# 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
For a 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

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%.

- 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.

Hyperbaric oxygen therapy:

**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 for normobaric oxygen therapy.

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 must be used for patients with respiratory failure who depend on hypoxia as a breathing incentive. In these cases, careful monitoring of the treatment is required, by measuring the arterial oxygen tension ($PaO_2$) or through pulsoxymetry (arterial oxygen saturation ($SpO_2$)) and clinical assessment.
Special caution is required in the treatment of new-born infant and pre-term new-born infant. In these cases, the lowest effective concentration must be used in order to achieve an adequate oxygenation appropriate for neonates and fluctuations in oxygen saturation should be avoided. Such caution is to minimise the risk of eye damage, retrolental fibroplasia or other potential adverse events, but still while achieving an adequate oxygenation appropriate for neonates and avoiding fluctuations in oxygen saturation.
Arterial oxygen pressure must be closely monitored and should be kept below 13.3 kPa (100mmHg).
High oxygen concentrations in the inhaled air or gas will cause the concentration and pressure of nitrogen to fall. This will also reduce the concentration of nitrogen in tissues and the lungs (alveoli). If oxygen is absorbed into the blood through the alveoli faster than it is supplied through ventilation, the alveoli may collapse (atelactasis). This may obstruct the oxygenation of the arterial blood, because no gases are exchanged despite perfusion.
In patients with reduced sensitivity to carbon dioxide pressure in arterial blood, high oxygen levels may cause carbon dioxide retention. In extreme cases, this may lead to carbon dioxide narcosis.
Hyperbaric oxygen therapy must be administered by nursing staff who are qualified for that purpose. Compression and decompression treatment must be carefully phased to minimise the risk of pressure-induced injury (barotrauma).
Preferably, hyperbaric oxygen therapy should not be used for patients with:

- COPD or pulmonary emphysema
- infections of the upper respiratory tract
- recent middle ear surgery
- recent thoracic surgery
- uncontrolled high fever
- serious epilepsy

Caution should be exercised in patients with claustrophobia.
In addition, caution is called for in patients with a medical history of thoracic surgery or epileptic fits.

In patients presenting with a pneumothorax treated with a chest tube and/or patients with a medical history of pneumothorax, the use should be evaluated for each individual patient with regard to the risk on a new (tension) pneumothorax. The treatment with hyperbaric oxygen in patients with a pneumothorax treated with a chest tube should be done in a situation where supportive care can be provided immediately such as in a hospital setting. Caution is called for in patients with a history of thoracic surgery or epileptic fits.

The pulmonary toxicity associated with drugs such as bleomycin, amiodarone, furadantin and similar antibiotics may be exacerbated by inhalation of increased concentration of oxygen. (See also section 4.5 of this document.)
Whenever oxygen is used, the increased risk for spontaneous ignition should be taken into account. This risk is increased in procedures involving diathermy, defibrillation/electro conversion therapy.

## 4.5 Interaction with other medicinal products and other forms of interaction

The pulmonary toxicity associated with drugs such as bleomycin, amiodarone, furadantin and similar antibiotics, may be exacerbated by inhalation of increased concentration of oxygen.
There are reports of interaction with amiodarone. Relapse of pulmonary damage induced by bleomycin or actinomycin may be fatal.
In patients who have been treated for oxygen radical-induced pulmonary damage, oxygen therapy may exacerbate that damage, for example in the treatment of paraquat poisoning.
Oxygen may also aggravate alcohol-induced respiratory depression.
Medicinal products known to provoke adverse events include: adriamycin, menadion, promazine, chloropromazine, thioridazine and chloroquine. The effects will be particularly pronounced in tissues with high oxygen levels, especially the lungs.
Corticosteroids, sympathicomimetics or X-rays may increase the toxicity of oxygen.
Hyperthyroidism or a lack of vitamin C, vitamin E or glutathione may also produce that effect.

## 4.6 Fertility, pregnancy and lactation

Women that can be pregnant
In case pregnancy cannot be excluded, hyperbaric oxygen should only be used if strictly necessary (for further information see “pregnancy”)

Pregnancy
A limited amount of data from documented experience of the use of (hyperbaric) oxygen therapy in pregnant women indicate no malformative or feto/neonatal toxicity. The available clinical data is insufficient to exclude a risk. Studies in animals, have shown reproductive toxicity after administration of oxygen at increased pressure and in high concentrations (see section 5.3). . Low concentrations of normobaric oxygen can be administered safely during pregnancy, if necessary. The use of high concentrations of oxygen and hyperbaric oxygen may be considered in the case of vital indications during pregnancy.

Hyperbaric oxygen should only be used in pregnancy if strictly necessary due to a potential risk of oxidative stress-induced damage in the foetus. In severe carbon monoxide intoxication the benefit vs. risk seems reassuring for the use of hyperbaric oxygen. The use should then be evaluated for each individual patient.

Lactation
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

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

## 4.8 Undesirable effects

Normobaric oxygen therapy

**Cardiac disorders**
- Slight reduction in pulse and cardiac output

**Respiratory, thoracic and mediastinal disorders:**
- Hypoventilation
- Atelectasis caused by reduced nitrogen pressure.
- Pleuritis
- Respiratory Distress Syndrome

In patients with respiratory failure who depend on hypoxia as a breathing stimulus, the administration of oxygen may result in a further reduction of ventilation, in an accumulation of carbon dioxide and in acidosis.
In new-born infants and pre-term new-born infants, the administration of oxygen may cause retinopathy, bronchopulmonary dysplasia, subependymal and intraventricular bleeding and necrotising enterocolitis.

Hyperbaric oxygen therapy

The undesirable effects of hyperbaric oxygen therapy tend to be mild and reversible. Hyperbaric oxygen therapy may provoke:

**Nervous system disorders:**
- Temporary loss of eyesight
- Toxicity to the central nervous system, with effects ranging from nausea, dizziness, anxiety and confusion to muscle cramp, loss of consciousness and epileptic fits

**Ear and labyrinth disorders:**
- Middle ear barotrauma

**Respiratory, thoracic and mediastinal disorders:**
- Pulmonary barotrauma
- 'Sinus squeeze' (sinus barotrauma)

**Musculoskeletal and connective tissue disorders**
- Myalgia

## 4.9 Overdose

The toxic effects of oxygen vary according to the pressure of the inhaled oxygen and the duration of exposure. Low pressure (0.5 to 2.0 bar) is more likely to cause pulmonary toxicity than toxicity to the central nervous system. The opposite applies to higher pressure levels (hyperbaric oxygen therapy).
The symptoms of pulmonary toxicity include hypoventilation, coughing and chest pain.
The symptoms of central nervous system toxicity include nausea, dizziness, anxiety and confusion, muscle cramp, loss of consciousness and epileptic fits.
Cases of overdose must be treated by reducing the concentration of inhaled oxygen. In addition, therapy must be provided to maintain the patient's normal physiological functions (such as breathing support in the case of respiratory depression).

# 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 Medical Oxygen may be kept up to 6 months after the date stated on the vessel/cistern.

## 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.
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 Medical 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.
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

No special precautions.

## 7 MARKETING AUTHORISATION HOLDER

Dolby Medical Home Respiratory Care Ltd
North Suite
Lomond Court
Castle Business Park
Stirling
FK9 4TU United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

Liquid Medical Oxygen: PL10414/0001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/12/2012

## 10 DATE OF REVISION OF THE TEXT

04/2013