a) Brand or Product Name
Leeden Nitrous Oxide/ Oxygen Mixture (50:50% v/v)

b) Name and Strength of Active Substance(s)
Nitrous Oxide 50% v/v and Oxygen 50% v/v, medicinal gas mixture, compressed.
There are no excipients.

c) Product Description
A pressurized and uniform gas mixture containing equal volumes of oxygen and nitrous oxide.

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

There are no excipients.

Properties: colourless, slightly sweet smelling, and non-irritating gas.
The finished product is filled into aluminium or steel cylinders fitted with pin index or bullnose valve.
The cylinder colour is blue on the body with blue and white quadrant stripes on its shoulder.

d) Pharmacodynamics
Pharmacotherapeutic Group – Medical Gas
ATC code – N01AX63

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 Oxygen + Nitrous Oxide mixture, oxygen has no discernible pharmaceutical effect other than 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 than 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.

e) Pharmacokinetics
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 than 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 deg. C is 0.46 compared with that of nitrogen of 0.015, causing nitrous oxide to expand into the internal gas spaces.

f) Indication
Oxygen + Nitrous Oxide mixture is used exclusively for the relief of pain without loss of consciousness.
Common examples of the use of Oxygen + Nitrous Oxide are:
• Acute trauma
• Short – term relief for procedures inevitably involving pain, such as wound and burn dressing, would debridement and suturing

• 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

g) Recommended Dosage

Nitrous Oxide/ Oxygen Mixture (50:50% v/v) should only be administered by competent personnel with access to adequate resuscitation equipment. Special precautions should be taken when working with nitrous oxide mixture. Nitrous oxide should be administered according to local guidelines.

Posology

Administration of Nitrous Oxide/ Oxygen Mixture (50:50% v/v) should commence shortly before the desired analgesic effect is required. The analgesic effect is seen after 4-5 breaths and reaches its maximum within 2- 3 minutes. Administration of Nitrous Oxide/ Oxygen Mixture (50:50% v/v) should continue throughout the painful procedure, or for as long as the analgesic effect is desired. Following discontinuation of the administration/inhalation, the effects wear off quickly within a few minutes.

Paediatric population

There is no difference in dose recommendations in the paediatric population

h) Route of Administration

Nitrous Oxide/Oxygen Mixture (50:50% v/v) is administered via inhalation.

i) Contraindications

Oxygen + Nitrous Oxide 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 SF6 or C3F8, until the intraocular gas has been completely absorbed

j) Warnings and Precautions

- Repeated administration or exposure to the nitrous oxide constituent of Oxygen and Nitrous Oxide mixture 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 Oxygen and Nitrous Oxide mixture causes inactivation of vitamin B12, which is a cofactor of methionine synthase. Folate metabolism is consequently interfered with and DNA synthesis is impaired following prolonged administration of Oxygen and Nitrous Oxide mixture. Prolonged or frequent use of Oxygen and Nitrous Oxide mixture may result in megaloblastic marrow changes, myeloneuropathy and sub-acute combined degeneration of the spinal cord.

- Oxygen and Nitrous Oxide mixture 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 hyper segmentation 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 Oxygen +Nitrous Oxide mixture may result in increased sedation, and consequently have effects on respiration, circulation, and protective reflexes. If Oxygen + Nitrous Oxide mixture is to be used in such patients, this should take place under the supervision of appropriately trained personnel.

- 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 Oxygen + Nitrous Oxide mixture 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.

- Oxygen + Nitrous Oxide mixture is non-flammable but strongly supports combustion and should not be used near sources of ignition.

- Smoking should be prohibited when using Oxygen + Nitrous Oxide mixture.

- Under no circumstances should oils or grease be used to lubricate any part of the 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 this product or equipment.

k) Interactions with Other Medicaments

The nitrous oxide constituent of Oxygen and Nitrous Oxide mixture inactivates vitamin B12and potentiates the effects of methotrexate on folate metabolism.

The use of higher levels of oxygen can increase the risk of pulmonary toxicity inpatients who have been administered Bleomycin, Amiodarone and Nitrofurantoin or similar antibiotics. In these cases, Oxygen + Nitrous Oxide mixture 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 Oxygen + Nitrous Oxide mixture) 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.

l) 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
Oxygen and Nitrous Oxide mixture during the breast-feeding period.

m) Side 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.

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.

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.

Due to the impact of nitrous oxide on vitamin B12 metabolism, megaloblastic anaemia and leucopoenia have been reported in cases of prolonged or frequently repeated administration of Nitrous Oxide/Oxygen Mixture (50:50% v/v). In instances of exceptionally high or frequent exposure, neurological complications such as myelopathy or polyneuropathy have also been observed.

n) Symptoms and Treatment of Overdose

Since administration of Nitrous Oxide/Oxygen Mixture (50:50% v/v) requires active patient participation, the risk of overdose is minimal under normal use. However, if during administration the patient exhibits decreased alertness, fails to respond to commands, or shows any other signs of pronounced sedation, Nitrous Oxide/Oxygen Mixture (50:50% v/v) administration must be stopped immediately. The patient should not receive further Nitrous Oxide/Oxygen Mixture (50:50% v/v) until full consciousness has been regained.

If cyanosis occurs at any point during use, treatment should be discontinued immediately. Should cyanosis not resolve quickly, supplemental oxygen must be administered, and ventilatory support should be provided if there are signs of respiratory depression.

Reversible neurological toxicity and megaloblastic changes in bone marrow have been reported in cases of exceptionally prolonged inhalation of nitrous oxide.

An overdose may also occur if the gas cylinders are stored improperly, particularly at temperatures below -5°C. At such low temperatures, separation of the component gases can occur, increasing the risk of inhalation of a hypoxic gas mixture.

Paediatric Population
The risk of overdose in children is considered to be equivalent to that in adults, assuming proper administration and monitoring protocols are followed.

o) Effects on Ability to Drive and Use Machine

Adverse psychometric effects will normally cease shortly after the administration of Oxygen and Nitrous Oxide mixture 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 Oxygen and Nitrous Oxide mixture 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 Oxygen and Nitrous Oxide mixture has ceased. Additional care is needed when Oxygen and Nitrous Oxide mixture is administered to a patient who has been given concomitant medication.

p) Instruction for Use

General:
All personnel handling Oxygen and Nitrous Oxide mixture 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:
To prepare the cylinder for use:

- Remove the tamper evident seal and the valve outlet protection. Ensure the cap is retained so that it can be refitted after use
- Do not remove and discard any batch labels fitted to the cylinder
- Ensure that an appropriate Oxygen + Nitrous Oxide mixture regulator or manifold tailpipes are 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

Leak check:
Having connected the regulator or manifold yoke/connector 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/connector, 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 LGSB

Use of cylinders:
When Oxygen and Nitrous Oxide mixture 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 Oxygen and Nitrous Oxide mixture 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 LGSB

q) Storage Conditions
Nitrous Oxide/Oxygen Mixture (50:50% v/v) cylinders should be:

- Prohibiting smoking and naked flame in the storage area.

- Cylinders should be stored indoor, kept dry and clean.
- Kept away from any flammable materials.
- Store in a well-ventilated place.
- Store in upright position and secure it.
- Full and used cylinders should be stored separately. Full cylinders should be used in strict rotation.
- Cylinders containing different gases should be segregated and identified within the store.
- Cylinders must not be repainted, have any markings obscured or labels removed.
- Store at temperature below 50°C.

r) Dosage forms and packaging available

Dosage: Medicinal gases, compressed.
Packaging:

Cylinder Material	Cylinder Size (L)	Valve	Pressure (bar)	Content (m^3)
Carbon Steel or Aluminium	5	Bullnose (BS 341) or Pin Index (ISO 407 or CGA910)	130	2
	10		130	2
	47		130	4.4

s) Name and address of manufacturer/ product registration holder
Leeden Gases Sdn. Bhd.
Lot PT 5074 & 5075, Jalan Jangur 28/43, Seksyen 28,
40400 Shah Alam, Selangor Darul Ehsan, Malaysia

t) Product Registration Number
MALxxxxxxx

u) Date of revision of PI
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