

Medical nitrous oxide.

Essential safety information.



Summary of Product Characteristics (SPC)

			Cylinders should only be used in conjunc
1 Name of the			Nitrous oxide should not be used for mo without close clinical supervision and ha
medicinal product	Medical hitrous oxide.		Nitrous oxide is usually not sufficient to therefore be used in combination with a
2. Qualitative and	Medical nitrous oxide cylinders are supplied to the following specification:		
quantitative composition	Nitrous oxide 98% (min). 4.3 Cont	4.3 Contraindications	Nitrous oxide should not be used with an expansion might be dangerous, such as:
	The nitrous oxide specification complies with the current European Pharmacopeia monograph (0416).		 head injuries with impairment of constant or spontaneous p air embolism decomprosesion cickness
3. Pharmaceutical form	Medicinal gas, liquefied.		 following a recent dive following air encephalography
4. Clinical particulars			 severe bullous emphysema during myringoplasty gross abdominal distension
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.		 intoxication maxillofacial injuries
	These supplements are required in approximately half of their normal anaesthetising dose because of the anaesthetic effect of nitrous oxide.		 after intraocular gas injection in opht has been completely absorbed
	4.4 Special v	warnings and	Repeated administration or exposure to
	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	utions for use	patients with a known history of substar to nitrous oxide.
	with oxygen		Nitrous oxide causes inactivation of vita
	 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 		Folate metabolism is consequently inter- administration of nitrous oxide.
	Occasionally as an insufflating agent in laparoscopy		Prolonged or frequent use of nitrous oxi
	In cryosurgery as a refrigerant		and sub acute combined degeneration o
4.2 Posology and method of administration	Nitrous oxide is administered through a face mask or tracheal tube by means of an anaesthetic apparatus.		Nitrous oxide should not be used for mo
	The gas is breathed in by the patient and absorbed through the lungs.		without close clinical supervision and ha
	Nitrous oxide should only be administered by medical personnel trained in the appropriate techniques.		change in red cells and hypersegmentat or macrocytosis and with B ₁₂ levels in the
	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 		In patients with undiagnosed subclinical single exposures to nitrous oxide during

and previous history of anaemia.

- 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 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

ction with medical nitrous oxide gas pressure regulators.

re than a total of 24 hours, or more frequently than every 4 days, aematological monitoring (see sections 4.4 and 4.8).

create an adequate anaesthetic effect on its own, and should ppropriate doses of another anaesthetics when used for general ive interaction with most other anaesthetics (see interactions 4.5).

ny condition where gas is entrapped within a body and where its

- sciousness
- neumothorax

thalmic surgery, for example with SF_6 or C_3F_8 , until the intraocular gas

nitrous oxide may lead to addiction. Caution should be exercised in nce abuse or in healthcare professionals with occupational exposure

min B₁₂, which is a co-factor of methionine synthase. fered with and DNA synthesis is impaired following prolonged

ide may result in megaloblastic marrow changes, myeloneuropathy of the spinal cord.

re than a total of 24 hours, or more frequently than every 4 days, aematological monitoring. Specialist advice should be sought from logical assessment should include an assessment for megaloblastic tion of neutrophils. Neurological toxicity can occur without anaemia ie normal range.

l deficiency of vitamin B₁₂, neurological toxicity has occurred after ng general anaesthesia.

Assessment of vitamin B_{12} levels should be considered in people with risk factors for vitamin B_{12} deficiency prior to using nitrous oxide anaesthesia. Risk factors include the elderly, those with poor or vegetarian diet, 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 ianition.

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.

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

administration (see section 4.4).

Addiction may occur.

is not known.

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 asked to report any suspected adverse reactions via:

HPRA Pharmacovigilance Earlsfort Terrace IRL - Dublin 2 Tel: +353 1 6764971 Fax: +353 1 6762517 Website: 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 1 bar)
- density 1.875 kg/m³ (at 15°C)

Nitrous oxide is not very soluble in water but is fifteen times more soluble then 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.

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

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).

The frequency of Addiction, Myeloneuropathy, Neuropathy and Subacute degeneration of the spinal cord

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

	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.	6.5 Nature and contents of container
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 then 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 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 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	36 months.	
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 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.	6.6 Instructions for use/handling

Care is needed when handling and using medical nitrous oxide cylinders.

container 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	1800	5	Steel	Pin Index (ISO 407)	44
F	3600	9.43	Steel	11/16" x 20 TPI (M) (BS 341 (Type 8))	44
G	9000	23.6	Steel	11/16" x 20 TPI (M) (BS 341 (Type 8))	44
J	18000	47.2	Steel	11/16" x 20 TPI (M) (BS 341 (Type 8))	44

Cylinders

All cylinders used for the supply of medical nitrous oxide are manufactured from either high tensile steel or aluminium and designed with working pressure of at least 137 bar (g).

(RAL 5010).

the nitrous oxide name on the body of the cylinder.

have the name nitrous oxide on the body of the cylinder.

will be completed by 2025.

Cylinder valves

valves.

TPI (M)).

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.

General

- properties of the gas
- correct operating procedures
- precautions and actions to be taken in the event of an emergency

6.5 Nature and contents of A summary of medical nitrous oxide cylinders, their size and construction, type of valve fitted and valve

- The colour coding of the shoulders of medical nitrous oxide cylinders is blue
- The colour coding of the cylinder body is white (RAL 9010). Cylinders also carry
- For a limited period, cylinders may have blue bodies. These cylinders do not
- The programme to convert all medical nitrous oxide cylinders to white bodies



- Medical nitrous oxide cylinders are supplied with two main types of cylinder
- 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
- These cylinder valves are constructed from high tensile brass with a steel spindle fitted with a Nylon

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

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 medicinal 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 BOC Gases Ireland Limited

holder | F Kennedy Drive Bluebell Dublin 12

8. Marketing authorisation PA 208/1/1 number(s)

9. Date of first Date of first authorisation: 01/04/1980. authorisation/renewal of

the authorisation Date of last renewal: 01/04/2010.

10. Date of revision of August 2018. the text

11. Dosimetry (if applicable) Not applicable.

12. Instructions Not applicable. for preparation of radiopharmaceuticals (if applicable)

Supply Classification Status

Product subject to prescription which may not be renewed (A) Supply through Pharmacies only.

Additional Safety Information

				No special protective equipment f	for fire fighters is required.
				Nitric oxide and nitrogen dioxide i involved in a fire.	may be produced as the products of combustion if medical nitrous oxide is
			4. Accidental release measures	If a large volume of nitrous oxideclose cylinder valvewhere possible, eliminate all s	is released, if it is safe to do so, you should: ources of ignition
				If the release continues, evacuate re-entry.	the area and ensure that the affected area is adequately ventilated before
				Self-contained breathing apparatu area without adequate ventilatior	us is required to be used if medical nitrous oxide is released into a confined n.
1. Contact information	BOC telephone number ROI 1890 355 255.	to be used in the event of an emergency:	5. Exposure controls	When using nitrous oxide cylinder	rs ensure adequate ventilation.
2. Hazards	Classification labelling	and packaging regulations		Caution: Long term exposure to m clinical use, may cause the user to	nedical nitrous oxide, if inhaled for periods longer than those indicated for o develop myeloneuropathy degeneration.
	May cause or intensify fire; oxidiser (H270). Contains gas under pressure; may explode if heated (H280). Keep/Store away from clothing, hydrocarbons and combustible materials (P220). Keep reduction valves free from grease and oil (P244). In case of fire: stop leak if safe to do so (P370 + P376). Brotect from suplicity, store in a well-ventilated place (P410 + P403)		The UK exposure limit for nitrous oxide (as defined in EH40/2005) specifies the Long Term Exposure Level (TWA over 8 hours) should not exceed 100 ppm.		
			A Short Term Exposure level is not specified.		
	Dangerous preperations directive		6. Disposal considerations	It is recommended that medical nitrous oxide cylinders should not be vented after use – they should be returned to BOC with any residual gas where they will be vented before refilling in a safe environment.	
	Keep away from combustible material (S17).	If, for safety reasons, a cylinder is required to be vented after use, the gas should be vented to atmosphere in a well ventilated area.			
	 Additional safety state Asphyxiant in high c 	ments oncentrations		Contact BOC if further guidance or	n venting cylinders is required.
	 Contact with liquid can cause frostourns No smoking or naked flames near medical nitrous oxide cylinders Use no oil or grease Keep away from extremes of heat and combustible material Store cylinders under cover in a clean, dry and well ventilated area 		7. Transport of cylinders	 When medical nitrous oxide cylinders are required to be transported, ensure that the cylinders are: located in a compartment separated from the driver adequately restrained not leaking and have their valves closed 	
	Medical nitrous oxide is subjected to extremely	supplied as a compressed gas in a high pressure cylinder. Cylinders may explode if high temperatures (if involved in a fire).		The vehicle must be adequately v and knows what to do in the ever	entilated. Ensure the driver is aware of the potential hazards of the load It of an accident or an emergency.
	Refrigerated liquefied gas. Contact with product may cause cold burns or frost bite. Medical nitrous oxide is a non-flammable gas but is a very strong oxidant. It will strongly support and intensify combustion.			It is advisable to provide the driver with written instructions that detail the actions to be taken in the event of an accident or emergency. Cylinders should be removed from the vehicle as soon as possible.	
	It may react violently w	ith combustible materials such as oils and grease.			
3. Fire fighting measures	If medical nitrous oxide	cylinders are involved in a fire:	8. IT an sport information	Material	Class 2
	If it is safe to move t	, he cylinders,		Labels	2.2, 5.1
	- close cylinder valv	e to stop flow of product		Hazard identification number	25
	- move cylinders aw	ay from source of heat		Emergency Action Code	2P
	• If it is not safe to mo	ve the cylinder,		Tunnel restriction code	E
	- cool with water fro	m a protected position		Transport category	3

All types of fire extinguishers may be used when dealing with a fire involving medical nitrous oxide.

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