

ENTONOX[®]

Essential safety information.



Summary of Product Characteristics (SPC)

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.

Common examples of the use of ENTONOX are:

- acute trauma
- short-term relief in dental work
- short-term relief for procedures inevitably involving pain, such as wound and burn dressing, wound debridement and suturing
- normal labour
- acute surgical or medical conditions in which the pain is relieved, 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 facemask 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 demand 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 occurs and the mask or mouthpiece drops away as the patient relaxes, or is removed if administration has been by attendant personnel.

There are no contraindications to the use of ENTONOX in any age group.

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 in any condition where gas is entrapped within a body and where its expansion might be dangerous, such as with:

- artificial, traumatic or spontaneous pneumothorax
- air embolism
- decompression sickness
- following a recent dive
- following air encephelography
- severe bullous emphysema
- use during myringoplasty
- gross abdominal distension
- in patients having received recent intraocular injection of gas (such as SF₆).

4.4 Special warnings and precautions for use The nitrous oxide constituent of ENTONOX 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 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 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.

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 gases containing more than 21% oxygen 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 100ppm.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The nitrous oxide constituent of ENTONOX inactivates vitamin B₁₂ 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 Pregnancy and lactation

Pregnancy

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 8 epidemiological studies and case reports in human beings.

There is no published material that 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.

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.

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 light-headedness and intoxication. 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 – medical gas
ATC code – N01AX63

The characteristics of oxygen are:

- odourless, colourless gas
- molecular weight: 32.00
- boiling point: -183.1°C (at 1bar[g])
- density: 1.335kg/m³ (at 15°C)

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 than the beneficial effects of an oxygen enriched mixture in certain cases.

The characteristics of nitrous oxide are:

- sweet smelling, colourless gas
- molecular weight: 44.00
- boiling point: -88.6°C (at 1bar[g])
- density: 1.875kg/m³ (at 15°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 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 concentrations is faster than that of any other anaesthetic agent. The elimination of nitrous oxide equally is faster than that of any other anaesthetic. This characteristic is especially valuable in analgesia for short-term pain relief.

The blood/gas partition co-efficient 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
- not stored near stocks of combustible materials
- not subjected to extremes of heat or cold
- 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 | Outlet flowrates | Nominal valve outlet pressure bar(g) |
|---------------|----------------------|----------------------------------|--|------------|--------------------|---------------------|------------------|--------------------------------------|
| EA | 350 | 1.0 | Aluminium (Carbon fibre full wrapped) | Valve type | Integral regulated | ISO 5145 (ENTONOX) | BS5682 Schrader | 4 |
| D | 500 | 2.32 | Steel | Valve type | Non regulated | Pin Index (ISO 407) | | 137 |
| ED | 700 | 2.0 | Aluminium (Carbon fibre hoop wrapped) | Valve type | Integral regulated | ISO 5145 (ENTONOX) | BS5682 Schrader | 4 |
| F | 2000 | 9.43 | Steel | Valve type | Non regulated | Pin Index (ISO 407) | | 137 |
| EX | 3500 | 10.0 | Steel | Valve type | Integral regulated | ISO 5145 (ENTONOX) | BS5682 Schrader | 4 |
| G | 5000 | 23.6 | Steel | Valve type | Non regulated | Pin Index (ISO 407) | | 137 |

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 137bar(g).

The ED and EX size cylinders are designed with a maximum working pressure of 230bar(g). The EA size cylinder is designed with a maximum working pressure of 300 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.

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 137bar(g). Pin index cylinder valves are constructed from high tensile brass with a steel spindle fitted with a Nylon 6.6 insert.

EA, ED and EX cylinders are fitted with valves that have an integral pressure regulator, with an outlet pressure of 4bar(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 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.

6.6 Special precautions for disposal and other handling

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°C for at least 24 hours before use to ensure the gases are mixed correctly.

If this is not possible, EA, 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. Do not remove and discard any batch labels fitted to the cylinder
- ensure that an appropriate ENTONOX 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
- open the cylinder valve slowly and check for any leaks.

Cylinders with an integral regulated valve

Sizes EA, 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 EA, 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 ENTONOX 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 the ENTONOX cylinder is 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 is replaced (where fitted)
- empty cylinders are immediately returned to the empty cylinder store for return to BOC.

| | |
|--|--|
| 7. Marketing authorisation holder | BOC Ltd The Priestley Centre 10 Priestley Road The Surrey Research Park GUILDFORD Surrey, GU2 7XY |
| 8. Marketing authorisation number(s) | PL 00735/5017R. |
| 9. Date of first authorisation/renewal of the authorisation | 23 January 1991. |
| 10. Date of revision of the text | 8 November 2013 |
| 11. Dosimetry (if applicable) | Not applicable. |
| 12. Instructions for preparation of radiopharmaceuticals (if applicable) | Not applicable. |

Additional Safety Information

1. Contact information BOC telephone number to be used in the event of an emergency
UK 0800 111 333

2. Hazards Classification labelling and packaging regulations



Danger.

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).

Protect from sunlight: store in a well-ventilated place (P410 + P403).

Dangerous Preparations Directive



Contact with combustible material may cause fire (R8).

Keep out of the reach of children (S2).

Keep away from combustible material (S17).

Label statements

- Contact with combustible material may cause fire.
- No smoking or naked flames near ENTONOX 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.

ENTONOX is supplied as a compressed gas in a high pressure cylinder.

Cylinders may explode if subjected to extremely high temperatures (if involved in a fire).

ENTONOX is a non-flammable gas but is a very strong oxidant. It will strongly support and intensify combustion.

It may react violently with combustible materials such as oils and grease.

3. Fire fighting measures If ENTONOX cylinders are involved in a fire:

- if it is safe to move the cylinders,
 - close cylinder valve to stop the flow of product
 - move cylinders away from source of heat
- if it is not safe to move the cylinders,
 - cool with water from a protected position.

All types of fire extinguishers may be used when dealing with a fire involving ENTONOX cylinders.

No special protective equipment for fire fighters is required. Nitric oxide and nitrogen dioxide may be produced as the products of combustion if ENTONOX is involved in a fire.

4. Accidental release measures

If a large volume of ENTONOX is released, if safe to do so, you should:

- close the cylinder valve
- where possible, isolate all sources of ignition
- if release continues, evacuate the area and ensure that the affected area is adequately ventilated before re-entry.

Self-contained breathing apparatus is not required to be used if ENTONOX is released in a confined area.

5. Exposure controls

When using ENTONOX cylinders ensure adequate ventilation. **Caution:** Long term exposure to ENTONOX, if inhaled for periods longer than those indicated for clinical use, may cause the user to develop myeloneuropathy degeneration (due to the nitrous oxide component of the gas).

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 100ppm.

A Short Term Exposure Level is not specified.

6. Disposal considerations

It is recommended that ENTONOX 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.

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.

Contact BOC if further guidance on venting cylinders is required.

7. Transport of cylinders

When ENTONOX 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.

The vehicle must be adequately ventilated. Ensure the driver is aware of the potential hazards of the load and knows what to do in the event of an accident or an emergency.

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.

8. Transport information

| | |
|------------------------------|---|
| UN number | UN3156 compressed gas oxidising, N.O.S. (oxygen, nitrous oxide) |
| Material | Class 2 |
| Labels | 2.2, 5.1 |
| Hazard identification number | 25 |
| Emergency Action Code | 2s |
| Tunnel Restriction Code | E |
| Transport category | 3 |

BOC Healthcare

Customer Service Centre, Priestley Road, Worsley, Manchester M28 2UT

Tel 0800 111 333, Fax 0800 111 555, bohealthcare-uk@boc.com, www.bohealthcare.co.uk

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