SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nitrous oxide Medicinal SOL 100 % v/v medicinal gas, liquefied

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Nitrous oxide (N_2O), 100% v/v

3 PHARMACEUTICAL FORM

Medicinal gas, liquefied
Colourless and odourless gas

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

- Nitrous oxide Medicinal SOL in equimolar concentration with oxygen (50% v/v nitrous oxide and 50% v/v oxygen) is indicated for the treatment of short-term pain conditions of mild to moderate intensity when rapid analgesic onset and offset effects are required, in adults and in children older than 1 month.
- Nitrous oxide Medicinal SOL is used as a basic anaesthetic in combination with inhalation anaesthetics or intravenous anaesthetics in adults and children from the age of 1 month. Medical oxygen is added at a concentration of at least 21% v/v.

4.2 Posology and method of administration

Posology

Analgesia
Administration of Nitrous oxide Medicinal SOL in an equimolar mixture with oxygen 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 Medicinal SOL 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.
Nitrous oxide, as an analgesic, in an equimolar mixture with oxygen, may not be administered for longer than 1 hour continuously and should not be used for more than 15 consecutive days.

Anaesthesia
Nitrous oxide acts as a basal anaesthetic to achieve anaesthesia. Nitrous oxide alone, with a maximum permitted concentration of 79 % v/v, cannot induce anaesthesia. In combination with other inhalation anaesthetics, nitrous oxide provides accelerated uptake of both inhalation anaesthetics by means of what is known as the “concentration and second gas” effect. Induction time is 2 – 5 minutes.

Nitrous oxide concentration during the induction phase is no more than 79 % v/v. After the induction phase, the quantity of nitrous oxide required as basic anaesthetic is between 50 and 70 % v/v, supplemented by medical oxygen. The quantity of the second inhalation anaesthetic required decreases by about 1 % of its minimal alveolar concentration (MAC) for every 1 % of volume of nitrous oxide inhaled. Refer to the relevant product information for maintenance dosages of nitrous oxide and additional inhalation anaesthetic.

In the event of combination with intravenous anaesthetic, a reduced dose of the intravenous anaesthetic, based on the theoretical minimal alveolar concentration value for nitrous oxide (approximately 105% v/v) is calculated in advance and administered. The inhaled concentration of nitrous oxide should not exceed 70% v/v and should be adjusted downwards depending on clinical parameters.

Continuous exposure (>24 hours) to nitrous oxide increases the risk of bone marrow depression.
Oxygen concentration must be increased in the event of overdose (see section 4.9).

<u>Method of administration</u>
For inhalation use.

Nitrous oxide is administered only after mixing with at least 21% oxygen, using appropriate equipment and a well-fitting mask.

Nitrous oxide should only be administered by adequately trained personnel, and according to local guidelines. Nitrous oxide should only be administered

where there is adequate equipment available to secure an open airway immediately and commence emergency cardiopulmonary resuscitation if necessary.

Administration must be undertaken by appropriately trained staff in well-ventilated areas, utilising gas scavenging and a double mask, for example. The use of a double nose mask is recommended for dental surgery. In ambulances, the administration equipment may be connected to an exhaust system or a double mask and a chin mask may be used. The current occupational guidelines and legislation for the administration of nitrous oxide, particularly in relation to pregnant staff, must be observed.

When nitrous oxide is used outside an operating theatre there is an increased risk of loss of consciousness and coma. In such situations, the administration of nitrous oxide as an analgesic is therefore only acceptable in equimolar combination with 50% oxygen. The equipment used must make it impossible to give mixtures containing over 50% nitrous oxide.

Paediatric population
Data regarding the use of nitrous oxide in neonates are scarce, and do not support its use in neonates (see 4.4).

4.3 Contraindications

Patients for whom ventilation with 100% medicinal oxygen is indicated.

Following cardiopulmonary bypass with heart lung machine or coronary bypass without heart lung machine.For analgesic use 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.

Conditions associated with body cavities containing gas (pneumothorax, bullous emphysema, Caisson disease or decompression sickness, free air in the abdomen).

Intracranial hypertension.

Acute intestinal obstruction.

Facial trauma in the area where the mask is positioned on the face.

After an intraocular gas injection (SF6, C3F8) because of the risk of further expansion of the gas bubble with the potential to cause blindness.

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.

4.4 Special warnings and precautions for use

Nitrogen should be expelled from the administration equipment prior to administration because of the high concentrations of nitrous oxide generally used for induction. The patient must be hyperventilated with oxygen at the same time.

The oxygen fraction in the inspired gas mixture (FiO_2) must be kept at a minimum of 21% during the induction phase. 30% is often used as the lower threshold in practice. The inspired oxygen fraction may be increased to 100% if necessary. Oxygen tension must be kept above 8.0 kPa or 60 mmHg with haemoglobin oxygen saturation > 90%. Regular monitoring by measuring arterial oxygen tension (PaO_2) or using pulse oximetry (arterial oxygen saturation (SpO_2)) and by means of clinical assessment is mandatory. The aim is to achieve effective oxygen concentration in the inspiration air that is as low as possible for the individual patient.
In unexpected cases of cyanosis during anaesthesia with a device delivering oxygen and nitrous oxide, the first step should be to stop the flow of nitrous oxide.
If the cyanosis does not rapidly disappear, the patient must be ventilated with a bag filled with air. If the cyanosis recurs, anaesthesia treatment in the treatment room should be discontinued and the gases being delivered through the relief valves should be analysed.

Hypoxia may develop after stopping the administration of the nitrous oxide/oxygen mixture, resulting from the excretion of nitrous oxide from the body into the lungs. It is recommended that the lungs be temporarily ventilated with 100% medical oxygen after discontinuation of the administration of nitrous oxide.
Oxygen tension and saturation monitoring should be continued for 15 minutes after the end of the administration of nitrous oxide.

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.

Continuous administration for periods of more than 6 hours should be applied with caution because of the potential risk for clinical manifestations (e.g. megaloblastic marrow changes, myeloneuropathy and subacute combined degeneration of the spinal cord) from the inhibitory effects on the methionine synthase.

Nitrous oxide 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 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 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 anaesthesia.

Monitoring of megaloblastic anemia and hypersegmentation of neutrophils is recommended in patient in poor nutritious condition and poor health.

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.

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

Administration of nitrous oxide should be undertaken with particular caution in the following situations:

- Administration of nitrous oxide may increase the pressure in the balloon of a tracheal tube.
- 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.
- Hypovolaemic patients as a result of shock or heart failure (severe hypotension).
- Patients with pernicious anaemia, Crohn’s disease or vegetarians.
- Patients being treated with bleomycin because the increased oxygen concentration during the inhalation sedation technique involves an increased risk of pulmonary toxicity.
- Sickle cell anaemia.
- During childbirth, where co-administration of nitrous oxide and opiates is not recommended because it could cause loss of consciousness.
- After intraocular injection, sufficient time must have passed in order to avoid the risk of visual problems.
- Concomitant use of benzodiazepines for anxiety relating to dental procedures because this could cause loss of consciousness.
- Especially during sevoflurane anesthesia in patients with reduced autoregulatory reserve and during neurosurgical interventions, an increase in cerebral blood flow and reduction in blood pressure, ventilation, and heart rate may occur.

Nitrous oxide is a colourless gas with a slightly sweet odour; it is neither toxic nor flammable but will feed a fire; it is heavier than air and will accumulate in lower-lying locations.

When using nitrous oxide, some of the gas will find its way into the ambient air as it is exhaled by the patient. The use of double-seal face masks and sufficiently high ventilation rates (20x/hour) should ensure that the mean concentration remains below the set MAC value (maximal allowable concentration: 50 ppm or 152 mg/m^3). Cases of reduced fertility and congenital

defects in medical and paramedical staff have been reported after repeated exposure to nitrous oxide in poorly ventilated areas. Peak exposure of pregnant women in the second and third months after their last menstruation has been held particularly responsible for this. If peak exposures during this period cannot be avoided, these employees may not undertake activities in areas in which these peak exposures may occur. 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.

Professionals are advised, in general, to avoid direct inhalation of air exhaled by patients for any length of time.

Paediatric population
The use in neonates (pre-term or a term) is not recommended.

4.5 Interaction with other medicinal products and other forms of interaction

No reports of pharmacokinetic interactions with other medicinal products are known.
Nitrous oxide interacts directly with opiate receptors (subtypes OP_2 and OP_3), GABA-receptors (subtype A) and glutamate receptors (subtype NMDA). Interactions with concomitant medication can be explained by these interactions.
All (inhalation) anaesthetics interact with GABA- and glutamate receptors and have an additive effect on the sedative action of nitrous oxide.
Nitrous oxide reduces the minimal alveolar concentration value of inhalation anaesthetics.
Nitrous oxide is used to reduce the required dose of other anaesthetics but is also used to reduce the induction time when using inhalation anaesthetics.
Opiates have an additive effect on the analgesic and sedative action of nitrous oxide.
Benzodiazepines and barbiturates interact with the benzodiazepine receptor and an allosteric binding site on the GABA-receptor complex respectively and enhance the effect of nitrous oxide.

Unsaturated haemoglobin may occur if nitrous oxide is combined with sedatives.

Nitrous oxide enhances the muscle-relaxing action of non-depolarising neuromuscular blocking muscle relaxants (including cisatracurium, pancuronium, gallamine, tubocurarine, vecuronium).

Nitrous oxide can affect vitamin B_{12}. Therefore, the administration of Nitrous oxide Medicinal SOL should be limited in time (see section 4.4).
This effect disappears on cessation of the administration of nitrous oxide and simultaneous administration of vitamin B_{12}. The inactivation of vitamin B_{12} by

nitrous oxide causes an increase in the toxicity of sodium nitroprusside and methotrexate (see sections 4.3 and 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
A large amount of data on pregnant women (more than 1000 exposed outcomes in the first trimester) indicate no malformative nor feto/ neonatal toxicity after a single administration of nitrous oxide. Animal studies have shown reproductive toxicity (see section 5.3). <Invented name> can be used during pregnancy if clinically needed. If nitrous oxide is used shortly before labour, the neonate must be checked for potential side effects (see section 4.4 and 4.8).

Lactation
It is unknown whether nitrous oxide is excreted in human milk. However, short-term administration of medicinal nitrous oxide does not require discontinuation of breastfeeding.

Fertility
There are no relevant human data pertaining to effects of nitrous oxide on fertility. Animal studies suggest that male and female fertility may be affected when exposed to low (≤1%) concentrations (see section 5.3)

4.7 Effects on ability to drive and use machines

Nitrous oxide affects the ability to drive and use machines. It is recommended that driving be avoided for 24 hours after full anaesthesia with nitrous oxide in combination with other anaesthetics or analgesics.

After completion of short-term administration of nitrous oxide for analgesia, outpatients who will have to drive or operate machines should be observed until any side effects have disappeared and the patient is as alert as prior to the administration of nitrous oxide.

4.8 Undesirable effects

The known undesirable effects are classified according to the various organ systems. Frequency-based classification is not really possible because no structured trials have been carried out in this context. If a reasonable estimation of frequency can be made on the basis of the literature, this has been indicated in the overview below.

Frequency convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (isolated reports) (<1/10,000); not known (cannot be estimated from the available data).

Blood and lymphatic system disorders:
Severe haematological disorders (megaloblastic anaemia, granulocytopenia) have been observed after administration for longer than 24 hours. It is assumed that a single exposure for up to 6 hours involves no risk.

Psychiatric Disorders:
Psychoses, confusion, anxiolytic and euphoric effects, headache.
Addiction may occur (frequency not known).

Nervous system disorders:
Decrease in local cerebral blood circulation and local cerebral glucose consumption.
Psychodysleptic effects may occur in the absence of combination with another anaesthetic agent.
Combination of this type is normal because nitrous oxide acts solely to mediate narcotic effects.
Neurological effects: epilepsy, generalised seizures (frequency not known), sedation, dizziness, increased intracranial pressure, spastic paraparesis.
Neurological effects such as neuropathy, pins and needles throughout the body, myeloneuropathy and subacute degeneration of the spinal cord (frequency not known), have been reported with exceptionally high and frequent exposure.
However, in patients with undiagnosed subclinical deficiency of vitamin B_{12}, neurological toxicity has occurred after a single exposure to Nitrous oxide for anaesthesia.
Temperature effects: malignant hypothermia and hyperthermia.

Eye disorders:
Reduction of the speed gain of eye movement.
Transient increase in pressure and/or volume of the eye after injection with gas-producing medicinal products.

Ear and labyrinth disorders:
Middle ear damage and ear drum rupture.

Cardiac disorders:
Nitrous oxide may cause arrhythmia, heart failure, pulmonary hypertension and systemic hypotension.

Respiratory, thoracic and mediastinal disorders:
Apnoea, pneumomediastinum, subcutaneous emphysema and symptoms comparable to reversible bronchiolitis.
Diffusion hypoxia lasting for several minutes after cessation of the administration of nitrous oxide.

There is no evidence that nitrous oxide causes hypoxaemia or increased mucus production.

Gastrointestinal disorders:
Nausea and vomiting (very common).
Transient increase in pressure and/or volume in the intestines and abdominal cavity.

Hepatobiliary disorders:
Jaundice and increased concentration of hepatic enzymes.

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 national reporting system listed in Appendix V.

4.9 Overdose

The consequences of an overdose of nitrous oxide result in an acute shortage of oxygen and are not related to effects linked to the receptor interaction of nitrous oxide or the inactivation of vitamin B_{12} by nitrous oxide. The shortage of oxygen may lead to hypoxia or cyanosis depending on severity and duration.

In the event of overdose, administration of nitrous oxide must be stopped, and the patient must be actively or passively ventilated with air or oxygen until oxygen saturation returns to normal.
Reversible neurological toxicity and megaloblastic bone marrow change have also been observed following exceptionally prolonged inhalation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other general anaesthetics, ATC code: N 01 AX 13

Nitrous oxide is a relatively weak anaesthetic with good analgesic properties. The analgesic action of nitrous oxide is based on an effect on opiate receptors and its anaesthetic action on an effect on GABA- and glutamate receptors. Nitrous oxide has no muscle-relaxing effect. At a concentration of 50%,

nitrous oxide has an analgesic action; an anaesthetic effect is only obtained at a concentration of 105% (MAC). Anaesthetic action is only achieved with the simultaneous administration of intravenous anaesthetics or other inhalation anaesthetics. A concentration of 50% - 70% nitrous oxide in such a combination with other inhalation anaesthetics reduces the mean minimal alveolar concentration (MAC) required for anaesthesia by about half.

Nitrous oxide has no direct effect on lung function and gas exchange. Nitrous oxide does have an indirect effect on gas exchange because nitrous oxide dissolves better in blood than nitrogen. This means that nitrous oxide is taken up into the lungs more quickly than nitrogen so that the concentrations (partial pressures) of other gases, oxygen and any other anaesthetics inhaled simultaneously, are increased. During the first phase (5 minutes) of administration of nitrous oxide, the uptake of other gases is increased until equilibrium is reached between inhaled and exhaled nitrous oxide. Carbon dioxide will be present at a higher concentration in expired air in the first phase of administration of nitrous oxide.

5.2 Pharmacokinetic properties

Absorption
Inhaled nitrous oxide is absorbed by pressure-dependent gas exchange between the alveolar gas and the capillary blood passing through the alveoli. Nitrous oxide is transported in dissolved form with the systemic circulation to all tissues in the body. Nitrous oxide is absorbed quickly after inhalation. Alveolar concentration approximates to the inhaled concentration within 5 minutes. The action takes effect after 2 – 5 minutes. The blood/gas partition coefficient is low at 0.47.

Distribution
The concentration in tissue that is well supplied with blood, particularly in the brain, approximates to the inhaled concentration within 5 minutes. Nitrous oxide dissolves 35 times better in blood than nitrogen. This means that it diffuses more quickly into a closed cavity containing air than nitrogen can diffuse out of it. If the cavity has rigid walls, the pressure will increase; if the walls are not rigid, the volume increases. This results in contraindications with pneumothorax, air embolism and free air in the abdomen, for example.

Metabolism
Nitrous oxide is not metabolised; the only conversion that takes place is on reaction with vitamin B_{12}.

Elimination
Nitrous oxide is eliminated rapidly in unchanged form via the lungs with a small fraction being eliminated through the intestines and the skin.

5.3 Preclinical safety data

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

Non-clinical data show that chronic exposure to trace concentrations of nitrous oxide ($\leq$ 1 %) is not embryotoxic or teratogenic in the rat but suggest that nitrous oxide may induce little alterations in male and female rats' fertility (small dose-related trend to low increase of resorptions and decrease of live births).

Reduced fertility increased foetal mortality, an increased risk of miscarriage, reduced foetal growth, skeletal abnormalities and *situs inversus* were observed in rodents continuously exposed to high concentrations of nitrous oxide.

Short-term exposure to nitrous oxide may cause reversible damage to neurones in the posterior cingulate/retrosplenial cortex. Additional exposure may result in neuronal cell death. These neurotoxic effects, including cell death, can be prevented with GABA-mimetic anaesthetics. The duration of blockade of the glutamate receptor (NMDA subtype) appears to be the determining factor in this process. It is unclear whether and, if so, to what extent these effects can be expected in humans and no effects have been reported to date, although nitrous oxide has been in use for more than 150 years.

Nitrous oxide inactivates vitamin B_{12}, a coenzyme of methionine synthase, an enzyme that provides for the synthesis of tetrahydrofolate and methionine, which are necessary for DNA synthesis and methylation processes in the body.

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

Store the gas cylinders between – 20°C and + 65°C.

- Store gas cylinders in a well-ventilated area that is intended exclusively for the storage of medicinal gases. This storage area may not contain any flammable materials.
  - All contact with fats, oils or other hydrocarbons is prohibited.
- Store gas cylinders upright; except for those gas cylinders with convex bases which should be stored lying down or in a crate.
- Protect gas cylinders from falling and from shocks by taking the following precautions, for example: fix the gas cylinders in position or place them in a crate.
- Gas cylinders containing a different type of gas or containing a different composition must be stored separately.
  - Store full and empty gas cylinders separately.
  - Do not store gas cylinders in the vicinity of heat sources.
  - Store gas cylinders covered and protected from atmospheric influences.
- The valves of gas cylinders for nitrous oxide are fitted with a rupture disc to prevent the cylinder bursting if pressure inside the cylinder becomes too high. The rupture disc may fail if the temperature is too high. This will release the entire contents of the cylinder.
  In this event, do not enter the storage area and ventilate the area well until it is cleared for use by an expert.

6.5 Nature and contents of container

Nitrous oxide Medicinal SOL is packaged in gas cylinders as a liquid under its own vapor pressure.
The cylinders are made of steel or aluminium. The valves are in brass, steel or aluminium.
The cylinders are colour-coded: body is pure white (RAL 9010) and the shoulder is gentian blue (RAL 5010).
Gas cylinders containing **x** litres contain **y** kilograms (unit of mass) nitrous oxide gas at a pressure of 45 bar (at 15°C).

Content in litres (x)	1	2	3	5	10	
Amount of kg	0.75	1.5	2.25	3.75	7.5	

nitrous oxide gas (y)						
Content in litres (x)	40	50	12*40	12*50	16*40	
Amount of kg nitrous oxide gas (y)	30	37.5	360	450	480	

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Follow the instructions of your supplier, particularly:

- Nitrous oxide may be administered only once suitable pressure and output regulation has been created between the cylinder and the patient.
- Before the valve on the cylinder is opened, the cylinder must be placed in a vertical position and kept in a vertical position during administration.
- Administration of nitrous oxide must take place at the same time as administration of oxygen by means of a secure mixer; the pressure of nitrous oxide in the lines must always be lower than the oxygen pressure.
- If a variable mixer is used, monitoring with an oxygen analyser is recommended.
- The gas cylinder may not be used if it has sustained visible damage or if it is suspected of being damaged or of having been exposed to extreme temperatures.
- All contact with oil, grease or other hydrocarbons must be avoided.
- Only apparatus that is suitable for use with the specific type of gas cylinder and the specific gas may be used.
- No tongs, forceps or other instruments may be used to open or close the cylinder valve to avoid the risk of damaging it.
- The packaging type may not be changed.
- In the event of a leak, the gas cylinder valve must be closed immediately if this can be achieved safely. If it is not possible to close the valve, the cylinder must be taken to a safe place out of doors and allowed to run empty.
- Close the valves of empty gas cylinders.
- Siphoning off compressed gas is not permitted.
- Installations to be used, with central storage, distribution networks, drainage, take-off points and connections must comply with the relevant current legislation.
- Nitrous oxide may cause glowing or smouldering materials to ignite suddenly; it is therefore prohibited to smoke or have an open flame in the vicinity of a gas cylinder.

- Nitrous oxide is a nontoxic gas that will feed a fire. It is heavier than air. It may form explosive mixtures in combination with flammable anaesthetic gases or vapours, even in the absence of oxygen.
- Return the cylinder to the supplier once it is empty.

7 MARKETING AUTHORISATION HOLDER

SOL S.p.A.

via Borgazzi, 27

20900 Monza

Italy

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

02/09/2020