Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Liquid Medical Oxygen 100% Medicinal gas, cryogenic

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxygen (O_2) 100 % v/v
(-183°C)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Medicinal gas, cryogenic.
Oxygen is a colourless, odourless and tasteless gas.
In liquid state it has a blue colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Liquid Medical Oxygen 100 % medicinal gas, cryogenic is in a physical form which is not intended for use. Medical gas is used after gasification for normobaric and hyperbaric oxygen therapy.

Normobaric oxygen therapy:

- Treatment or prevention of acute or chronic hypoxia.
- Treatment of cluster headache.

Hyperbaric oxygen therapy

- Treatment of serious carbon monoxide poisoning. (In the case of carbon monoxide poisoning, hyperbaric oxygen therapy is considered essential for patients who have lost consciousness; neurological symptoms, cardiovascular failure or serious acidosis; or pregnant patients (all of these indications irrespective of COHb content)).
- Treatment of decompression sickness, or of air/gas embolism of a different origin.
- As supporting treatment in cases of osteoradionecrosis.
- As supporting treatment in cases of clostridial myonecrosis (gas gangrene).

4.2 Posology and method of administration

Posology
The concentration, flow and duration of the treatment will be determined by a physician, according to the characteristics of each pathology.
Hypoxemia refers to a condition where the arterial partial pressure of oxygen (PaO_2) is lower than 10 kPa (<70 mmHg). An oxygen pressure level of 8 kPa (55 / 60 mmHg) will result in respiratory insufficiency.
Hypoxemia is treated by enriching the patient's inhalation air with extra oxygen. The decision to introduce oxygen therapy depends on the degree of hypoxemia and the patient's individual tolerance level.
In all cases, the objective of the oxygen therapy is to maintain a PaO_2 > 60 mm Hg (7,96 kPa) or oxygen saturation in the arterial blood ≥ 90%.
If oxygen is administered diluted in another gas, the oxygen concentration in the inspired air (FiO_2) must be at least 21%.

Oxygen therapy at normal pressure (Normobaric oxygen therapy):
Administration of oxygen should be performed cautiously. The dose should be adapted to the individual needs of the patient, oxygen tension should remain higher than 8.0 kPa (or 60 mmHg) and oxygen saturation of haemoglobin should be > 90%. Regular monitoring of arterial oxygen tension (PaO_2) or pulsoxymetry (arterial oxygen saturation (SpO_2)) and clinical signs is necessary. The aim is always to use the lowest possible effective oxygen concentration in the inhaled air for the individual

patient, which is the lowest dose to maintain a pressure of 8 kPa (60 mmHg)/saturation > 90 %. Higher concentrations should be administered as short as possible accompanied by close monitoring of blood gas values.
Oxygen can be administered safely in the following concentrations, for the periods indicated:

Up to 100%	less than 6 hours
60-70%	24 hours
40-50%	during the second 24-hour period

Oxygen is potentially toxic after two days in concentrations in excess of 40%.

Neonates are excluded from these guidelines because retrolental fibroplasia occurs with a much lower FiO_2. The lowest effective concentrations should be sought in order to achieve an adequate oxygenation appropriate for neonates.

• Spontaneously breathing patients:
The effective oxygen concentration is at least 24%. Normally, a minimum of 30% oxygen is administrated to ensure therapeutic concentrations with a safety margin.
The therapy with high oxygen concentration (> 60%) is indicated for short periods in case of serious asthmatic crisis, pulmonary thromboembolism, pneumonia and alveolitic fibrosis, etc.
A low oxygen concentration is indicated for the treatment of patients with chronic respiratory insufficiency due to a chronic obstructive upheaval of the airways or other causes. The oxygen concentration must not be more than 28%, for some patients even 24% can be excessive.
Administration of higher oxygen concentrations (in some cases up to 100%) is possible, although when using most administration devices it is very difficult to obtain concentrations > 60% (80% in the case of children).
The dose should be adapted to the individual needs of the patient, at flow rates ranging from 1 to 10 litres of gas per minute.

• Patients with chronic respiratory insufficiency:
Oxygen must be administered at flow rates ranging from 0.5 to 2 liters/minute, rates should be adjusted on the basis of blood gas values. The effective oxygen concentration will be kept below 28% and sometimes even lower than 24% in patients suffering from breathing disorders who depend on hypoxia as a breathing stimulus.

• Chronic respiratory insufficiency resulting from Chronic Obstructive Pulmonary Disease (C.O.P.D.) or other conditions:
The treatment is adjusted on the basis of blood gas values. Arterial partial oxygen pressure (PaO_2) should be > 60 mm Hg (7,96 kPa) and oxygen saturation in the arterial blood ≥ 90%.
The most common administration rate is 1 to 3 liters/minute for 15 to 24 hours/day, also covering paradoxical sleep (the most hypoxemia-sensitive period within a day). During a stable disease period, CO_2 concentrations should monitored twice every 3-4 weeks or 3 times per month as CO_2 concentrations can increase during oxygen administration (hypercapnia).

• Patients with acute respiratory insufficiency:
Oxygen must be administered at a rate ranging from 0.5 to 15 liters/minute, flow rates should be adjusted on the basis of blood gas values. In case of emergency, considerably higher doses (up to 60 liters/minute) are required in patients with severe respiratory difficulties.

• Mechanically ventilated patients:
If oxygen is mixed with other gases, the oxygen fraction in the inhaled gas mixture (FiO_2) may not fall under 21%. In practice, 30% tends to be used as the lower limit. If necessary, the inhaled oxygen fraction can be raised to 100%.

• Paediatric population:
New-born infant:
In new-born infant, concentrations of up to 100% can be administered in exceptional cases; however, the treatment must be closely monitored. The lowest effective concentrations should be sought in order to achieve an adequate oxygenation. As a rule, oxygen concentrations in excess of 40% in inhalation air must be avoided, considering the risk of eye damage (retinopathy) or pulmonary collapse. Oxygen pressure in the arterial blood must be closely monitored and kept below 13.3 kPa (100 mmHg). Fluctuations in oxygen saturation should be avoided. By preventing substantial fluctuations in oxygenation, the risk of eye damage can be reduced. (Also see section 4.4.)

• Cluster headache:
In the case of cluster headache, 100% oxygen is administered at a flow rate of 7 liters/minute for 15 minutes using a close-fitting facial mask. The treatment should begin in the earliest stage of a crisis.

<u>Hyperbaric oxygen therapy:</u>

Dosage and pressure should always be adapted to the patient's clinical condition and therapy should only be given after doctor's advice. However, some recommendations based on current knowledge are given below.

Hyperbaric oxygen therapy is done at pressures higher than 1 atmosphere (1.013 bars) between 1.4 and 3.0 atmosphere (usually anywhere between 2 and 3 atmosphere). Hyperbaric oxygen is administered in a special pressure room. Oxygen therapy at high pressure can also be given using a close-fitting facial mask with a hood covering the head, or through a tracheal tube.

Each treatment session lasts 45 to 300 minutes, depending on the indication.

Acute hyperbaric oxygen therapy may sometimes last just one or two sessions, whereas chronic therapy may take up to 30 or more sessions. If necessary, the sessions can be repeated two to three times a day.

• Carbon monoxide poisoning:

Oxygen should be given in high concentrations (100%) as soon as possible following carbon monoxide poisoning until the carboxyhaemoglobin concentration has fallen below dangerous levels (around 5%). Hyperbaric oxygen (starting at 3 atmospheres) is indicated for patients with acute CO poisoning or have exposure intervals ≥24 hours. In addition, pregnant patients, patients with loss of consciousness or higher carboxyhemoglobin levels warrant hyperbaric oxygen therapy. Normobaric oxygen should not be used between multiple hyperbaric oxygen treatments as this can contribute to toxicity. Hyperbaric oxygen seems to also have potential in the delayed treatment of CO poisoning using multiple treatments of low dose of oxygen.

• Patients with decompression sickness:

Rapid treatment at 2.8 atmosphere is recommended, repeated up to ten times if symptoms persist.

• Patients with air embolism:

In this case, the dosage is adapted to the patient's clinical condition and blood gas values. The target values are: PaO_2 > 8 kPa, or 60 mmHg, haemoglobin saturation > 90%.

• Patients with osteoradionecrosis:

Hyperbaric oxygen therapy in radiation injury usually consist of daily 90-120 min sessions at 2.0-2.5 atmosphere for about 40 days.

• Patients with clostridial myonecrosis:

It is recommended that a 90-min treatment should be given at 3.0 atmosphere in the first 24h, followed by twice-daily treatments for 4-5 days, until clinical improvement is seen.

Method of administration

Normobaric oxygen therapy

Oxygen is administered through inhaled air, preferably using dedicated equipment (e.g., a nose catheter or facial mask) via this equipment, oxygen is administered with inhaled air. The gas plus any excess oxygen subsequently leaves the patient in the exhaled air, and mixes with the ambient air ("non-rebreathing" system). In many cases, during anaesthesia special systems with a rebreathing system or recycling system are used so that the exhaled air is inhaled once again ("rebreathing" system).

If the patient cannot breathe independently, artificial breathing support can be provided.

In addition, oxygen can be injected into the bloodstream directly using a so-called oxygenator. The application of extracorporeal gas exchange devices facilitate oxygenation and decarboxylation without the harm associated with aggressive mechanical ventilation strategies. The oxygenator, which acts as an artificial lung, provides improved oxygen transfer and therefore, blood gas levels are kept within clinical acceptable ranges. After recovery of lung function extracorporeal blood and gas flow is reduced and eventually, stopped. This happens, for example, during cardiac surgery using a cardio-pulmonary by-pass system, as well as in other circumstances that require extracorporeal circulation including acute respiratory insufficiency.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy is administered in a specially constructed pressure room where the ambient pressure can be increased to up to three times the atmospheric pressure. Hyperbaric oxygen therapy can also be provided through a close-fitting facial mask with a hood covering the head, or through a tracheal tube.

4.3 Contraindications

Normobaric oxygen therapy

There are no absolute contraindications.

Hyperbaric oxygen therapy
One absolute contraindication for hyperbaric oxygen therapy is an untreated pneumothorax, including restrictively treated pneumothorax (without a chest tube).

4.4 Special warnings and precautions for use

Low oxygen concentrations should be used in patients with respiratory failure who depend on hypoxia as a breathing incentive. In such cases, careful monitoring of the treatment is required, by measuring the arterial oxygen pressure (PaO_2) or through pulsoxymetry (arterial oxygen saturation (SpO_2)) and clinical assessment.

High oxygen concentrations should be given for the shortest possible time required to achieve the desired result, and must be monitored with repeated checks of arterial gas pressure (PaO2) or haemoglobin oxygen peripheral saturation (SpO2) and clinical assessment.

Patients with risk of hypercapnic respiratory failure
Special precaution should be adopted in patients with low sensitivity to carbon dioxide in arterial blood or at risk of hypercapnic respiratory failure ("hypoxic drive") (e.g. patients with chronic obstructive pulmonary disease (COPD), cystic fibrosis, pathological obesity, chest wall deformities, neuromuscular disorders, breathing depressants overdose) and in patients with drug-induced respiratory failure (opioids, barbiturates), because in these patients oxygen administration could further aggravate respiratory failure due to hypercapnia caused by the high blood levels of carbon dioxide, which neutralizes the effects of oxygen on receptors. Supplemental oxygen administration can cause respiratory depression and increase of $PACO_2$ with subsequent symptomatic respiratory acidosis (see section 4.8). In these patients, oxygen therapy should be carefully titrated. The target oxygen saturation to be reached can be lower than in other patients, and oxygen should be administered at a lower flow rate.

Special cautions in patients with bleomycin-lung injury
The pulmonary toxicity of high dose oxygen therapy can potentiate lung injury, even if given several years after the initial lung injury by bleomycine, and the target oxygen saturation to be achieved may be lower than in other patients (see section 4.5).

Paediatric population
Because of the higher sensitivity of newly born to supplemental oxygen, the lowest effective concentration should be sought in order to achieve an adequate oxygenation appropriate for neonates (see section 4.2). In preterm and newborn infants, increased PaO_2 may lead to retinopathy of prematurity (see section 4.8). It is recommended to start resuscitation of term or near-term neonates with air instead of 100% oxygen. In preterm, the optimal concentration of oxygen and oxygen target are not precisely known. Supplemental oxygen, if required, will then be closely monitored and guided by pulsoxymetry.

Hyperbaric oxygen therapy (HBOT)

Hyperbaric oxygen therapy must be administered by qualified staff and in specialized centers aware and equipped for insuring appropriate precautions for hyperbaric use.
Compression and decompression treatment must be carefully phased to minimise the risk of pressure-induced injury (barotrauma).
Confinement anxiety and claustrophobia can occur during the HBOT session chamber. The benefit/risk ratio of HBOT should be thoroughly evaluated in patients with claustrophobia, severe anxiety and psychosis.

Diabetic patients
HBOT may interfere with glucose metabolism. The vasoconstrictive effects of hyperbaric therapy can also impair subcutaneous absorption of insulin, making the patient hypoglycaemic. Blood glucose decrease during HBOT session has been reported. Hence, it may be preferable to monitor blood glucose before HBOT session in diabetic patients.

Respiratory disorders
Because of the decompression, at the end of the hyperbaric session, the gas volume increases, while the pressure in the chamber decreases that may lead to partial pneumothorax or aggravation of an underlying pneumothorax. In a patient with an undrained pneumothorax, decompression could lead to the development of a tension pneumothorax. In cases of pneumothorax, pleural cavities must be drained before the session and it may be required to continue the drainage procedure during the HBOT session (see section 4.3).

Moreover, considering the risk of gas expansion during the decompression phase of HBOT, the benefit/risk ratio of HBOT should be thoroughly evaluated in patients with insufficiently controlled asthma, pulmonary emphysema, chronic obstructive pulmonary disease (COPD), recent thoracic surgery.

Coronary diseases
The benefit/risk ratio of HBOT should be thoroughly evaluated in patients with coronary diseases. In patients with acute coronary syndrome or acute myocardial infarction who also require HBOT, such as in case of CO intoxication, HBOT should be used cautiously because of the vasoconstriction potential of hyperoxia in the coronary circulation.

Arterial Hypertension
HBOT causes an increase in both systolic and diastolic blood pressure. This holds true for both hypertensive and non hypertensive patients. Overall the effect on blood pressure is mild. Anyhow care to hyperbaric therapy must be taken to subject patients suffering from arterial hypertension and in particular to calcium channel blockers and beta-blockers users.

Glaucoma, retinal detachment even after surgical treatment
Retinal function is very sensitive to fluctuations in haemoglobin oxygen concentration. Several concomitant factors as increased ROS (reactive oxygen species) production and imbalance between pro-oxidative and antioxidant capacity have been postulated as the crucial factors in early retinal injury, together with the reduced ocular perfusion pressure in the blood vessels. Local and temporally limited disturbance of perfusion have been postulated as a potential source of trouble in patients with glaucoma. The benefit/risk ratio of HBOT should be thoroughly evaluated in patients with glaucoma or retinal detachment, even after surgical treatment.

Ear, nose and throat disorders
In relation to the compression/decompression of HBOT, caution and thorough assessment of the benefit/risk ratio of HBOT are required in patients with sinusitis, otitis, chronic rhinitis, laryngocele, mastoid cavity, vestibular syndrome, hearing loss and recent middle ear surgery.

Relating to hyperoxia induced by HBOT, the benefit/risk ratio of HBOT should be thoroughly evaluated in patients with:
- History of seizure, epilepsy
- Uncontrolled high fever

Risk of fire:
Oxygen is an oxidizing product and promotes combustion. Whenever oxygen is used, the increased risk of fire ignition should be taken into account:

- Risk of fire in domestic environment: Patients and caregivers should also be warned about the risk of fire in presence of other sources of ignition (smoking, flames, sparkles, cooking, ovens etc.) and/or highly combustible substances, especially greasy substances (oils, grease, creams, ointments, lubricants etc.). Only water-based products should be used on the hands and face or inside the nose while using oxygen.
- Risk of fire in medical environment: this risk is increased in procedures involving diathermy, defibrillation and electro conversion therapy.
- Fires can occur at valve opening (frictional heating).

Thermal burns have occurred related to accidental fires in presence of oxygen.

Handling of the cylinders:

Caretakers and all people who handle medicinal oxygen cylinders should be warned about the need to carefully handle cylinders to prevent damages to the equipments, especially the valve. Equipment damage may cause obstruction of the outlet and/or wrong information displayed on the manometer with regards to remaining oxygen content and flow delivery leading to insufficient or lack of oxygen administration.

Frostbites related to direct contact with liquid oxygen:
Oxygen becomes a fluid at approximately -183°C. At such low temperatures, the contact of liquid oxygen with skin or mucous membranes can cause frostbites. Special safety precautions must be taken when handling cryogenic containers: appropriate protective clothing must be worn (gloves, goggles, loose clothing and trousers to cover the shoes). If liquid oxygen comes into

contact with the skin or eyes, the affected areas must be washed with copious amounts of cold water, or cold compresses applied; medical assistance should be sought immediately if such injuries occur.

4.5 Interaction with other medicinal products and other forms of interaction

Inhalation of high concentration of oxygen can exacerbate the pulmonary toxicity associated with drugs such as bleomycin (even if oxygen is given several years after the initial bleomycin-induced lung injury), amiodarone, nitrofurantoin and with paraquat intoxication. Unless the patient is hypoxemic, supplemental oxygen should be avoided.

Oxygen may also aggravate alcohol-induced respiratory depression.

In the presence of oxygen, nitric oxide is rapidly oxidized to form superior nitrated derivatives that are irritant for the bronchial epithelium and the alveolar-capillary membrane. Nitrogen dioxide (NO_2) is the principal compound formed. The oxidation rate is proportional to the initial concentrations of nitric oxide and of oxygen in the inhaled air and to the duration of contact between NO and O_2.
There is a risk of fire in the presence of other sources of ignition (smoking, flames, sparkles, ovens etc.) and/or highly combustible substances (oils, grease, creams, ointments, lubricants etc.) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
Animal studies, have shown reproductive toxicity after administration of oxygen at high pressure and concentration levels (see section 5.3).
The clinical importance of this finding for humans is not known.

Normobaric oxygen therapy
Normobaric oxygen (pressure below 0.6 atmospheres) may be administered during pregnancy only, if necessary, i.e. in case of vital indications, in women presenting critical conditions or hypoxaemia.

Hyperbaric oxygen therapy
The amount of documented experience with the use of HBOT in pregnant women is limited, but has shown a benefit of HBOT for the foetus in case of CO intoxication in pregnant women. In other situations, HBOT should be used with caution in pregnancy as the impact on the foetus of a potential increase of oxidative stress from excess oxygen is unknown. The use of HBOT should then be evaluated in each individual patient but is permissible in the case of vital indications during pregnancy.

Breast-feeding
Medicinal oxygen can be used during lactation without risks to the infant.

Fertility
There are no data available regarding potential effects of oxygen treatment on male or female fertility.

4.7 Effects on ability to drive and use machines

Normobaric oxygen therapy
Oxygen has no influence on the ability to drive and use machines.

Hyperbaric oxygen therapy
Sight and hearing disorders that can influence the ability to drive and use machines have been reported after HBOT (see section 4.8).

Patients should avoid driving and using machines until all negative effects on attention and alertness have completely disappeared.

4.8 Undesirable effects

Different tissues exhibit different sensitivities to hyperoxia; the most sensitive being the lungs, the brain and the eyes.

Description of selected adverse reactions

Respiratory adverse reactions

- At an ambient pressure, the first signs (tracheobronchitis, substernal pain and dry cough) appear as soon as after 4 hours of exposure to 95% oxygen. A reduction forced vital capacity can occur within 8 -12 hours of exposure to 100% oxygen but serious injuries require much longer exposure.

  Interstitial oedema can be seen after 18 hours of exposure to 100% oxygen and can lead to pulmonary fibrosis. Respiratory effects reported with HBOT are generally similar to those encountered during normobaric oxygen treatment, but the time to symptoms onset is shorter.

- With high concentrations of oxygen in the inspiratory air/gas, the concentration/pressure of nitrogen is reduced. As a result, the concentration of nitrogen in tissues and lungs (the alveoli) falls. If oxygen is taken up from the alveoli into the blood more rapidly than it is supplied in the inspiratory gas fraction, alveolar collapse can occur (development of atelectasis). The development of atelectatic sections of the lungs leads to a risk of poorer arterial blood oxygen saturation, despite good perfusion, due to the lack of gas exchange in the atelectatic sections of the lungs. The ventilation/perfusion ratio worsens, causing intrapulmonary shunts.

- There may be a change in the modalities of ventilation control in patients with long-term diseases associated with chronic hypoxia and hypercapnia. Under these circumstances, administration of too high concentrations of oxygen can cause respiratory depression inducing aggravated hypercapnia, respiratory acidosis and, finally, respiratory arrest (see section 4.4). The administration of oxygen in patients with drug-induced respiratory depression (opioids, barbiturates) or with COPD might further suppress ventilation since, in these conditions, hypercapnia is unable to stimulate central chemoreceptors, while hypoxia is still capable of stimulating peripheral chemoreceptors.

Central nervous toxicity

Central nervous toxicity can be observed in HBOT settings. Central nervous toxicity can develop when patients breathe 100% oxygen at pressure above 2 ATA. Early manifestations include blurred vision, peripheral vision decreased, tinnitus, respiratory disturbances, localized muscular twitching especially eyes, mouth, forehead. Continuation of exposure can lead to vertigo and nausea, followed by altered behaviour (anxiety, confusion, irritability), and finally generalized convulsions. The hyperoxia-induced discharges are believed to be reversible, causing no residual neurological damage, and disappearing upon reduction of the inspired oxygen partial pressure.

Adverse events related to HBOT procedure:

- Undesirable effects of HBOT are barotraumas or consequences of multiple and rapid compressions/decompressions. Most of them are not specific to the use of oxygen and can occur in patients under oxygen as well as in attending healthcare professionals under hyperbaric ambient air. These are ear, sinuses and throat barotraumas, pulmonary barotraumas, other barotraumas (teeth, etc.).

- Due to the relatively small size of some hyperbaric chambers, patients may develop confinement anxiety that is not due to a direct effect of oxygen.

Eye toxicity

Progressive myopia has been reported in cases of multiple hyperbaric treatments. The mechanism remains obscure but an increased refractory index of the lens was suggested. Most cases were spontaneously reversible. However, risk of irreversibility increased after more than 100 therapies. After stopping HBOT, reversal of myopia was usually rapid for the first few weeks and then continued more slowly for periods ranging from several weeks to as long as a year.

The threshold of number of HBOT sessions, periods or duration can not be estimated. It was ranged from 8 to more than 150 sessions.

Retinopathy of prematurity: see below.

Paediatric population

In premature neonates who have been subjected to high oxygen concentrations, retinopathy of prematurity (retrolental fibroplasia) may occur.

Adverse reactions listed in tables below are presented by system organ class (SOC) and frequencies.
Frequency is defined using the following 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 (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions related to normobaric oxygen treatment

	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 (<1/10,000)	Not known (cannot be estimated from the available data)
Respiratory, thoracic and mediastinal disorders			atelectasis			Pulmonary toxicity: • Tracheobronchitis (substernal pain, dry cough) • Interstitial oedema • Pulmonary fibrosis Aggravation of hypercapnia in patients with chronic hypercapnia treated with extremely high FiO_2 • Hypoventilation • Respiratory acidosis • Respiratory failure
Eye disorders	Retinopathy of prematurity					
General disorders and administration site conditions						Dry mucous tissue, local irritation and inflammation of mucosa

Adverse reactions related to hyperbaric oxygen treatment

	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 (<1/10,000)	Not known (cannot be estimated from the available data)
Respiratory, thoracic and mediastinal disorders				Dyspnoea		Respiratory disorders
Nervous system disorders		Seizures				
Musculoskeletal and connective tissue disorders						Localised muscle twitching
Ear and labyrinth disorders	Ear pain		Perforated tympanic membrane			Dizziness, Hearing impaired, Acute serous otitis media, Tinnitus
Gastrointestinal disorders						Nausea

Psychiatric disorders						Abnormal behaviour
Eye disorders	Progressive myopia					Reduced peripheral vision; Blurred vision; Cataract
Injury, poisoning and administration site conditions	Barotrauma (paranasal sinuses, ear, lungs, teeth etc.)					
Metabolism and nutrition disorders				Hypoglycaemia in diabetic patients		

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

The toxic effects of oxygen vary according to the pressure of the inhaled oxygen and the duration of exposure.
Symptoms of oxygen intoxication are those of hyperoxia.

The symptoms of pulmonary toxicity include tracheobronchitis (substernal pain, dry cough), interstitial oedema and pulmonary fibrosis.
The symptoms of central nervous system toxicity with HBOT include tinnitus, sight and hearing disorders and localised, spasms, especially of eyes, mouth and forehead. Prolonged exposure can cause dizziness and nausea, followed by personality changes (anxiety, confusion, irritability) and loss of consciousness and generalized convulsions at the end.

Ocular toxicity with HBOT includes blurred vision and reduced peripheral vision.

Paediatric population
Toxicity in neonates: in preterm infants exposed to high oxygen concentration retinopathy of prematurity can occur.

Patients in risk of hypercapnic respiratory failure
Administration of supplemental oxygen can cause respiratory depression and $PaCO_2$ increase with subsequent symptomatic respiratory acidosis.

In case of oxygen intoxication related to hyperoxia, oxygen therapy should be reduced or, if possible, interrupted and symptomatic treatment initiated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Medical gases, ATC code: V03AN01

Oxygen is vital to living organisms, and all tissues must be oxygenated continuously in order to fuel the energy production of the cells. Oxygen in inhaled air enters the lungs, where it diffuses along the walls of the alveoli and surrounding blood capillaries and then enters the bloodstream (mainly bound to haemoglobin), which transports it to the rest of the body. This is a normal physiological process that is essential to the body's survival.

The administration of additional oxygen in hypoxia patients will improve the supply of oxygen to the bodily tissues.

Pressurised oxygen (hyperbaric oxygen therapy) helps to significantly increase the amount of oxygen that can be absorbed into the blood (including the part not bound to haemoglobin), and, as a result, also improves the supply of oxygen to the bodily tissues.

In the treatment of gas/air embolisms, high-pressure hyperbaric oxygenation will reduce the volume of the gas bubbles. As a result, the gas can be absorbed from the bubble into the blood more effectively, and will then leave the lungs in the exhaled air.

5.2 Pharmacokinetic properties

Inhaled oxygen is absorbed in a pressure-dependent exchange of gases between the alveoli and the capillary blood that passes them.

The oxygen (mostly bonded to haemoglobin) is transported to all body tissues in the systemic circulation system. Only a very small proportion of the oxygen in the blood is freely dissolved into the plasma.

Oxygen is an essential component in the generation of energy in intermediary cell metabolism – aerobic ATP production in the mitochondria. Virtually all the oxygen absorbed by the body is exhaled as the carbon dioxide created in this intermediary mechanism.

5.3 Preclinical safety data

In animal experiments, oxidative stress has led fetal dysmorphogenesis, abortions, and intrauterine growth restriction. Excess oxygen during pregnancy may induce abnormalities in the development of the neural tube. Prolonged hyperbaric oxygen treatment during gestation in mice, rats, hamsters and rabbits was foetotoxic and teratogenic. Other animal experiments suggested that lower level exposure to hyperbaric oxygen did not have adverse developmental effects. Oxygen has shown mutagenic effects in *in vitro* tests with mammalian cells. Although available data do not suggest a tumor promoting effect for hyperbaric oxygen, conventional carcinogenicity studies are not known. As regards pharmacodynamics and toxicity after repeated administration no risks have been known to occur other than those already described in other sections.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

There are no excipients.

6.2 Incompatibilities

Medicinal oxygen strongly supports combustion and will cause substances to burn vigorously, including some materials that will not normally burn in air. 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 medicinal oxygen in relatively high concentrations.

6.3 Shelf life

Liquid medicinal oxygen may be kept up to 6 months after the date stated on the vessel.

6.4 Special precautions for storage

Keep the vessel in a well-ventilated area within a temperature range of -20°C and +50°C.
Keep away from inflammable and combustible materials and sources of heat or open fire. If at risk of fire – move to a safe place.
Do not smoke near the vessel.
The transport must be conducted in accordance with international regulations for transporting dangerous materials.
Avoid any contact with oil, grease or hydrocarbons.

6.5 Nature and contents of container

Liquid medicinal oxygen is packed in mobile cryogenic vessels. Mobile cryogenic vessels are made of an outer and an inner vessel of stainless steel with a vacuum insulation layer in between and fitted with dedicated filling port and withdrawal hose connection. The valves are made of brass, stainless steel and/or bronze and are specially designed for low temperatures.
These vessels contain oxygen in the liquid state at very low temperature.
The content of the vessels varies from 10 to 1100 litres.
Each litre of liquid oxygen delivers 853 litres of oxygen gas at 15°C and 1 bar.

Vessel content in litres	**Capacity for liquid oxygen in litres**	**Equivalent amount of gaseous oxygen in m^3 at 15°C and 1 atm**
10	10	8,53
to		
1100	1100	938,3

Not all vessel sizes may be marketed.

6.6 Special precautions for disposal and other handling

General
Medicinal gases must only be used for medicinal purposes.
Different gas types and gas qualities must be separated from each other.
Full and empty containers must be stored separately.
Never use grease, oil or similar substances for lubricating screw threads that jam or are difficult to connect.
Handle valves and devices to match with clean and grease-free (hand cream, etc.) hands.
Use only standard equipment that is intended for medicinal oxygen.

Preparation for use
Use only dosing devices that are intended for medicinal oxygen.
Check that the automatic coupling or dosing device is clean, and that the gaskets are in working order. Never use tools on pressure-/flow regulators that are intended for manual connection, as this may damage the coupling.
Open the valve slowly – at least one half turn.
Check for leakage in accordance with the instructions supplied with the regulator.
In case of leakage, the valve must be closed and the regulator disconnected. Label defective vessels, store them separately and return them to the supplier.

Use
Smoking and open flames are strictly forbidden in rooms where oxygen therapy is being carried out.
Close down the apparatus in the event of fire or if it is not being used.
Carry to safety in the event of fire.
Larger vessels must be transported by means of vehicles meant for this purpose.
Pay special attention to connected devices which should not be accidentally loosened.
When the vessel is empty, the gas flow is dropping. Close the exit valve and remove any couplings after the pressure has been released.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA1848/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th May 2018
Date of last renewal: 2nd May 2023

10 DATE OF REVISION OF THE TEXT

September 2023