Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Donopa, 50 %/50 % v/v, medicinal gas, compressed

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each cylinder contains:
Nitrous oxide (N_2O) 50% v/v
and
Oxygen (O_2, medicinal oxygen) 50 % v/v
at a pressure of either 135 or 185 bar (15C)

3 PHARMACEUTICAL FORM

Medicinal gas, compressed
Colourless, odourless gas

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Donopa is indicated in adults and children older than 1 month for:

- The treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are wanted.
- Sedation during dental surgery in anxious patients.

4.2 Posology and method of administration

Posology
Donopa can be administered for up to 6 hours without haematological monitoring in patients with no risk factors (see Section 4.4).

Paediatric population
The success rate is lower in children under 3 years since the minimum effective alveolar concentration is higher than in older children.

Method of administration
Special precautions should be taken when working with nitrous oxide. Nitrous oxide should be administered according to local guidelines.

Donopa is administered via inhalation in spontaneously breathing patients via a face mask.
Administration of Donopa is governed by the patient's breathing. By holding the mask securely around the mouth and nose and breathing via the mask, a so-called "demand valve" is opened and Donopa flows out of the equipment and is administered to the patient via the airways. Uptake occurs from the lungs.

In dentistry, the use of a double mask is recommended, alternatively, a nasal mask or nasobuccal mask with adequate scavenging/ventilation is used.

Administration via endotracheal tubes is not recommended. If Donopa is to be used in patients breathing through an endotracheal tube, the administration should only be done by health care personnel skilled in the delivery of anaesthesia.

Donopa should only be administered by personnel with knowledge of its use. Administration of Donopa should only occur under supervision of, and with instruction from, personnel familiar with the equipment and its effects. Donopa should only be administered when the possibility of oxygen supplementation and equipment for resuscitation are readily available.

Ideally, the patient should hold the mask through which Donopa is administered. The patient should be instructed to hold the mask to his/her face and breathe normally. This is an additional safety measure to minimise the risk of overdose. If for any reason the patient receives more Donopa than is necessary, and wakefulness becomes affected, the patient will drop the mask and administration will cease. By breathing ambient air, the effect of Donopa rapidly wears off and the patient will regain consciousness.

Donopa should preferably be used in patients capable of understanding and following instructions about how the equipment and the mask should be used.
In children or in other patients that are not capable of understanding and following the instructions, Donopa might be administered under the supervision of competent medical personnel who can help them keep the mask in place and actively monitor the administration. In such cases, Donopa may be administered with a constant gas flow. Due to the increased risk of the patient becoming markedly sedated and unconscious, this form of administration should, however, only take place under controlled conditions. Continuous gas flow should only be used in the presence of competent personnel and with equipment available to manage the effects of the more pronounced sedation/decreased level of consciousness. The potential risk of possible inhibition of protective airway reflexes should be acknowledged and preparedness to secure the airway and assist ventilation available whenever constant flow is used.

When administration is ended the patient should be allowed to recover under calm and controlled conditions for around 5 minutes or until the patient's degree of alertness/consciousness has recovered satisfactorily.

Use in the treatment of short term pain conditions, during gynaecological and urological surgery and procedures,
Administration of Donopa 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 Donopa 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.

According to the individual pain relieving reaction in the patient, additional analgesics may be required.

Use in odontics
A nasal or oronasal mask may be used, depending on how the patient is ventilated.
For disabled patients who are unable to keep the mask in place, it must be held by an operating nurse without strong physical constraint.
After a period of at least 3 minutes, the procedure may be performed, continuously if a nasal mask is used, or during periods of 20 to 30-second for the oronasal mask which may be pushed up on the nose during these periods.
At the end of treatment, the mask is removed and the patient must left to rest in the chair for 5 minutes.

Use in obstetrics
Inhalation should begin as soon as contraction starts. Women in labour must breathe normally during contraction and not hyperventilate because of the risk of oxygen desaturation between contractions. Inhalation must be discontinued after relief of pain.
Nitrous oxide should not be applied during pushing.
Because of this risk of oxygen desaturation between contractions, the SaO2 must be continually monitored in this indication.

4.3 Contraindications

When Donopa is inhaled, gas bubbles (gas emboli) and gas-filled cavities may expand due to the increased ability of nitrous oxide to diffuse. Consequently, Donopa is contraindicated in the following conditions:

- In patients with signs or symptoms of pneumothorax, pneumopericardium, severe emphysema, gas emboli or head injury.
- Following deep sea diving with risk of decompression sickness (bubbles of nitrogen).
- Following cardiopulmonary bypass with heart lung machine or coronary bypass without heart lung machine.
- In patients recently having undergone intraocular injection of gas (e.g. SF_6, C_3F_8) until the gas in question is fully absorbed, because the gas volume may increase in pressure/volume and consequently result in blindness.
- In patients with a severely dilated gastrointestinal tract. Donopa is also contraindicated:

- In patients with heart failure or cardiac dysfunction (e.g. after cardiac surgery) in order to avoid the risk of further deterioration in heart function.
- In patients presenting signs of confusion or in some other way showing signs of increased intracranial pressure.

- In patients with a decreased level of consciousness or impaired ability to cooperate and follow instructions due to the risk that further sedation from the nitrous oxide may affect natural protective reflexes.
- In patients with diagnosed but untreated vitamin B12- or folic acid deficiency (including in early pregnancy) or diagnosed genetic disorder of the enzyme system involved in metabolism of these vitamins.
- In patients with facial injury where use of a facemask may present difficulties or risks.

4.4 Special warnings and precautions for use

Donopa should only be administered by competent personnel with access to adequate resuscitation equipment. (see 4.2)

Repeated administration or exposure to nitrous oxide may lead to addiction. Caution should be excercised in patients with a known history of substance abuse or in healthcare professionals with occupational exposure to nitrous oxide.

When a constant flow of the gas mixture is used, the risk of pronounced sedation, unconsciousness and effects on protective reflexes, e.g. regurgitation and aspiration, should be considered.

Warnings
Reduced fertility in medical and paramedical personnel has been reported after repeated exposure to nitrous oxide in inadequately ventilated rooms. It is not currently possible to confirm or exclude the existence of any causal connection between these cases and nitrous oxide exposure.
It is important that the nitrous oxide content in the ambient air is kept as low as possible and well below the nationally set limit value.
Areas in which Donopa is used should be adequately ventilated and/or equipped with scavenging equipment in order that the concentration of nitrous oxide in ambient air is below set national hygienic limit values; according to TWA (time weight average), the mean value over a working day and STEL (short term exposure limit) mean value during shorter exposure, national set values must always be followed.

The gas mixture should be stored and used only in areas/rooms where the temperature exceeds 0C. At lower temperatures the gas mixture can separate and result in administration of a hypoxic gas mixture.

Paediatric population
Donopa can be used in children that are able to follow instructions on how to use the equipment. In the treatment of younger children, or in other patients that are not capable of following instructions, the use of constant gas flow may be required. Constant gas-flow should only be provided by healthcare personnel trained in use of the gas, with equipment available to secure the airway and for provision of assisted ventilation. (see also 4.2.)

Use of Donopa is not recommended in neonates.
Nitrous oxide may cause in rare cases respiratory depression in the neonate. The neonate should be checked for possible respiratory depression when Donopa is used during childbirth.

Precautions for use
Avoid hyperventilation as this may cause abnormal movements.

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 subacute combined degeneration of the spinal cord. Nitrous oxide should not be used 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 vitamin B12 levels in the normal range. In patients with undiagnosed subclincial deficiency of vitamin B12, neurological toxicity has occured after single exposures to Nitrous Oxide during anaesthesia.

Due to its nitrous oxide content, Donopa can increase pressure in the middle ear and other air-filled cavities. (see also 4.3.)

In patients taking other centrally acting medicinal products, e.g. morphine derivatives and/or benzodiazepines, concomitant administration of Donopa may result in increased sedation, and consequently have effects on respiration, circulation and

protective reflexes. If Donopa is to be used in such patients, this should take place under the supervision of appropriately trained personnel. (See 4.5)

Following discontinuation of administration of Donopa, the patient should be advised to recover under proper supervision until these potential risks resulting from use of Donopa have subsided and the patient has recovered satisfactorily. Recovery of the patient should be assessed by health care personnel.

After cessation of Donopa administration, nitrous oxide rapidly diffuses from blood to the alveoli. Due to the rapid wash-out dilution, a decrease of the alveolar oxygen concentration, diffusion hypoxia, might occur. This can be prevented by oxygen supplementation

Nitrous oxide exerts synergistic effects on folate metabolism when administered with methotrexate (MTX), and this may impair tolerability to MTX. Alternative treatment options for nitrous oxide may be considered in patients using MTX.

4.5 Interaction with other medicinal products and other forms of interaction

Combination with other medicinal products
The nitrous oxide component of Donopa interacts in an additive manner with inhaled anaesthetics and/or other active substances with effects on the central nervous system (e.g. opiates, benzodiazepines and other psychomimetics). If concomitant central acting agents are used the risk for pronounced sedation and depression of protecting reflexes should be acknowledged.
Donopa enhances the inhibiting effect of methotrexate on methionine synthase and folic acid metabolism.
The pulmonary toxicity associated with active substances such as bleomycin, amiodarone, furadantin and similar antibiotics may be exacerbated by inhalation of increased concentrations of oxygen.

Other interactions
The nitrous oxide component of Donopa causes inactivation of Vitamin B^{12}(a co-factor of methionine synthesis), which interferes with folic acid metabolism. Thus, DNA synthesis is impaired following prolonged nitrous oxide administration. These disturbances can result in megaloblastic bone marrow changes and possibly polyneuropathy and/or subacute combined degeneration of the spinal cord (see also 4.8). Therefore the administration of Donopa should be limited in time. (see also 4.4).

High oxygen fraction may potentiate pulmonary toxicity caused by exposure to agents such as paraquat which are toxic to the lung.

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women exposed during the 1st trimester (more than 1000 exposed outcomes) indicates no malformative toxicity.
Moreover, no fetal or neonatal toxicity has been specifically associated with nitrous oxide exposure during pregnancy.
Therefore, Donopa can be used during pregnancy if clinically needed.
When Donopa is used close to delivery, newborns should be supervised for possible adverse effects.

Lactation
There are no data on excretion of nitrous oxide in breast milk. However, after a short-term administration of nitrous oxide, taking into account the very short half-life, interruption of lactation is not necessary.

Fertility
Animal studies at low concentration of nitrous oxide (≤ 1%) suggest that there is a slight alteration in male or female fertility (see section 5.3).
The potential risk associated to chronic work place exposure cannot be ruled out (see section 4.4).

4.7 Effects on ability to drive and use machines

The nitrous oxide component of Donopa has effects on the cognitive and psychomotor functions.

It is rapidly eliminated from the body after brief inhalation and adverse psychometric effects are rarely evident 20 minutes after the administration has stopped while its influence on the cognitive capabilities can persist for several hours.

When used as the sole analgesic/sedative agent, driving and use of complex machinery is not recommended for at least 30 minutes after cessation of the administration of Donopa and until the patient has returned to their initial mental status as judged by the attending healthcare professional.

4.8 Undesirable effects

Megaloblastic anaemia and leukopenia have been reported following prolonged or repeated exposure to nitrous oxide. Neurological effects such as polyneuropathy and myelopathy have been reported with exceptionally high and frequent exposure. However, in patients with undiagnosed subclinical deficiency of vitamin B12, neurological toxicity has occurred after a single exposure to Nitrous Oxide for anaesthesia. Substitution treatment should be considered in all cases where vitamin B12 or folate deficiency may be suspected or where signs or symptoms of nitrous oxide-triggered effects on methionine synthesis have arisen.

The table shows the adverse drug reactions associated with Donopa. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10000 to <1/1000); very rare (<1/10000; including isolated reports), not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse reaction
Blood and lymphatic system disorders	Not known	Megaloblastic anaemia, leukopenia.
Psychiatric disorders	Not known	Psychosis, confusion anxiety. Addiction.
Nervous system disorders	Common	Dizziness, light-headedness, euphoria.
	Uncommon	Severe fatigue.
	Not known	Polyneuropathy, paraparesis and myelopathy, respiratory depression, headache, abnormal movements have sometimes been observed in particular against a background of hyperventilation, myeloneuropathy, neuropathy, subacute degeneration of the spinal cord. Generalised seizures.
Ear and labyrinth disorders	Uncommon	Feeling of pressure in the middle ear.
Gastrointestinal disorders	Common	Nausea and vomiting.
	Uncommon	Bloating, increased volume of gas in the intestines.

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
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

Since participation of the patient is required to administer the gas mixture, the risk of overdose is very small.
If during use of Donopa the patient shows signs of decreased alertness, does not respond, or does not respond adequately to command, or in some other way shows signs of pronounced sedation, administration should be stopped immediately. The patient should not receive further Donopa until full consciousness has been restored.
If the patient becomes cyanotic during use of Donopa, treatment must immediately be discontinued and pure oxygen should be supplied, assisted ventilation may be required.

Overdose of nitrous oxide and or hypoxic gas mixture can occur if the equipment is exposed to cold, below 5C. This can result in separation of the gas mixture, and consequently an excessively high nitrous oxide concentration can be supplied from the equipment with a risk of a hypoxic gas mixture being supplied.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other general anaesthetics, ATC code: N01AX63

Nitrous oxide in concentrations of 50% has analgesic effects, raises the pain threshold for various painful stimuli, such as wound and burn dressing, wound debridement and suturing. The intensity of the analgesic effect depends mainly on the psychological state of the patient. At this concentration (50%), nitrous oxide has limited anaesthetic effects. At these concentrations nitrous oxide provides a sedative and calming effect but the patient remains conscious, easily arousable but with a certain detachment from his/her surroundings.

The 50% concentration of oxygen (more than twice the concentration in ambient air) guarantees good oxygenation and optimally oxygen saturation of the haemoglobin.

5.2 Pharmacokinetic properties

Absorption/Distribution/Elimination
Both uptake and elimination of nitrous oxide occur exclusively via the lungs. Due to the low solubility of nitrous oxide in blood and other tissues, saturation of both blood and the target organ (CNS) is achieved rapidly. These physio-chemical properties explain the rapid onset of analgesia and the fact that the effects of nitrous oxide rapidly subside following discontinuation of administration. The gas is eliminated exclusively by respiration; nitrous oxide is not metabolised in the human body.

The rapid diffusion of nitrous oxide from both gas and blood explains some of the contraindications and special precautions which should be taken into consideration when using nitrous oxide/Donopa.

5.3 Preclinical safety data

Nitrous oxide
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential.

Prolonged continual exposure to 15% to 50% nitrous oxide has been shown to induce neuropathy in fruit bats, pigs and monkeys.

Nitrous oxide is teratogenic in the rat only after repeated exposure at high concentrations (≥ 50 %) during pregnancy (day 6 to 12) and for long time each day (24 hours exposure each day). However, chronic exposure to trace concentration of nitrous oxide (≤1%) adversely affected fertility in male and female rats (small dose-related trend to low increase of resorptions and decrease of live births). No effect has been described in the rabbit and mouse.

Oxygen
Non-clinical data reveal no special hazards for humans. Effects in non-clinical studies were observed only at exposures sufficiently in excess of 50% oxygen.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Medicinal product related storage precautions
Store between 0°C and 50°C. Do not freeze.

On suspicion that Donopa has been stored in too cold conditions, the cylinders should be stored in horizontal position at a temperature above +10C for at least 48 hours before use.

Storage precautions related to gas cylinders and pressurized gases
Keep away from combustible material.
Contact with combustible material may cause fire.
No smoking or naked flames near Donopa.
Must not be exposed to strong heat.
If at risk of fire – move the cylinder to a safe place.

Keep the cylinder clean, dry and free from oil and grease.
Keep the cylinder in locked storage reserved for medicinal gases.
Store and transport with valves closed.
Make sure the cylinder is not knocked or dropped.
Inhaling vapour may cause drowsiness and dizziness.

6.5 Nature and contents of container

The shoulder of the gas cylinder is marked in white and blue (oxygen/nitrous oxide). The body of the gas cylinder is white (medicinal gas).

Steel or aluminium gas cylinder, filling pressure 135 bar.
2, 2.7, 5, 10, 15 or 20 Litre gas cylinder with shut-off valve with or without integrated pressure regulator.

Steel or aluminium gas cylinder, filling pressure 185 bar:
2 or 5 Litre gas cylinder with shut-off valve with or without integrated pressure regulator.

Cylinders filled to 135/185 bar delivers approximately X cubic meter gas at atmospheric pressure and 15^{o}C according to the table below:

Cylinder size in litre	2 (135 bar)	2.7 (135 bar)	5 (135 bar)	10 (135 bar)	15 (135 bar)	20 (135 bar)	2 (185 bar)	5 (185 bar)
m^3 of gas	0.44	0.59	1.1	2.2	3.3	4.4	0.6	1.5

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Rooms in which Donopa is frequently used must be equipped with a satisfactory scavenging of waste gases or ventilation (see section 4.4).

Instructions for use and handling

General
Medicinal gases must be used for medicinal purposes only.

Different gas types must be separated from each other. Full and empty gas cylinders must be stored separately.
Never use oil or grease, even if the cylinder valve is stiff or if the regulator is difficult to connect. Handle valves and accompanying equipment with clean, grease-free (hand cream etc.) hands.
Shut off the equipment in the event of fire, or if not in use. If at risk of fire, move to a safe place.
Use only standard equipment that is intended for the gas mixture 50% N_2O / 50% O_2.
Check that the cylinders are sealed before they are taken into use.

Preparation prior to use
Remove the seal from the valve and the protective cap before use.
Use only regulators intended for the gas mixture 50% N_2O / 50% O_2.
Check that the quick connector and regulator are clean and that the connections are in good condition.

Never use a tool to connect a pressure/flow regulator that is intended to be connected manually, as this can damage the coupling.

Open the cylinder valve slowly – at least half a turn.

Always follow the instructions accompanying the regulator. Check for leakage in accordance with the instructions accompanying the regulator. Do not try to deal with leakage from the valve or equipment yourself, other than by changing the gasket or O-ring.

In the event of leakage, close the valve and uncouple the regulator. If the cylinder continues to leak, empty the cylinder out of doors. Label defective cylinders, place them in an area intended for claims and return them to the supplier.

For cylinders with an inbuilt pressure regulator valve, it is not necessary to use a separate pressure regulator. The inbuilt pressure regulator valve has a quick connector for connecting 'on demand' valves, but also a separate outlet for constant flow of gas, where the flow can be regulated from 015 litres/min.

Using the gas cylinder

Larger gas cylinders must be transported by means of a suitable type of cylinder trolley. Take special care that connected devices are not inadvertently loosened.

Smoking and open flames are strictly forbidden in rooms where treatment with Donopa is taking place.

When the cylinder is in use it must be fixed in a suitable support.

One should consider replacing the gas cylinder when the pressure in the bottle has dropped to a point where the indicator on the valve is within the yellow field.

When a small quantity of gas is left in the gas cylinder, the cylinder valve must be closed. It is important that a small amount of pressure be left in the cylinder to avoid the entrance of contaminants.

After use the cylinder valve must be closed hand-tight. Depressurise the regulator or connection.

7 MARKETING AUTHORISATION HOLDER

SOL S.p.A.
Via Borgazzi 27
20900 Monza
Italy

8 MARKETING AUTHORISATION NUMBER

PA1848/003/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 15th July 2016
Date of Last Renewal: 6th June 2017

10 DATE OF REVISION OF THE TEXT

January 2023