SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nitronox Inhalation Gas

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxygen	50% v/v
Nitrous oxide	50% v/v

3. PHARMACEUTICAL FORM

Inhalation gas

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Nitronox is used exclusively for the relief of pain.

Common examples of the use of Nitronox 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.

Nitronox is indicated in adults and children of all ages.

4.2 Posology and method of administration

Nitronox is for inhalation use.

Posology

In nearly all cases, Nitronox is self-administered, but it may be administered by attendant medical personnel.

Doses may be self-regulated by the use of a face mask or mouthpiece connected through a demand valve to the Nitronox cylinder. 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.

Nitronox 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).

Paediatric population

As for adults

Method of administration

Nitronox is administered through a face mask or mouthpiece. The face mask or mouthpiece is connected to a Nitronox supply through a demand valve system which allows the Nitronox 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.

Nitronox may be administered by personnel trained in its use (obstetric units, accident units and accident ambulances).

For instructions on use, see section 6.6.

4.3 Contraindications

Hypersensitivity to nitrous oxide.

Nitronox should not be used in any condition where air is entrapped within the 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 encephalography
- severe bullous emphysema
- use during myringoplasty
- gross abdominal distension
- patients that have received recent intraocular injection of gas (such as SF6)

4.4 Special warnings and precautions for use

Repeated administration or exposure to nitrous oxide 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.

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. Nitronox 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 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 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 Nitronox may result in increased sedation, and consequently have effects on respiration, circulation and protective reflexes. If Nitronox 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 100 ppm.

Nitronox is non-flammable but strongly supports combustion (including some materials which do not normally burn in the air) and should not be used near sources of ignition. Smoking should be prohibited when using Nitronox.

Nitronox is highly dangerous when in contact with oils, greases, tarry substances and many plastics.

Under no circumstances should oils or grease be used to lubricate any part of the Nitronox 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.

Use soap and water to wash the hands before handling Nitronox cylinders or equipment to control cross-contamination. If alcohol gels are used on the hands ensure that all alcohol has evaporated before handling Nitronox cylinders or equipment.

Where isopropyl alcohol (IPA) wipes are used ensure that all alcohol has fully evaporated before further handling of the cylinder or associated equipment.

Care is needed in the handling and use of Nitronox gas cylinders (see section 6.6).

4.5 Interaction with other medicinal products and other forms of interaction

The nitrous oxide constituent of Nitronox inactivates vitamin B12 (see section 4.4) 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, or nitrofurantoin or similar antibiotics. In these cases Nitronox 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 Nitronox) is used in combination with drugs having a central depressant action (e.g. opiates, benzodiazepines and other psychotropics). If concomitant centrally-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 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 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.

Breast-feeding

There are no known adverse effects in relation to breast-feeding. Nitronox can be used during the breast-feeding period, but should not be used during breast-feeding itself.

Fertility

It has been suggested that prolonged occupational exposure to high levels of nitrous oxide may affect a woman's ability to become pregnant (see section 4.4).

4.7 Effects on ability to drive and use machines

Adverse psychometric effects will normally cease shortly after the administration of Nitronox has stopped due to the rapid elimination of the nitrous oxide component of the medical gas mixture from the body.

When Nitronox 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 Nitronox has ceased.

Additional care is needed when Nitronox is administered to a patient who has been given concomitant medication.

4.8 Undesirable effects

Summary of the safety profile

Events such as euphoria, disorientation, sedation, nausea, vomiting, dizziness and general tingling are commonly described. These events are generally minor and rapidly reversible.

Addiction may occur.

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.

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).

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 list of adverse reactions

Adverse reaction frequencies are defined using the following convention:
Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Event
Blood and lymphatic system disorders	Not known	Megaloblastic anaemia, agranulocytosis
Psychiatric disorders	Common	Euphoria, sedation, disorientation
	Not known	Addiction, confusion
Nervous system disorders	Common	Dizziness, tingling, light-headedness
	Uncommon	Somnolence
	Not known	Generalised seizures, myeloneuropathy, neuropathy, subacute degeneration of the spinal cord
Ear and labyrinth disorders	Uncommon	Feeling of pressure in the middle ear
	Not known	Middle ear damage, perforated ear drums
Gastrointestinal disorders	Common	Nausea, vomiting
	Uncommon	Bloating, increased gas volume in the intestines
	Not known	Abdominal distension
General disorders and administration site conditions	Common	Sense of intoxication
Respiratory, thoracic and mediastinal disorders	Not known	Respiratory depression

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 the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

When used appropriately, there is no risk of overdose with Nitronox.

Inappropriate, unwitting or deliberate inhalation of Nitronox will ultimately result in unconsciousness, passing through stages of increasing light- headedness and intoxication.

Treatment should be: 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: Other general anaesthetics. ATC code: N01AX63

Oxygen

Oxygen is present in the atmosphere at 21% and is an absolute necessity for life.

At the concentrations of Nitronox, oxygen has no discernible pharmaceutical effect other than the beneficial effects of an oxygen enriched mixture in certain cases.

Nitrous oxide

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.

The characteristics of oxygen are:

- colourless, odourless gas
- molecular weight 32.00
- boiling point -183.1°C (at 1 bar) density 1.355 kg/m^3 (at 15°C)

Nitrous oxide is a low potency inhalation anaesthetic and high potency analgesic. The characteristics of nitrous oxide are:

- sweet smelling, colourless gas
- molecular weight 44.00
- 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 than oxygen. Water dissolves nitrous oxide, taking 100%, and blood plasma 45 vol%.

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.

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

5.3. Preclinical safety data

All relevant information for the prescriber is provided elsewhere in the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Storage of cylinders

1. Cylinders should be stored under cover, preferably inside, kept dry and clean and not subjected to extremes of heat or cold.
2. Cylinder should not be stored near stocks of combustible materials or near sources of heat.
3. Warning notices prohibiting smoking or naked lights should be posted clearly.
4. Emergency services should be advised of the location of the cylinder store.
5. Medical cylinders containing different gases should be segregated within the store.
6. Full and empty cylinders should be stored separately. Full cylinders should be used in strict rotation.
7. Medical cylinders should be stored separately from industrial and other non-medical cylinders.
8. Cylinders must not be repainted, have any markings obscured or labels removed.
9. Precautions should be taken to protect cylinders from theft.

6.5 Nature and contents of container

Nitronox Inhalation Gas is a compressed gas mixture that is held within a pressure vessel made of a limited list of materials. These can include steel, aluminium, aluminium liners with carbon wrap on either sides of the cylinder or all over. The cylinders conform to the requirements set out in the current Carriage of Dangerous Goods and Transportable Pressure Equipment Regulations. All cylinders used for Nitronox Inhalation Gas are designed and tested to conform to these regulations.

Nitronox Inhalation Gas cylinders are fitted with a valve; the valve can be pin- index conforming to BS EN ISO 407 or an integral pressure regulator valve that is CE marked for Medical Device Regulations.

The cylinders have a variety of nominal water capacities ranging from 1 to 50 litres and are filled to 137 or 200 bar.

This gives the following range of nominal Nitronox content in litres of the cylinders at 15°C and 1013.2 mbar:

428, 536, 1071, 2020, 2140, 4280, 5056, 6420, 10100.

Not all pack sizes may be marketed.

The colour scheme for Nitronox cylinders is changing from a blue body with a blue and white quartered shoulder (top) to a white body with a blue and white quartered shoulder (top).

Your cylinder may be of either colour scheme.

6.6 Special precautions for disposal and other handling

Instructions for use

Use in accordance with the doctor's instructions.

It has been suggested that prolonged occupational exposure to high levels of nitrous oxide may affect a woman’s ability to become pregnant (see section 4.6)

Avoid rapid opening of the valve as this could lead to re-liquefaction of the discharged gas. In its liquid form the substance in contact with the skin can cause cold burns.

Nitronox supports combustion more vigorously than does air.

There is danger of spontaneous combustion when organic substances come into contact with the high pressure gas. This applies to substances such as grease, oil and some plastics.

If storage has taken place below 0°C then the contents of the cylinder must be re-mixed, using one of the following methods:

- store the cylinder horizontally for 24 hours at above 10°C; or
- mix the contents by fully inverting the cylinder three times, after warming it at above 10°C for at least two hours.

Preparation for use

1. Cylinder valves must be opened slowly.
2. Cylinder valves should be opened momentarily prior to use to blow any grit or foreign matter out of the outlet.
3. Ensure that the connecting face of the pin index yoke, or regulator is clean and the sealing washer or ‘O’ ring where fitted is in good condition.

4. Where an integral valve is not used only the appropriate regulator should be used for the particular gas concerned.
5. Pipelines for medical gases should be controlled 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 would usually be evident by a hissing noise.
2. Leaks can be found by brushing the suspected area with an approved leak detection solution
3. Sealing or joining compounds must never be used to cure a leak.
4. 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. Medical gases must only be used for medicinal purposes.
5. Smoking and naked lights must not be allowed within the vicinity of cylinders or pipeline outlets.
6. After use, cylinder valves should be closed using moderate force only and the pressure in the regulator or tailpipe released.
7. When empty, the cylinder valve must be closed.
8. Immediately return empty cylinders to the empty cylinder store for return to Medical Gas Solutions Ltd.

Contact Medical Gas Solutions to refill the cylinder. Any cylinders that are no longer required should be returned to Medical Gas Solutions.

7 MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 17872/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15th September 2005/ 1st July 2011

10 DATE OF REVISION OF THE TEXT

06/01/2022