Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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 without loss of consciousness.

Common examples of the use of Entonox are:

Acute Trauma
Short – term relief for procedures inevitably involving pain, such as wound and burn dressing, wound debridement and suturing, post-operative physiotherapy.

Normal labour
Acute surgical or medical conditions in which the pain is relieved, during exposure only to return on cessation of the analgesia so allowing an unfettered
assessment to be made.

4.2 Posology and method of administration

Entonox is administered through a face mask or mouthpiece. The face mask 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 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 supervenes and the
mask drops away as the patient relaxes, or is removed if administration has been by attendant personnel.

There are no contra-indications to the use of Entonox in any age group.

Where Entonox is used for more than a total of 6 hours but less than a total of 24 hours within a four day period it should be used with caution.

Entonox 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).

4.3 Contraindications

Entonox 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 SF_6 or C_3F_8, until the intraocular gas has been completely absorbed.

4.4 Special warnings and precautions for use

Repeated administration or exposure to the nitrous oxide constituent of Entonox may lead to addiction. Caution should be exercised in patients with a known history of substance abuse or in healthcare professionals with occupational exposure to nitrous oxide.
The nitrous oxide constituent of Entonox causes inactivation of vitamin B_{12}, which is a co-factor of methionine synthase. Folate metabolism is consequently interfered with and DNA synthesis is impaired following prolonged administration of Entonox. Prolonged or frequent use of Entonox may result in megaloblastic marrow changes, myeloneuropathy and sub acute combined degeneration of the spinal cord.
Entonox 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 B_{12} levels in the normal range.

In patients with undiagnosed subclinical deficiency of vitamin $B_{12,}$ neurological toxicity has occurred after single exposures to Nitrous Oxide during general anaesthesia.

Caution should be issued before using Entonox with patients who have known Chronic Obstructive Pulmonary Disease (COPD) or other conditions where compromised chemoreceptor sensitivity/function may be present. This is due to the relatively high concentration of oxygen contained in Entonox and as such may cause respiratory depression and increases in PaCO2.

Reduced fertility in healthcare personnel has been reported where they have been repeatedly exposed to 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.

In patients taking other centrally acting depressant 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 additional oxygen such as within Entonox should be avoided.

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.

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.

It is essential that cylinders are stored according to manufacturer's instruction, in order to avoid the separation of nitrous oxide from oxygen, which occurs at low temperatures, with consequent hypoxic mixture in the lower part of the cylinder.

4.5 Interaction with other medicinal products and other forms of interactions

The nitrous oxide constituent of Entonox inactivates vitamin B
12 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
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 Entonox during the breast-feeding period.

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 while its influence on the subjective cognitive capabilities may persist for several hours.
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.

Tabulated summary of adverse reactions

System organ class	**Very common (≥1/10)**	**Common (≥1/100to <1/10)**	**Uncommon (≥1/1000 to 1/100)**	**Rare (≥1/10 000 to 1/1000)**	**Veryrare (<1/10000)**	**Not known (cannot be estimated fromthe available data)**
Blood and lymphatic system disorders	-	-	-	-	-	Megaloblastic anaemia
Psychiatric disorders	-	Euphoria	-	-	-	Confusion, Addiction
Nervous system disorders	-	Dizziness, light-headedness,	Somnolence	-		Myelopathy, neuropathy, subacute degeneration of the spinal cord Generalised seizures
Ear and labyrinth disorders	-	-	Feeling of pressure in the middle ear	-	-	
Gastrointestinal disorders	-	Nausea, vomiting	Bloating, increased gas volume in the intestines	-	-	
General disorders and administration site conditions	-	Sense of intoxication	-	-	-	
Respiratory, thoracic and mediastinal disorders						Respiratory depression

Reportingof suspectedadversereactions

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 Centre 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 Entonox.

Inappropriate, unwitting or deliberate inhalation of Entonox will ultimately result in unconsciousness, passing through stages of increasing lightheadedness and intoxication. The treatment is removal to fresh air, mouth-tomouth resuscitation and, if necessary, the use of an oxygen resuscitator.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group – Medical Gas
ATC Code: NO1AX63

Oxygen

The characteristics of oxygen are:
- Odourless, colourless gas.

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 then the beneficial effects of an oxygen enriched mixture in certain gases.

Nitrous Oxide

The characteristics of nitrous oxide are: -
- sweet smelling colourless gas

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

Water dissolves nitrous oxide, taking 100% and blood plasma 45%.

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 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 characteristic is especially valuable in analgesia for short term pain.

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.

5.3 Preclinical safety data

The current published toxic-pharmacological data indicates that Entonox is not harmful to humans.

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

36 Months

6.4 Special precautions for storage

Entonox cylinders should be:
- stored under cover, preferably inside, kept dry and clean, and not subjected to extremes of heat or cold and away from stocks of combustible 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. D size cylinders and smaller may be stored horizontally.

To ensure that the gas is suitable for immediate use, Entonox cylinders should be maintained at a temperature above 10˚C for at least 24 hours before use.

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 cylinders from theft.
Care is needed when handling and using Entonox cylinders

6.5 Nature and contents of container

A summary of Entonox 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	Valve Type Filling Port Outlet Connections	Nominal Valve Outlet Pressure

				Outlet Flowrates		Bar(g)
D	500	2.32	Steel	Valve Type	Non Regulated	137
				Outlet	Pin Index (ISO 407)	
ED	700	2.0	Aluminium (Carbon Fibre hoop wrapped)	Valve Type	Integral Regulated	4
				Filling Port	ISO 5145 (Entonox)	
				Outlet	BS5682 Schrader	
				Flowrate	40 litres / min (max)	
F	2000	9.43	Stell	Valve Type	Non Regulated	137
				Outlet	Pin Index (ISO 407)	
EX	3500	10.0	Steel	Valve Type	Integral Regulated	4
				Filling Port	ISO 5145 (Entonox)	
				Outlet	BS5682 Schrader	
				Flowrate	40 litres / min (max)	
G	5000	23.6	Steel	Valve Type	Non Regulated	137
				Outlet	Pin Index (ISO 407)	
EW	16275	46.6	Steel	Valve Type	Non	217

					Regulated	
				Outlet	ISO 1545 (Entonox)	

Cylinders
All cylinders used for the supply of Entonox are manufactured from either high tensile steel or aluminium. The D, F and G size cylinders are designed with working pressure of at least 137 bar (g).

The ED, EX and EW size cylinders are designed with a maximum working pressure of 230 bar (g).

The colour coding of the shoulders of Entonox cylinders is quartered blue (RAL 5010) and white (RAL 9010).
The colour coding of the cylinder body is white (RAL 9010). Cylinders also carry the ENTONOX name on the body of the cylinder.
For a limited period, cylinders may have blue bodies. These cylinders do not have the name ENTONOX on the body of the cylinder.
The programme to convert all Entonox cylinders to white bodies will be completed by 2025.

Cylinder Valves
Entonox cylinders are supplied with two main types of cylinder valves, dependant upon the cylinder filling pressure and the type of application.
Pin index cylinder valves are fitted to D, F and G cylinders, which are designed to be used with a pressure regulator.

These cylinders valves have outlet connections that conform to ISO 407 (pin index) and are filled to 137 bar (g). Pin index cylinder valves are constructed from high tensile brass with a steel spindle fitted with a Nylon 6.6 insert.

ED and EX cylinders are fitted with valves that have an integral pressure regulator, with an outlet pressure of 4 bar (g). These regulated valves are fitted with an ISO 5145 product specific filling connection and a product specific BS 5682 Schrader outlet. Integral cylinder valves are constructed from high tensile brass with a steel spindle fitted with a Nylon 6.6 insert.

The side outlet hand wheel valve fitted to EW cylinders has an ISO 5145 product specific valve outlet. The valve design incorporates a residual pressure device to prevent the cylinder from being fully emptied and prevent the cylinder from being contaminated should the valve be left open. The valve is constructed from brass and is fitted with a brass spindle with a Nylon 6.6 insert. The residual pressure device is fitted with EDPM O-ring seals.

The internal valve components in the integral regulator are made from Oxygen compatible materials, designed to not produce poisonous fumes if the cylinder is subjected to high temperatures, causing ignition of any of the valve components and compliant with the requirements of ISO 15001.

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

General
All personnel handling Entonox 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
Ensure Entonox cylinders are maintained at a temperature above 10^{o}C for at least 24 hours before use to ensure the gases are mixed correctly.
If this is not possible, D and ED size cylinders may be used immediately if inverted three
times before use to ensure mixing.

Cylinders used with a Pressure Regulator (Sizes D, F and G)

To prepare the cylinder for use

- remove the tamper evident seal and the valve outlet protection.
- for cylinders which have a replaceable cap, retain the cap for refitting after use
- do not remove and discard any batch labels fitted to the cylinder
- ensure that an appropriate Entonox regulator or manifold tailpipe is selected for connection to the cylinder
- ensure the connecting face on the regulator or tailpipe is clean and the sealing washer fitted is in good condition
- connect the regulator or tailpipe, using moderate force only and where appropriate connect the tubing to the regulator / flowmeter outlet.
- open the cylinder valve slowly and check for any leaks.

Cylinders with an integral regulated valve (Sizes ED and EX)

To prepare the cylinder for use:

• check the cylinder contents gauge on the cylinder valve to ensure that there is sufficient gas contents in the cylinder

• remove the tamper evident seal and cover fitted over the valve outlets

• ensure that the correct equipment is selected for connection to the cylinder. The tubing should be designed for use with Entonox and the Schrader probe should be specific to Entonox use

• connect the Entonox Schrader probe to the Schrader outlet

• open the cylinder valve slowly and check for any leaks.

Leaks

Cylinders used with a pressure regulator (Sizes D, F and G)

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.

Cylinders with an integral regulated valve (Sizes ED and EX)

Check the connection for leaks using the following procedure:

• should leaks occur this will usually be evident by a hissing noise

• close valve, remove connection, check and refit

• 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 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

• 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 in a well ventilated area to maintain the average occupational exposure level of the healthcare professional to less than 100ppm (over an 8 hour period).

After use

When Entonox cylinders are empty ensure that the:

• cylinder valve is closed using moderate force only and the pressure in the regulator or tailpipe is vented

• valve outlet cap, where fitted, is replaced

• empty cylinders are immediately returned to the empty cylinder store for return to BOC.

7 MARKETING AUTHORISATION HOLDER

BOC Gases Ireland Ltd
Bluebell
Dublin
12
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0208/005/001

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

May 2022

11 DOSIMETRY

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable