SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Medical Oxygen 100% Medicinal gas, compressed

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, compressed.

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

[...]

- Bullous emphysema
- Developmental age asthma

- Pneumothorax, past history of pneumothorax
- Chronic obstructive pulmonary disease (COPD)
- Pneumonia caused by *Pneumocystis carinii*
- Status epilepticus
- Claustrophobia
- Normal pregnancy (first trimester) for non-acute diseases
- Upper airway infections
- Hyperthermia
- Hereditary spherocytosis
- Optical nerve neuritis
- Malignant tumours
- Acidosis
- Concomitant use of certain medications such as doxorubicin, adriamycin , bleomycin, daunorubicin , cisplatin, steroids, disulfiram, and substances such as alcohol, aromatic hydrocarbons and nicotine
- Pre-term infants

4.4 Special warnings and precautions for use

Administration of oxygen should be performed with caution. The dose should be adapted to the individual needs of the patient, oxygen tension should remain higher than 8 kPa (or 60 mmHg).
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 h
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%.
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.
Oxygen administration in patients with drug-induced respiratory failure (opioids, barbiturates) or with chronic obstructive pulmonary disease (COPD) could further aggravate respiratory failure due to hypercapnia caused by the high blood levels of carbon dioxide, which neutralises the effects of oxygen on receptors.
High oxygen concentrations of oxygen in air or in the inhaled air, will cause the concentration and pressure of nitrogen to fall. This will also reduce nitrogen levels both 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 hinder the oxygenation of ~~the~~ arterial blood, because no gasexchange~~d~~ takes place despite perfusion.
In patients with reduced sensitivity to carbon dioxide pressure in arterial blood, high oxygen levels can cause carbon dioxide retention. In extreme cases, this may lead to carbon dioxide narcosis.

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 training") (e.g. patients with chronic obstructive pulmonary disease (COPD), cystic fibrosis, pathological obesity, chest wall deformities, neuromuscular disorders, breathing depressants overdose).
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 precautions in patients with bleomycin-induced pulmonary lesions

Pulmonary toxicity of high dose oxygen therapy can aggravate pulmonary lesions, even if administered several year after the initial lung lesion induced by bleomycine, and the target oxygen saturation level to be reached can be lower than in other patients (see section 4.5).

Paediatric population

Due to the greater sensitivity of the neonate to supplemental oxygen, the lowest effective concentration of oxygen must be administered to obtain adequate oxygenation for neonates. Increase in PaO_2 in preterm and term-born infants can cause retinopathy in prematurity (see section 4.8), chronic pulmonary disease and intraventricular haemorrhage. It is recommended to start resuscitation in late-preterm or near-term infants with breathing room air instead with 100% oxygen. For preterm neonates, the optimal concentration of oxygen and the oxygen target are not precisely defined. When required, supplemental oxygen should be carefully monitored and guided through pulsoxymetry.

Hyperbaric oxygen therapy (HBOT)

Administration of oxygen in the hyperbaric chamber should be carefully evaluated based on the benefit /risk balance, in the event of:

- Recurrent otitis and/or sinusitis, laryngocele, mastoid cavities, vestibular syndrome, loss of hearing and recent middle ear surgery
- Ischaemic and/or congestive heart disease; in patients with acute coronary syndrome or acute myocardial infarction also requiring hyperbaric therapy, as well as in the case of carbon monoxide intoxication, hyperbaric therapy must be administered with caution due to the potential vasoconstriction associated with hyperoxia in coronary circulation
- Arterial hypertension not treated pharmacologically
- Restrictive and/or highly restrictive lung diseases
- Glaucoma, retinal detachment even after surgical treatment (compensation manoeuvres)
- History of seizures, epilepsy
- Uncontrolled high fever
- Severe anxiety, psychosis, claustrophobia

Patients with *diabetes mellitus*

HBOT may interfere with glucose metabolism. The vasoconstrictive effects of hyperbaric therapy can also impair subcutaneous absorption of insulin, making the patient hypoglycaemic. The physician may also consider monitoring blood glucose levels between hyperbaric therapy sessions.

Respiratory disorders

Due to decompression, at the end of the HBOT, the volume of gas increases, while pressure in the chamber diminishes, and this can generate partial pneumothorax or aggravate an underlying pneumothorax. In a patient with a pneumothorax that has not been drained, decompression could cause tension pneumothorax to develop.

Moreover, considering the risk of expansion of the gas during the decompression phase of hyperbaric therapy, the benefit/risk balance of hyperbaric therapy should be carefully assessed in patients with insufficiently controlled asthma, pulmonary emphysema, chronic obstructive pulmonary disease (COPD), and recent chest surgery.

SAFETY (also see section 6.6)

Oxygen is an oxidizing agent and, therefore, supports combustion. When there are combustible substances, such as oils (grease, fuels) and organic substances (fabric, wood, paper, plastic materials, etc.) oxygen may spontaneously activate combustion when exposed to a trigger (sparkle, naked flame, source of ignition), or resulting from adiabatic compression in pressure reducing devices (reducers) during a sudden reduction in gas pressure. As a result,

all substances that come in contact with oxygen may be classified as product compatible under regular terms of their use.

- Any oxygen supply system or container should be kept away from the heat source due to the combustibility of oxygen; hence, due precautions should be taken in this regard both in hospitals and in-home settings when there is medicinal oxygen.
- Oxygen can cause a sudden fire of incandescent materials or of embers; therefore it is not allowed to either smoke or keep naked flames that are not screened nearby oxygen containers and supplying systems.
- Do not smoke in the room where oxygen therapy is being administered.
- Do not place the cylinders or containers near heat sources.
- Do not use any electrical equipment that can issue sparks near patients receiving oxygen.
- All interventions on connector junctions, supply devices and related accessories or components are absolutely forbidden (**OIL AND GREASE CAN SPONTANEOUSLY CATCH FIRE IN CONTACT WITH OXYGEN**).
- All contact with oil, grease or hydrocarbons must be avoided.
- It is absolutely forbidden to handle devices or components with hands, face or clothes soiled with grease, oil, creams or miscellaneous ointments. Do not use either oil-based moisturising creams or lipsticks.
- In an overfilled area oxygen can “saturate” your clothing.
- It is absolutely forbidden to touch frozen parts (for cryogenic containers).
- Cylinders and mobile cryogenic containers cannot be used if there is any evident damage or a suspicion that they have been damaged or exposed to extreme temperatures.
- Only suitable device that are compatible with oxygen for the specific container model can be used.
- Neither pliers nor other tools can be used to either open or close the cylinder’s valve in order to prevent risk of damage.
- In case of leakage, the cylinder’s valve should be immediately closed if this can be done safely. If the valve cannot be closed, the cylinder must be moved to a safer outdoor place to allow the oxygen to be freely released.
- The valves of empty cylinders should be kept closed.
- Oxygen has a powerful oxidising effect and can react violently with organic substances. This is why handling and storage of the containers require special precautions.
- Administering gas under pressure is not allowed.

4.5 Interaction with other medicinal products and other forms of interaction

Oxygen should not be administered concomitantly with the intake of medicines known to increase its toxicity, such as catecholamines (e.g. epinephrine, norepinephrine), corticosteroids (e.g. dexamethasone, methylprednisolone), hormones (e.g. testosterone, thyroxin), chemotherapeutics (bleomycin, cyclophosphamide, 1,3-bis-(2-chloroethyl)-1-nitrosourea) and antimicrobial agents (e.g. nitrofurantoin). X-rays may increase oxygen toxicity. Even hyperthyroidism or vitamin C, vitamin E or glutathione deficiency may produce the same effect.

Pulmonary toxicity associated with medicines such as bleomycin, actinomycin, amiodarone, nitrofurantoin and similar antibiotics, can be increased by concomitant inhalation of high

oxygen concentrations.
In patients treated for pulmonary damage induced by free radicals, oxygen therapy can aggravate the damage, for instance in the treatment of paraquat poisoning.

Oxygen may also aggravate alcohol-induced respiratory depression.

Medicinal products known to induce adverse events include: adriamycin, menadione, promazine, chloropromazine, thioridazine and chloroquine. The effects will be particularly pronounced in tissues with high oxygen levels, especially the lungs.
In the presence of oxygen, nitric oxide is rapidly oxidized to form larger nitric derivatives that irritate the bronchial epithelium and the alveolar-capillary membrane. Nitrogen dioxide (NO_2) is the main resulting compound. Oxidation rate is proportional to the initial concentrations of nitric oxide and of oxygen in the air inhaled and the duration of contact.

4.6 Fertility, pregnancy and ~~lactation~~ and breast-feeding

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

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

Hyperbaric oxygen therapy
The use of hyperbaric treatment is controindicated for non-acute diseases during normal pregnancy (first trimester). The use of hyperbaric therapy during poregnancy might induce oxidative stress from excess oxygen, thus damaging the foetus. In cases of severe intoxication with carbon monoxide, the benefit/risk balance seems to be reassuring for regarding the use of hyperbaric oxygen therapy.

Brest 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

Tissues present different degrees of sensitivity to hyperoxaemia; the most sensitive are lungs, brain and eyes.

Description of selected adverse reactions

Respiratory adverse reactions

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

Interstitial oedema can be observed 18 hours of exposure to 100% oxygen and with a possible evolution towards pulmonary fibrosis. Respiratory side effects of hyperbaric therapy generally resemble those observed during treatment with normobaric oxygen, but the time of onset of symptoms is shorter.

Inhalation of high concentrations of oxygen can cause atelectasis due to the reduction in alveolar nitrogen and direct effect of oxygen on alveolar surfactant. Development of atelectasis in the lungs generates a risk of low oxygen saturation in arterial blood, despite good perfusion, due to the lack of gas exchange in atelectatic areas of the lungs. The ventilation/perfusion ratio worsens, causing intrapulmonary shunts.

In patients with long-term diseases associated with chronic hypoxia and hypercapnia a change in the way to control ventilation may occur. In these circumstances, the administration of oxygen concentrations that are too high can cause respiratory depression produced by suppression of the ventilation stimulus triggered by the brusque increase in partial oxygen pressure in carotid and aortic chemoreceptors, including 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.

Toxic effects on the CNS

Toxic effects might occur when patients are inhaling 100% oxygen at pressure levels over 2 bars. Early signs include blurred vision, reduced peripheral vision, tinnitus, respiratory disorders and localized muscle contractions, especially of eyes, mouth and forehead. Prolonged exposure can cause dizziness and nausea, followed by change of behaviour (anxiety, confusion, irritability), reduced consciousness (up to the loss of conscience) and generalized convulsions. It is deemed that discharges induced by hyperoxia are reversible, do not cause any residual neurological damage, and clear when the partial pressure of inhaled oxygen is reduced.

Adverse reactions related to hyperbaric oxygen therapy (HBOT)

HBOT can trigger barotrauma generated by excessive pressure against the walls of closed cavities, such as the inner ear, with the risk of rupture, oedema or a tear in the tympanum (with pain and even haemorrhage), in paranasal sinuses or in the lungs, with consequent risk of pneumothorax, toothache, implosion or tooth extraction. Due to the relatively small size of certain hyperbaric chambers, patients can develop close space anxiety, not being a direct consequence of oxygen action.

Ocular toxicity

Progressive myopia has been observed in multiple hyperbaric treatments. Mechanism of its occurrence is unknown, but it is assumed to be dependent on the increase in the refraction index of the lens. Majority of cases resolved spontaneously. However, risk of irreversibility has been increased after more than 100 therapies. Upon cessation of HBOT, remission of myopathy usually is usually rapid during the first weeks and then it slows down for periods ranging from few weeks to one year.

Neither the threshold number of hyperbaric therapy sessions nor their duration can be estimated.

Paediatric population

In infants, particularly preterm babies exposed either to high oxygen concentration (FiO_2> 40%, PO_2> 80 mmHg), or for prolonged time (more than 10 days at FiO_2> 30%) there is a risk of temporary or permanent retrolental fibroplastic retinopathy (retinopathy of prematurity, see section 4.4).

The administration of oxygen modifies the quantity of oxygen conveyed and released in different tissues. An increase of local oxygen concentration, mainly its dissolved fraction, leads to an increased production of reactive oxygen species, with a subsequent increase in antioxidant enzymes or endogenous antioxidant compounds. Potential direct oxidative damage caused by oxygen should be assessed in the management of preterm babies who might experience persistent negative effects of lipid peroxidation in cell membranes. In these subjects, who still do not possess protective endogenous antioxidants, the administration of oxygen can contribute to the development of persistent pathological conditions in pulmonary parenchyma (bronchopulmonary dysplasia, pulmonary fibrosis), even leading to respiratory failure.

Risk of fire: the risk of fire increases with higher oxygen concentrations and ignition sources that can cause burns (see section 4.4).

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

	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						Pulmonary toxicity: - Tracheobronchitis (substernal pain, dry cough) - Interstitial oedema - Pulmonary fibrosis Aggravation of hypercapnia in patients with chronic hypercapnia treated wi extremely high FiO_2 • Hypoventilation • Respiratory acidosis • Respiratory failure
Eye disorders	Retinopathy of prematurity					
General disorders and						Dry mucous tissue, loc

administration site conditions						irritation and inflammation of mucos

Adverse reactions related to normobaric oxygen treatment

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 (cann 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, Hearin impaired, Acute serous otitis med Tinnitus
Gastrointestinal disorders						Nausea
Psychiatric disorders						Abnormal behaviour
Eye disorders	Progressive myopia					Reduced periphe vision; Blurred vision; Cataract*
Injury, poisoning and administration site conditions	Barotrauma (paranasal sinuses, ear, lungs, teeth etc.)					
Metabolism and nutrition disorders				Hypoglycae mia 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 the national reporting system listed in Appendix V*.

4.9 Overdose

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

The symptoms of pulmonary toxicity include tracheobronchitis (substernal pain, dry cough), interstitial oedema and poulmonary fibrosis.
The symptoms of central nervous system toxicity with BOHT include tinnitus, sight and

hearing disorders and localizedspams, 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

Medical Oxygen may be kept up to 5 years after the date stated on the cylinder.

6.4 Special precautions for storage

- The gas cylinders should be stored between -20°C and +65°C.
- The gas cylinders should be stored vertically, except gas cylinders with a convex bottom; these should be stored horizontally, or in a crate.
- The gas cylinders should be protected from falling over or from mechanical shocks, for example, by fixing the gas cylinders or placing them in a crate.
- The gas cylinders should be stored in a well-ventilated room that is exclusively used for the storage of medicinal gases. This storage room must not contain any inflammable materials.
- Gas cylinders containing a different kind of gas, or a gas that has a different composition, should be stored separately.
- Full and empty gas cylinders should be stored separately.
- The gas cylinders must not be stored near sources of heat.
- Gas cylinders must be stored covered and protected against the effects of the weather.
- Close the valves of the cylinders after use.
- Return cylinder to the supplier when empty.
- Warning notices prohibiting smoking and naked lights must be posted clearly in the storage area.
- Emergency services should be advised of the location of the cylinder storage.

6.5 Nature and contents of container

Medical Oxygen is stored in gas cylinders in a gaseous state and under a pressure of 200, 230 or 300 bar (at 15°C). The cylinders are made of steel or aluminium. The valves are made of brass, steel or aluminium.

Gas cylinders with a content of (x) litres deliver (y) m³ of oxygen at 15°C and 1 bar when filled to 200 bar.

Content in litres (x)	*1*	*2*	*5*	*10*	*20*	*30*
Number of m³ of oxygen (y)	0.212	0.425	1.125	2.12	4.33	6.37
Content in litres (x)	*50*	*4x50*	*8x50*	*12x50*	*16x50*	*20x50*
Number of m³ of oxygen (y)	10.61	42.5	85.0	127.5	170.0	212.0

Gas cylinders with a content of (x) litres deliver (y) m³ of oxygen at 15°C and 1 bar when filled to 230 bar.

Content in litres (x)	*1*	*2*	*5*	*10*	*20*	*30*
Number of m³ of oxygen (y)	0.240	0.480	1.200	2.400	4.800	7.200
Content in litres (x)	*50*	*4x50*	*8x50*	*12x50*	*16x50*	*20x50*
Number of m³ of oxygen (y)	12.00	48.00	96.00	144.0	192.0	240.0

Gas cylinders with a content of (x) litres deliver (y) m³ of oxygen at 15°C and 1 bar when filled to 300 bar.

Content in litres (x)	*1*	*2*	*5*	*10*	*20*	*30*
Number of m³ of oxygen (y)	0.308	0.616	1.54	3.08	6.16	9.24
Content in litres (x)	*50*	*4x50*	*8x50*	*12x50*	*16x50*	*20x50*
Number of m³ of oxygen (y)	15.4	61.6	123	185	246	308

Packaging	**Available sizes (l)**
Aluminium cylinder with valve with integrated pressure regulation	1, 2, 5, 10, 20, 30, 50
Steel cylinder with valve with integrated pressure regulation	1, 2, 5, 10, 20, 30, 50
Aluminium cylinder with traditional or step down valve	1, 2, 5, 10, 20, 30, 50
Steel cylinder with traditional or step down valve	1, 2, 5, 10, 20, 30, 50
Steel cylinder bundles with traditional or step down valve	4x50, 8x50, 12x50, 16x50, 20x50
Aluminium cylinder bundles with traditional or step down valve	4x50, 8x50, 12x50, 16x50, 20x50

Type of the valve	**Outlet pressure**	**Remarks**

Valve with integrated pressure regulation	4 bar (at the socket outlet)	
Traditional valve	200, 230 or 300 bar (when the gas cylinder is full)	Use only with a suitable reducing device.
“step down” valve	60-70 bar	For 300 bar cylinders only Use only with a suitable reducing device.

Gas cylinders comply with the requirements of Dir. 1999/36/EC
Colour marking conforms to EN 1089-3: white body and white shoulder.
Valves conform to the requirements of EN ISO 10297.
Traditional and step down valves conform to NEN 3268 (NL), DIN 477 (DE), BS 341-3 (UK), NBN 226 (BE), EN ISO 407, ISO 5145.
Valves with integrated pressure regulator conform also with EN ISO 10524-3.

Not all cylinder sizes may be marketed.

6.6 Special precautions for disposal

Preparation prior to use

Follow the instructions of your supplier, particularly:

- If the gas cylinder is visibly damaged, or if there is a suspicion of damage or exposure to extreme temperatures has occurred, the gas cylinder may not be used
- All contact with oil, grease or hydrocarbons must be avoided
- Remove the seal from the valve and the protective cap before use
- Only equipment suitable for use with a specific gas cylinder and that specific gas may be used
- Check that the quick connector and regulator are clean and that the connections are in good condition
- Open the cylinder valve slowly – at least half a turn
- When opening and closing the valve of a gas cylinder, no pliers or other tools must be used so as to avoid the risk of damage
- No modifications to the form of packaging must be made
- 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 outdoor. 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.

Using the gas cylinder

- The transferring of gas under pressure is prohibited.
- Smoking and open flames are strictly forbidden in rooms where treatment with medicinal oxygen takes 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 is left in the cylinder to avoid the entrance of contaminants.
- Valves of empty gas cylinders must be closed.

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

7 MARKETING AUTHORISATION HOLDER

Dolby Medical Home Respiratory Care Ltd
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FK9 4TU United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

Medical Oxygen: PL10414/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

11/11/2019