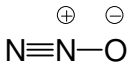
Entonox

NAME OF THE DRUG

Entonox®-Nitrous oxide 50% v/v and Oxygen 50% v/v

Chemical structure

Nitrous oxide, N_2O is a linear but unsymmetrical molecule of the form 
Oxygen has a molecular structure of O=O

DESCRIPTION

Pharmaceutical form

Compressed medical gas mixture (for medicinal use only).
Entonox is an homogenous gas mixture of oxygen and nitrous oxide in equal volumetric proportions.
Nitrous oxide is the active ingredient.

Specification

The specifications for each of the main components are presented separately.

Nitrous oxide
Complies with the requirements of the current European Pharmacopoeia monograph for Nitrous oxide.
Nitrous oxide, N_2O, CAS number 10024-97-2

Nitrous oxide	98.0% v/v minimum
Carbon dioxide	300 ppm v/v maximum
Carbon monoxide	5 ppm v/v maximum
Oxides of nitrogen (NO/NO_2)	2 ppm v/v maximum
Water (vapour)	67 ppm v/v maximum

Oxygen
Complies with the requirements of the current European Pharmacopoeia monograph for Oxygen.
Oxygen, O_2, CAS number 7782-44-7

Oxygen	99.5% v/v minimum
Carbon dioxide	300 ppm v/v maximum
Carbon monoxide	5 ppm v/v maximum
Water (vapour)	67 ppm v/v maximum

Physical data

Molecular weight	N_2O 44.01, O_2 32.00
Physical state in the cylinder	High pressure gas at ambient temperature
Combustion characteristics	Non flammable, strongly supports combustion

Nitrous oxide is a sweet smelling colourless non-irritating gas. Oxygen is a colourless, odourless and tasteless gas.
Nitrous oxide is not very soluble in water and has a low solubility in blood and tissues.

Chemical characteristics

Nitrous oxide and oxygen are oxidising substances which will support combustion of materials which may not normally burn in air. Nitrous oxide is stable and comparatively unreactive at ordinary temperatures and pressures. At elevated temperatures it decomposes to nitrogen and oxygen. Nitrous oxide will react with powerful reducing agents such as phosphine, stannous chloride and hydrogen. Rust and other impurities, especially oil and grease may cause ignitions.

PHARMACOLOGY

Nitrous oxide
Nitrous oxide is an inhalational anaesthetic. The MAC (Minimum Alveolar Concentration) in oxygen is greater than 100%.

Nitrous oxide has analgesic and weak anaesthetic properties. It has no dose related muscle relaxant effect. Onset and recovery from its effects are relatively rapid. Pain reduction may be achieved at a concentration of around 25%.

Nitrous oxide alone may increase pulse rate and have depressant effects on respiration.

Oxygen
Oxygen comprises approximately 21% of atmospheric air and acts in the maintenance of various metabolic processes in the body.

Pharmacokinetics

Nitrous oxide
Nitrous oxide is rapidly absorbed via inhalation.

The alveolar concentration of N_2O rises rapidly due to its low blood:gas partition coefficient. Likewise, its elimination is very rapid.

The blood:gas partition coefficient of nitrous oxide at 37ºC is 0.47 compared with that of nitrogen of 0.015, causing nitrous oxide to expand into internal gas spaces.

The metabolism of nitrous oxide is minimal.

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

Oxygen
Oxygen is rapidly absorbed via inhalation, distributed mostly in combination with haemoglobin, consumed and exhaled along with carbon dioxide.

INDICATIONS

Nitrous oxide with oxygen (Entonox) is indicated in adults and children for analgesia.

CONTRAINDICATIONS

Hypersensitivity to nitrous oxide or any other component in the gas is a contraindication.

Nitrous oxide should not be used with any condition where air is entrapped within a body and where its expansion might be dangerous, such as: the presence of intracranial air; artificial, traumatic or spontaneous pneumothorax; air (or gas) embolism; decompression sickness; following a recent dive; severe bullous emphysema; during myringoplasty; occluded middle ear; cysts; gross abdominal distension; maxillofacial injuries, following cardiopulmonary bypass or air encephalography and after intraocular gas injection in ophthalmic surgery, for example with sulphur hexafluoride (SF_6) or perfluoropropane (C_3F_8), until the intraocular gas had been completely absorbed.

Nitrous oxide should not be used on intoxicated or heavily sedated patients.

After inhaling nitrous oxide for 5-7 days, leucopenia and megaloblastic anaemia have been described, in some case fatal. A poyneuritic type of neuropathy and spinal cord sclerosis can appear during chronic administration of high concentrations of nitrous oxide. Where there is prolonged exposure, monitoring of peripheral blood for features of megaloblastic anaemia and leucopenia is recommended

There are no absolute contraindications to the use of oxygen but the inspired concentration should be limited in the case of premature infants and patients with chronic bronchitis and emphysema or whose respiration is dependent upon hypoxic drive.

PRECAUTIONS

General

Nitrous oxide is a simple asphyxiant in the absence of oxygen. Classified as hazardous according to the criteria of Worksafe Australia.

Addiction and abuse of nitrous oxide have been reported. Delirium has been reported upon withdrawal.

Care should be taken with long term usage of nitrous oxide. Chronic exposure to nitrous oxide, such as in abuse, can inactivate vitamin B_{12} and may result in polyneuropathy, megaloblastic anaemia, bone marrow depression and reproductive effects (see Adverse Reactions). A full blood examination should be performed in abusers, professionals chronically exposed and patients receiving ongoing therapy for evidence of megaloblastic change in red blood cells and hypersegmentation of neutrophils.

Scavenging of waste nitrous oxide gas should be used to reduce operating theatre and equivalent treatment room levels to a level below 25 ppm exposure limit of nitrous oxide (Worksafe exposure standard TLV TWA). Rescue personnel are advised to monitor nitrous oxide concentration before entering confined spaces and poorly ventilated areas which have been contaminated by a nitrous oxide leak. Chronic occupational exposure to nitrous oxide may lead to bone marrow or neurological impairment (see Use in Pregnancy).

At high altitude or in the presence of disorders affecting oxygenation, the amount of nitrous oxide required will vary. Entonox contains 50% Nitrous oxide / 50% oxygen.

Nitrous oxide passes into gas containing spaces in the body faster than nitrogen passes out. Prolonged usage may result in bowel distension and expansion of other non-vented gas containing cavities.

Nitrous oxide should be used with caution in patients with severe hypotension or those at risk of vitamin B_{12} deficiency.

Nitrous oxide has not been known to trigger malignant hyperthermia (see Adverse Reactions).

Smoking is prohibited when the product is in use and no naked flames should be allowed.

Check the following before use

Cylinders should not have been stored below 0ºC (see Storage).

Nitrous oxide is non-flammable but strongly supports combustion (including some materials which do not normally burn in air). It is highly dangerous when nitrous oxide comes into contact with oils, greases and tarry substances due to the risk of spontaneous combustion.

Dispensing equipment connection matches cylinder valve pin index outlet and demand valve is operational.

Cylinder pressure may be used as an indicator of the quantity of the gas remaining in the cylinder.

Use of gas cylinders

Cylinders should be kept out of the reach of children.

Care is needed in the handling and use of Entonox gas cylinders. Entonox is stored in high pressure gas cylinders under pressure at ambient temperature.

Entonox cylinders must be stored above 0ºC. At temperatures below this the nitrous oxide component may separate. Should this occur, the cylinder should be placed in a warm room for at least 2 hours, then rolled horizontally for at least 5 minutes to remix the components.

Additional information is contained in the Material Safety Data Sheet for Entonox from the sponsor.

Occupational exposure standard

Worksafe exposure standard TLV TWA is 25 ppm.

Carcinogenicity and mutagenicity

Nitrous oxide was tested for carcinogenic potential in rats and mice. No carcinogenic effect was seen in mice exposed to nitrous oxide (40%, 4 hours per day) or rats exposed to low concentrations of halothane-nitrous oxide (10 ppm:500 ppm, 7 hours per day).

Nitrous oxide gave mixed results in limited assays for genotoxicity. In assays for gene mutations nitrous oxide was negative in the Ames test and sex-linked recessive lethal assay in *Drosophilia melanogaster*, but was positive in Chinese hamster lung cells. The potential to cause chromosomal damage has not been investigated. An increased frequency of chromosomal aberrations was observed in bone marrow cells and spermatogonia of rats treated with a mixture of nitrous oxide and halothane. Nitrous oxide also caused an increased incidence of sister chromatid exchanges (SCE) in human lymphocytes *in vitro.*

Clinical studies have suggested that nitrous oxide may be associated with genotoxic events. DNA strand breaks were reported in surgical patients treated with isoflurane-nitrous oxide-oxygen, 1 day after surgery. An increased frequency of SCE, but not micronuclei, was found in the lymphocytes of operating room personnel exposed to nitrous oxide and isoflurane. An increase in SCE was also found in operating room personnel exposed to halothane and nitrous oxide.

Impairment of fertility

The germ cells of mice exposed to nitrous oxide for 14 weeks (50% nitrous oxide, 4 hours/day) showed no evidence of toxic effects due to nitrous oxide.

The fecundity of female dental assistants was reduced by 60% for those women working greater than or equal to 5 hours per week with unscavenged nitrous oxide. Similarly, fecundity was reduced in a Swedish study of midwives in those women assisting at more than 30 deliveries per month.

Use in pregnancy (Category A)

Inhalation anaesthetics cross the placenta. Treatment of rats with nitrous oxide (75% or 60% for each 24 hour period during organogenesis) resulted increased incidences of resorptions (days 8 and 11 of gestation), visceral abnormalities (day 8, right sided aortic arch and left-sided umbilical artery) and minor skeletal anomalies (days 8 and 9). Increased rates of resorptions, decreased fetal size and skeletal abnormalities have been reported in rats exposed to nitrous oxide concentrations of 0.1% throughout gestation. There were no adverse effects on the fetuses of mice exposed to 50% nitrous oxide during organogenesis.

There was no evidence of teratogenic effects in pregnant women exposed to single, brief anaesthetic exposure to nitrous oxide during pregnancy.

Studies of operating room personnel chronically exposed to low concentrations of inhalation anaesthetics show that pregnancies in female personnel and the wives of male personnel may be subject to increased incidences of spontaneous abortions, stillbirths and possibly birth defects. However, the methods used in obtaining and interpreting the data in these studies have been questioned. Studies on dental staff's exposure to anaesthetic gases had conflicting results. One study showed an increased risk of spontaneous abortion among dental assistants exposed to nitrous oxide. Another showed no increased risk for dental assistants either practising in private clinics or working in dental school services (OR 0.4). Others demonstrated increased risk of spontaneous abortion among dental assistants exposed to nitrous oxide for 3 or more hours weekly in places without scavenging systems. A study of Swedish midwives exposed to nitrous oxide in more than 50% of deliveries showed no increased risk of spontaneous abortion (OR 0.95). The effect of scavenging was excluded because many midwives were unsure about whether such equipment had been present in the delivery rooms. Several animal studies (in which operating room conditions were simulated) have failed to show fetotoxic or teratogenic effects following chronic exposure of male and/or female animals to low concentrations of inhalation anaesthetics prior to and /or during gestation.

Use in lactation

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when nitrous oxide is administered to a nursing woman.

Effects on the ability to drive and to use machines

Nitrous oxide is rapidly eliminated from the lungs and little data exists on the effects of Entonox on the ability to drive and use machinery.

Interactions with other drugs

Nitrous oxide and CNS depressants may lead to increased CNS depression, increased respiratory depression and increased hypotensive effects.

Nitrous oxide and opioids together may lead to further circulatory depression. High dose fentanyl with nitrous oxide may decrease heart rate and cardiac output.

Nitrous oxide potentiates the effects of methotrexate on folate metabolism, leading to stomatitis and myelosuppression.

The pharmacokinetic activity of oxygen is modified by changes in the blood carbon dioxide tension but this has little clinical significance.

Effects on Laboratory Tests

There are no known significant effects on laboratory tests, other than those associated with megaloblastic anaemia.

ADVERSE REACTIONS

Cardiovascular
Cardiovascular depression, hypotension, arrhythmia, increased pulmonary vascular resistance

Respiratory
Hypoxia, diffusion hypoxia, asphyxia, pulmonary toxicity

Neurological
Headache, dizziness, confusion, CNS excitation and depression, raised intracranial pressure, anxiolytic effects, euphoria, neuropathy, seizures, drowsiness. Exceptionally heavy occupational exposure and addiction have resulted in myeloneuropathy and subacute combined degeneration of the cord.

Gastrointestinal
Nausea, vomiting, bowel distension following prolonged usage.

Haematological
Inactivation of vitamin B_{12} (a cofactor in methionine synthesis). Folate metabolism is consequently interfered with and DNA synthesis is impaired following prolonged nitrous oxide administration. This results in symptoms similar to vitamin B_{12} deficiency and megaloblastic bone marrow changes. Bone marrow depression with resultant leukopenia, thrombocytopenia and severe megaloblastic anaemia have been noted.

Pregnancy and Lactation
See Use in Pregnancy and Use in Lactation.
Prolonged occupational exposure to high levels of nitrous oxide may affect a woman's ability to become pregnant.

Addiction and abuse of nitrous oxide have been reported.

Retrolental fibroplasia can occur in premature infants exposed to oxygen concentrations of greater than 40%.

DOSAGE AND ADMINISTRATION

Routes of administration

Entonox is self administered and inhaled via a demand valve through a face mask or mouthpiece. The gas is breathed in by the patient on demand and absorbed through the lungs.

Entonox should only be administered by medical personnel trained in the appropriate techniques and in an adequate environment.

Cylinders should only be used in conjunction with special Entonox gas pressure regulators and demand valves.

OVERDOSAGE

Symptoms and signs

Inappropriate or deliberate inhalation of nitrous oxide will ultimately result in unconsciousness, passing through stages of increasing light-headedness and intoxication, and, if the person were to be within a confined space, death from anoxia could result.

Other signs may include: bradycardia, respiratory depression, cardiovascular depression and severe hypotension.

Treatment

There is no specific antidote. Treatment measures include: discontinuation of Entonox, basic life support, assisted or controlled ventilatory support with oxygen and other symptomatic and supportive treatment.

PRESENTATION

Please consult the Material Safety Data Sheet for Entonox from the sponsor.

Pharmaceutical form

Compressed medical gas (for medicinal use only) supplied in cylinders in accordance with AS2030 and fitted with AS2472, figure 11 single pin index valve outlet.

Cylinder colour:	AS4484	Body colour - Ultramarine AS2700 B21 Shoulder colour - Ultramarine AS2700 B21 and White quadrants
Cylinder pressure:		12000 kPa (max) at 15ºC

Cylinder size (nominal water capacity, litres): B (1.5L), C (3.0L), D (10L), E (25L),G (50L)

Combinations of the above cylinders may be supplied in a unit called a pack (or bundle). Actual water capacity may vary about the nominal figures indicated.

Storage

The normal precautions required in the storage and use of medical gas cylinders are applicable. Please refer to Commonwealth, State and Territory Dangerous Goods legislation and the appropriate Australian Standards.eg AS 4332. Cylinders should be stored away from sources of ignition, poisons, flammable or combustible materials. They should preferably be stored upright, in a secure area, below 45ºC but above 0ºC, in a dry well ventilated area constructed of non-combustible material with a firm, level floor (preferably concrete) away from heavy traffic and emergency exits.

At temperatures below 0ºC the nitrous oxide component may separate. Should this occur, the cylinder should be placed in a warm room for at least 2 hours, then rolled horizontally for at least 5 minutes to remix the components.

NAME AND ADDRESS OF THE SPONSOR

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TGA Approval date: 1 November 2001
Date of this amendment: 09 April 2008[1]
AUST R 34470

[1] Date annotated at request of TGA Office 7th November, 2008