SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Medical Nitrous Oxide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitrous Oxide Ph. Eur. 100%

3 PHARMACEUTICAL FORM

Inhalation gas

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

As an inhalation anaesthetic.

As an analgesic where rapid-onset powerful short-term relief of severe pain is required.

4.2 Posology and method of administration

Use in adults, including the elderly and children

For respiratory use at concentrations of 79% or less.

Medical 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)

Instructions for Use and Handling of Medical Nitrous Oxide cylinders

Care is needed in the handling and use of medical nitrous oxide gas cylinders as 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.

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.

Preparation for use

1. Cylinder valves should be opened momentarily prior to use to blow any foreign matter out of the outlet.

2. Ensure that the connecting face on the yoke, manifold or regulator is clean and the sealing washer or 'O' ring where fitted is in good condition.
3. Cylinder valves must be opened slowly.
4. Only the appropriate regulator should be used for the particular gas concerned.
5. Pipelines for medical gases should be installed in accordance with the conditions set out in HTM 02.
6. Cylinder valves and any associated equipment must never be lubricated and must be kept free from oil and grease.

Leaks

1. Should leaks occur this will usually be evident by a hissing noise.
2. Leaks can be found by brushing the suspected area with an approved leak test solution.
3. There are no user serviceable parts associated with these valves, do not attempt to correct any problems with leakage from any part of the valve itself. Label any faulty containers, and return them to Air Liquide for repair.
4. Sealing or jointing compounds must never be used to cure a leak.
5. Never use excessive force when connecting equipment to cylinders.

Use of Cylinders

1. Cylinders should be handled with care and not knocked violently or allowed to fall.
2. Cylinders should only be moved with the appropriate size and type of trolley.
3. When in use cylinders should be firmly secured to a suitable cylinder support.
4. Cylinders containing liquefiable gas must always be used vertically with the valve uppermost.
5. Medical gases must only be used for medicinal purposes.
6. Smoking and naked lights must not be allowed within the vicinity of cylinders or pipeline outlets.
7. After use cylinder valves should be closed using moderate force only and the pressure in the regulator or tailpipe released.
8. When only a small amount of gas remains in a cylinder, the cylinder valve must be closed. It is important to leave a small residual pressure in each cylinder after use, in order to protect the inside of the cylinder from contamination.

4.3 Contraindications

Nitrous oxide should not be used with any condition where air is entrapped within the body and where its expansion might be dangerous such as:

- head injuries with impairment of consciousness
- maxillofacial injuries

- pneumothorax (artificial, traumatic or spontaneous)
- air embolism
- decompression sickness and following a recent dive
- following a recent underwater dive
- following air encephalography
- severe bullous emphysema
- during middle ear, inner ear and sinus surgery
- gross abdominal distension (e.g. intestinal obstruction)
- if air has been injected into the epidural space to determine the placement of the needle for epidural anaesthesia

Nitrous oxide should not be used in heavily sedated patients.

Nitrous Oxide should not be used in patients having received recent intraocular injection of gas (such as SF_6, C_3F_8, C_2F_6) as long as an intraocular gas bubble persists and at least for 3 months.

4.4 Special warnings and precautions for use

Nitrous oxide should never be given with less than 21% oxygen.

Nitrous oxide causes inactivation of vitamin B12 (a co-factor of methionine synthase) which interferes with folate metabolism. Thus DNA synthesis is impaired following prolonged nitrous oxide administration. Prolonged or frequent use of nitrous oxide may result in megaloblastic bone marrow changes and possibly myeloneuropathy and subacute combined degeneration of the spinal cord (see also 4.8).

Nitrous oxide should not be used as an analgesic or anaesthetic agent 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 blood 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.

At altitude, in the presence of disorders affecting oxygenation and in obstetrical anaesthesia the proportion of nitrous oxide should be less than 70% with oxygen greater than 30% for anaesthesia.

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.

Care should be exercised in the administration of nitrous oxide to patients who have had epidural anaesthesia. If air has been injected into the epidural space to determine the placement of the needle for epidural anaesthesia nitrous oxide should not be given unless the volume of air injection was limited. If any other technique was used to determine needle placement nitrous oxide may be given.

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

4.5 Interaction with other medicinal products and other forms of interaction

The use of nitrous oxide causes inactivation of vitamin B12

Administration of nitrous oxide in patients having persistence of intraocular gas bubble after they received intraocular injection of gas and/or patients having received intraocular injection of gas less than 3 months before can cause severe vision impairment caused by expansion of an intraocular gas.

4.6 Pregnancy and lactation

Mild skeletal teratogenic changes have been observed in 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 various 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.

Medical Nitrous Oxide can be used during lactation.

The current UK work place exposure limit (WEL) for nitrous oxide is 100ppm (8 hour time weighted average reference period). This occupational exposure level is sufficient to protect against any potential adverse reproductive effect of exposure to nitrous oxide in an occupational setting.

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 use.

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.

Nausea and vomiting has been reported to occur post-operatively in approximately 15% of patients.

Prolonged or frequent use of nitrous oxide, including heavy occupational exposure and addiction, may result in megalobastic 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 sub-clinical deficiency of vitamin B12, neurological toxicity has occurred after a single exposure to nitrous oxide for anaesthesia (see section 4.4) .

Nitrous oxide passes into all gas containing spaces in the body faster than nitrogen passes out. Prolonged anaesthesia may therefore result in bowel distension, middle ear damage and rupture of ear drums.

Addiction to nitrous oxide has been reported.

Severe vision impairment caused by expansion of an intraocular gas (see sections 4.3 and 4.5)

4.9 Overdose

Excessive 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

Nitrous oxide is a colourless, odourless gas with molecular weight 44.01, a boiling point of -88.6^{o}C (at 1 bar) and a density of 1.875 kg/m^{3} (at 15°C and 1013mb).

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 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 high potency analgesic. It is only slightly soluble. The advantage of this is that concentrations not greater than 70% are used and induction of anaesthesia and recovery occur quickly.

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

5.3 Preclinical safety data

There is no additional data of relevance to the prescriber.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

There are no major incompatibilities with Medical Nitrous Oxide.

6.3 Shelf life

Five years.

6.4 Special precautions for storage

Cylinders should be kept out of the reach of children.

Medical Nitrous Oxide is non-flammable but strongly supports combustion (including some materials which do not normally burn in air). It is highly dangerous when in contact with oils, greases, tarry substances and many plastics due to the risk of spontaneous combustion with high pressure gases.

Nitrous oxide will decompose at temperatures above 400^{o}C and the speed of decomposition increases with increasing temperature. Explosive decomposition can occur at 650^{o}C at atmospheric pressure.

The normal precautions required in the storage of medical gas cylinders as described below are applicable.

- Cylinders should be stored under cover, preferably inside, kept dry and clean and not subjected to extremes of heat or cold.
- Cylinders should not be stored near stocks of combustible materials or near sources of heat.
- Warning notices prohibiting smoking and naked lights must be posted clearly.
- Emergency services should be advised of the location of the cylinder store.
- Medical cylinders containing different gases should be segregated and identified within the store.

- Full and used cylinders should be stored separately. Full cylinders should be used in strict rotation.
- Cylinders must not be repainted, have any markings obscured or labels removed.
- F size cylinders and larger should be stored vertically E size cylinders and smaller should be stored horizontally.
- Precautions should be taken to protect cylinders from theft.

6.5 Nature and contents of container

Nitrous oxide is supplied in a gas cylinder, with valve, suitable for the pressure required for the product.

The types of cylinders normally used are specified in the following table.

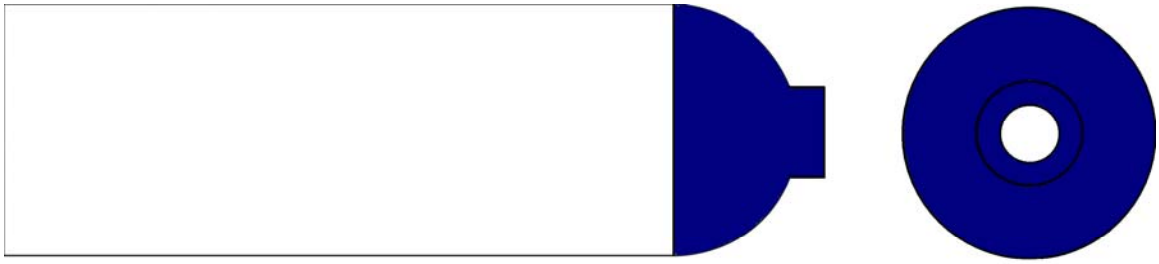
Cylinder Size	**Water Volume (litres)**	**Fill Pressure (bar)**	**Fill Volume (m3)**	**Valve Type (1)**
D	2.32	51.4	0.9	Pin-index
E	4.68	51.4	1.8	Pin-index
AE	5.0	51.4	1.8	Pin-index
F	9.43	51.4	3.6	Handwheel 11/16" x 20 tpi male
G	23.6	51.4	9.0	Handwheel 11/16" x 20 tpi male
J	50	51.4	18.0	Handwheel 11/16" x 20 tpi male

Note: (1) Cylinder valves conform to BS341 (non pin-index) and BS EN ISO 407 (pin-index)

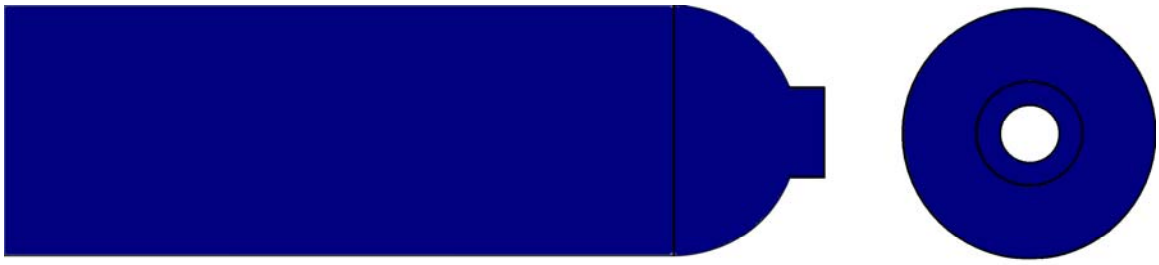
The colour of Medical Nitrous Oxide cylinders in the UK is in a period of change.

The colour coding of the shoulder of Medical Nitrous Oxide is blue. The body of the cylinder will be either blue or white.

The aim is to complete a period of change over from the blue body to the white bodied cylinder. The shoulder colour of the cylinder will remain as blue. This period of change will be completed by January 1st 2026. The images below represent the new and current colour coding of Medical Nitrous Oxide cylinders:



New white bodied Medical Nitrous Oxide cylinder colour coding



Current Medical Nitrous Oxide cylinder colour coding

6.6 Special precautions for disposal

Immediately return used cylinders to the used cylinder store for return to Air Liquide.

7 MARKETING AUTHORISATION HOLDER

Air Liquide Ltd
Station Road
Coleshill
Birmingham
West Midlands
B46 1JY

8 MARKETING AUTHORISATION NUMBER

PL 15929/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

4th February 1998 / 16th April 2003

10 DATE OF REVISION OF THE TEXT

18/03/2024