 100 ppm.

In patients taking other centrally acting medicinal products, such as 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 Section 4.5).

Where the patient has been exposed to agents which are toxic to the lungs, such as Paraquat, the use of gases containing more than 21% oxygen should be avoided.

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

Smoking should be prohibited when using ENTONOX.

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

Where moisturising preparations are required for use with a facemask or in nasal passages, 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 ENTONOX cylinders or equipment.

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 three 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

The nitrous oxide constituent of ENTONOX inactivates vitamin B12 and potentiates the effects of methotrexate on folate metabolism.

The use of higher levels of oxygen can increase the risk of pulmonary toxicity in patients who have been administered Bleomycin, Amiodarone and Nitrofurantoin or similar antibiotics. In these cases, ENTONOX should be administered with caution and at levels kept as low as possible.

There is a risk of additive effects when nitrous oxide (contained in ENTONOX) is used in combination with drugs having a central depressant action (e.g. opiates, benzodiazepines and other

psychotropics). If concomitant central acting agents are used the risk for pronounced sedation and depression of protecting reflexes should be acknowledged.

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.

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

4.7 Effects on ability to drive and use machines

Adverse psychometric effects will normally cease shortly after the administration of ENTONOX has stopped due to the rapid elimination of the nitrous oxide component of the medical gas mixture from the body.

When ENTONOX is used as a sole analgesic/sedative agent, driving and use of complex machinery is not recommended until:

- The healthcare professional has judged that the patient has returned to their normal mental status
- The patient feels that they are competent to drive after the relevant procedure is completed
- At least 30 minutes has elapsed after the administration of Entonox has ceased

Additional care is needed when ENTONOX is administered to a patient who has been given concomitant medication.

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

When used appropriately, there is no risk of overdose with ENTONOX.

Inappropriate, unwitting or deliberate inhalation of ENTONOX will ultimately result in unconsciousness, passing through stages of increasing light-headedness and intoxication. 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 - Medical Gas
ATC Code - N01AX13

The characteristics of oxygen are:

- Odourless, colourless gas
- Molecular weight 32.00
- Boiling point -183.1^{0}C (at 1 bar)
- Density 1.335 kg/m3 (at 15^{0}C)
-

Oxygen is present in the atmosphere at 21% and is an absolute necessity for life.

At the concentrations in ENTONOX, oxygen has no discernible pharmaceutical effect other than the beneficial effects of an oxygen enriched mixture in certain cases.

The characteristics of nitrous oxide are:
- Sweet smelling, colourless gas
- Molecular weight 44.00
- Boiling point -88.6 ^{0}C (at 1 bar)
- Density 1.875 kg/m3 (at 15^{0}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

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

Nitrous oxide is a low potency inhalation anaesthetic and high potency analgesic.

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 equally is faster than that of any other anaesthetic. This characteristic is especially valuable in analgesia for short-term pain relief.

The blood/gas partition co-efficient of nitrous oxide at 37^{0}C is 0.46 compared with that of nitrogen of 0.015 causing nitrous oxide to expand into the internal gas spaces.

5.3 Preclinical safety data

The current published toxico-pharmacological data indicates that ENTONOX is not 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 three years of age in humans.

In primates, exposure to three hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of five 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 five 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

ENTONOX strongly supports combustion and will cause substances to burn vigorously, including some materials that do not normally burn in air due to the high concentration of oxygen within the mixture.

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 oxygen in relatively high concentrations.

6.3 Shelf life

Not listed.

6.4 Special precautions for storage

ENTONOX 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
- Cylinder should preferably be stored upright in a secure area. Cylinders should have suitable restraints

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 ENTONOX cylinders

6.5 Nature and contents of container

ENTONOX 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 ENTONOX 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 Entonox 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

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 ENTONOX 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 eight hour period)

When the ENTONOX 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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9 Date of first approval.

27 Feb 1986

10 Date of revision of the text.

5 Jun 2017

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.