

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Medical Nitrous Oxide.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Medical Nitrous Oxide cylinders are supplied to the following specification:
Nitrous Oxide 98% (min).

The Nitrous Oxide specification complies with the current European Pharmacopeia monograph (0416).

3 PHARMACEUTICAL FORM

Medicinal gas, liquefied.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nitrous Oxide is used with oxygen, and provides a background anaesthesia which is usually supplemented with either a potent or intravenous anaesthetic. These supplements are required in approximately half of their normal anaesthetising dose because of the anaesthetic effect of the nitrous oxide.

Nitrous oxide is used as an analgesic agent, in conjunction with oxygen:

When an inhalation anaesthetic is required, the administration of nitrous oxide is usually accompanied by simultaneous administration of a volatile agent such as Halothane, Ethrane, etc in conjunction with oxygen.

In the relief of severe pain, usually in emergency situation, 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.

Occasionally as an insufflating agent in laparoscopy. In cryosurgery as a refrigerant.

4.2 Posology 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.

Nitrous oxide should only be administered by medical personnel trained in the appropriate techniques.

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.

- 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 results of these changes mean that susceptibility to anaesthesia is increased. Nitrous oxide may, therefore be particularly useful in the elderly and reduce the dose of supplementary agents.
- There are no essential differences in clinical indications between the adult and child.
- Nitrous oxide is recommended in the anaesthesia of neonates.
- 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.

Cylinders should only be used in conjunction with medical nitrous oxide gas pressure regulators.

Nitrous Oxide 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 (see sections 4.4 and 4.8).

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 an 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 dive
- following air encephalography
- severe bullous emphysema
- during myringoplasty
- gross abdominal distension
- intoxication
- maxillofacial injuries
- after intraocular gas injection in ophthalmic surgery, for example with SF₆ or C₃F₈, until the intraocular gas has been completely absorbed.

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 sub acute combined degeneration of the spinal cord.

Nitrous Oxide 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.

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 never be given with less than 21% oxygen, but a maximum of 30% oxygen should be used during anaesthesia (except when used in combination with a volatile anaesthetic agent) and more at altitude and in the presence of disorders affecting oxygenation.

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 100ppm 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 should be 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 burns 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.

4.5 Interaction with other medicinal products 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 practice, 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

Mild skeletal teratogenic changes have been observed in pregnant rat embryos when the dam has been exposed to a high concentration 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 contra-indication 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 it is recommended that 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, polyneuropathy 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: <http://www.hpra.ie>
E-mail: medsafety@hpra.ie

4.9 Overdose

When used appropriately, there is no risk of overdose with Nitrous Oxide

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.

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:	-88.6°C (at 1bar)
Density:	1.875kg/m ³ (at15°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 concentration is faster than that of any other anaesthetic agent. The elimination of nitrous oxide equally 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 the internal gas spaces.

Under normal anaesthesia, the adult body contains 25 litres of gaseous nitrous oxide (this give some notion of its essential safety a 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 is not harmful to humans.

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

1 year.

6.4 Special precautions for storage

Medical Nitrous Oxide cylinders should be:

- stored under cover, preferably inside, kept dry and clean, not subjected to the extremes of heat or cold and stored away from stocks of material.
- 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
- F size cylinders and larger should be stored vertically. E size cylinders and smaller should be stored horizontally.

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

A summary of Medical Nitrous Oxide cylinders, their size and construction, type of valve fitted and valve outlet pressure is detailed below:

Cylinder Size	Gas Content (litres)	Cylinder Water Capacity (litres)	Cylinder Construction	Outlet Connection	Valve Outlet Pressure bar (g)
AZ	450	1.2	Aluminium	Pin Index (ISO 407)	44
D	900	2.3	Steel	Pin Index (ISO 407)	44
E	1 800	5	Steel	Pin Index (ISO 407)	44
F	3 600	9.43	Steel	11/16'' X 20 TPI (M) (BS 341 (Type 8))	44
G	9 000	23.6	Steel	11/16'' X 20 TPI (M) (BS 341 (Type 8))	44
J	18 000	47.2	Steel	11/16'' X 20 TPI (M) (BS 341 (Type 8))	44

Cylinders

All cylinders used for the storage of Medical Nitrous Oxide are manufactured from high tensile steel designed with working pressure of at least 137 bar (g).

The colour coding of the shoulders of Medical Nitrous Oxide cylinders is blue (RAL 5010).

The colour coding of the cylinder body is white (RAL 9010). Cylinders also carry the nitrous oxide name on the body of the cylinder.

For a limited period, cylinders may have blue bodies. These cylinders do not have the name nitrous oxide on the body of the cylinder.

The programme to convert all Medical Nitrous Oxide cylinders to white bodies will be completed by 2025.

Cylinder Valves

Medical Nitrous Oxide cylinders are supplied with two main types of cylinder valves.

D and E size cylinders are fitted with valves with outlet connections that conform to ISO 407 (pin index) and F, G and J size cylinders are fitted with outlet connections that conform to BS 341 (Type 8) (11/16" x 20 TPI (M)).

All cylinder valves are constructed from high tensile brass with a steel spindle fitted with a Nylon 6.6 insert.

Cylinders for use with MRI scanners

The AZ Medical Nitrous Oxide cylinder shell is manufactured from aluminium and the valve from high tensile brass

and other non-magnetic components that are not attracted by high magnetic fields. The AZ Medical Nitrous Oxide cylinder label carries the statement 'Suitable for use with MRI scanners' and is the only package that is specified as suitable for use within the vicinity of MRI scanners.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

All personnel handling Medical Nitrous Oxide gas cylinders should have adequate knowledge of :

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

Preparation for Use

To prepare the cylinder for use:

- Remove the tamper evident seal and the valve outlet protection cap. Ensure the cap is retained so that it can be refitted after use.
- 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

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 medical purposes
- Turned off when not in use using only 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
- 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)

Use of Cylinders with MRI Scanners

When Nitrous Oxide cylinders are required to be used in the vicinity of MRI scanners, they should be tested with the appropriate equipment to ensure that they have no components that are attracted by high magnetic fields. It is recommended that only AZ Nitrous Oxide cylinders are used in the vicinity of MRI scanners.

After Use

When Medical Nitrous Oxide cylinders are empty ensure that:

- the cylinder valve is closed using moderate force only and the pressure in the regulator or tailpipe released.
- the valve outlet cap, where fitted, is replaced
- the empty cylinders are immediately returned to the empty cylinder store for return to BOC.

7 MARKETING AUTHORISATION HOLDER

BOC Gases Ireland Limited
J F Kennedy Drive
Bluebell
Dublin 12

8 MARKETING AUTHORISATION NUMBER

PA0208/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1980

Date of last renewal: 01 April 2010

10 DATE OF REVISION OF THE TEXT

September 2015

11 DOSIMETRY

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable