MEDICAL OXYGEN, 100% INHALATION GAS
PL 17872/0002

UKPAR

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MEDICAL OXYGEN, 100% INHALATION GAS  
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LAY SUMMARY

On 1st July 2011, the MHRA granted Medical Gas Solutions Limited a Marketing Authorisation (licence) for Medical Oxygen, 100% inhalation gas.

Medical Oxygen 100% inhalation gas is used to increase levels of oxygen in the body’s tissues. It may be used in the following circumstances:

• at high concentration when there is a reduced amount of oxygen being taken into the body through the lungs due to acute or severe asthma or lung diseases such as pulmonary thrombo-embolism (a blockage of one of the arteries in the lung), pneumonia fibrosing alveolitis (inflammation and scarring of the air sacs of the lungs) and pulmonary oedema (a disease affecting the heart).

• in low concentrations when there are breathing difficulties due to conditions such as chronic obstructive airways disease (COAD/COPD) (a collection of lung diseases caused by damage to the lungs).

• in the treatment of acute and severe asthma, sleep apnoea (a sleep disorder in which a person has irregular breathing at night and is excessively sleepy during the day), cluster headaches (attacks of severe, one sided headaches over several weeks), shock (a dramatic reduction in blood flow that, if left untreated, can lead to collapse, coma and even death) and in other situations where localised blood supply is poor.

• for resuscitation purposes by trained persons, where oxygen supply to the body is reduced due to medical emergency.

• when the oxygen capability of the blood is reduced such as in carbon monoxide poisoning or severe anaemia (a condition which occurs when there is a reduced number of red blood cells or haemoglobin concentration).

• when gas is trapped in body spaces such as in pneumothorax (air that is trapped next to a lung resulting in collapse of the lung) or air embolism or other gas disturbances such as decompression sickness (associated with diving).

• as a carrier gas or as a diluent for anaesthetic gases or vapours.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits Medical Oxygen, 100% inhalation gas outweigh the risks; hence a Marketing Authorisation has been granted.
MEDICAL OXYGEN, 100% INHALATION GAS  
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Medical Oxygen, 100% inhalation gas (PL 17872/0002) to Medical Gas Solutions Limited on 1st July 2011. This general sales list (GSL) medicine is used:

1. At high concentrations in the treatment of acute severe asthma, pulmonary thrombo-embolism, pneumonia and fibrosing alveolitis.
2. For the treatment of carbon monoxide poisoning.
3. To reduce the volume of air trapped in body cavities, as for example, in patients with pneumothorax and air embolism. Inhalation of air containing a high concentration of oxygen (and hence low concentration of nitrogen) enhances removal of trapped nitrogen.
4. As a diluent or carrier gas in anaesthesia.

This application for Medical Oxygen, 100% inhalation gas is submitted according to Article 10.a of Directive 2001/83/EC, a ‘well established use’ application.

The product is manufactured from licensed products namely Liquid Oxygen, which was licensed to Air Products PLC on 31st July 1985 (PL 06183/0001).

Oxygen is given by inhalation to correct hypoxaemia in conditions causing respiratory failure and in conditions where the oxygen content of the air breathed is inadequate such as in high-altitude disorders. Oxygen is of value in the treatment of poisoning with a number of substances, including carbon monoxide, cyanides, and dichloromethane. It provides enhanced oxygenation in inhalation injury. Oxygen is also given by inhalation to subjects working in pressurised spaces and to divers to reduce the concentration of nitrogen inhaled. It is used as a diluent of volatile and gaseous anesthetics.

No non-clinical or clinical studies have been performed and none are required for this bibliographic application as the use of medical oxygen is well-established.

A Risk Management Plan (RMP) has not been submitted and is not required for an application of this type.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Medical Oxygen, 100% inhalation gas outweigh the risks; hence a Marketing Authorisation has been granted.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
INN/Ph.Eur name: Oxygen
Chemical name: Oxygen

Physical form: Colourless, odourless and tasteless gas, in its liquid form it is a pale blue liquid
Solubility: Slightly soluble in water and soluble in alcohol.

Molecular formula: O
Molecular weight: 31.9988

Oxygen is the subject of a European Pharmacopoeia monograph.

Information has been provided covering the manufacture and control of oxygen.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls are applied. No specification has been provided for the starting material, since this is atmospheric air and the manufacturing process is physical separation, this is acceptable.

All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance, with suitable test methods and limits. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for all reference standards used.

Satisfactory specifications and Certificates of Analysis have been provided for all aspects of the container-closure system.

An appropriate retest period has been proposed based on stability data submitted for the drug substance.

DRUG PRODUCT
Other ingredients
There are no excipients.

Product development
The applicant has provided a suitable product development section. Medical oxygen is a well established, well known product; therefore a brief overview of the historic development of liquid oxygen is satisfactory.

Manufacture
A description of the manufacturing method has been provided.
In-process controls are satisfactory based on process validation data and controls on batches of the finished product. Process validation has been carried out on batches of finished product and the results appear satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis for all working standards used have been provided and are satisfactory.

**Container-Closure System**
The product is a compressed gas that is held within a pressure vessel made of a limited list of materials. These can include steel, aluminium, aluminium liners with carbon wrap on either the sides of the cylinder or all over. Cylinders are fitted with a valve, the valve can be a pin-index valve conforming to BS EN 407, a bullnose valve that complies with BS341 or an integral pressure regulator valve that is CE marked for Medical Device regulations.

The cylinders have a variety of water capacities ranging from 0.5 to 68 litres and are filled to either 137, 200 or 300 bar. This gives the following range of nominal oxygen content in litres of the cylinders at 15 C and 1013.2 mbar:


The cylinders conform to the requirements set out in the current Carriage of Dangerous Goods and the Transportable Pressure Equipment Regulations 2004 control these cylinders. All cylinders used for Medical Oxygen are designed and tested to conform to these regulations. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with EU legislation.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 36 months for the product has been set with the following storage information:

'**Storage area to be free from oil or grease. Segregate from flammable gases and other flammable materials in store. Keep container below 50° C and not subject of temperature extremes, in a well ventilated place. Keep storage area free from debris. Medical cylinders containing different gases to be segregated and identified. Medical cylinders not to be stored with other types of cylinders. Full cylinders should be used in strict rotation and full and empty cylinders separated.’**

**ADMINISTRATIVE**

**Expert Report**
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

**Summary of Product Characteristics (SPC)**
This is pharmaceutically satisfactory.
Labelling
This is pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. A satisfactory bridging report has also been provided.

MAA Form
This is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application from a quality point of view.
NON-CLINICAL ASSESSMENT

This application for Medical Oxygen, 100% inhalation gas is submitted according to Article 10.a of Directive 2001/83/EC, a ‘well established use’ application. The pharmacodynamics, pharmacokinetics and toxicological properties of oxygen are well-known. The applicant has not provided any new non-clinical data and none are required.

An overview based on literature review is, thus, appropriate.

Oxygen is a stable element that is life sustaining. It therefore poses no environmental risk.
CLINICAL ASSESSMENT

No bioequivalence studies have been performed and none are required for this application, as this is a bibliographic application and oxygen is a well-known, widely used substance. An overview based on literature review is, thus, appropriate.

CLINICAL PHARMACOLOGY

Biopharmaceutics
Oxygen is a stable gas and there is no potential for the formation of degradation products. There are no other excipients. The method of manufacture is a standard method and has been used by many medical gas manufacturers for a number of years.

PHARMACOKINETICS (PK)

Absorption
Oxygen is inhaled into the alveoli and then diffuses into the pulmonary capillary bed. The uptake from the lungs is rapid and carbon dioxide is simultaneously excreted in the expelled air.

Distribution
The delivery of oxygen to the tissues depends on arterial oxygenation, cardiac output, regional perfusion, local oxygen carriage systems and oxygen utilisation. Oxygen is carried in the blood mostly in chemical combination with haemoglobin and to a small extent in physical solution in plasma.

Metabolism
Oxygen is metabolised in all tissues, almost entirely within the mitochondria where the major oxidative enzymes are located oxygen is reduced by a series of four electron transfers in the presence of the enzyme cytochrome oxidase to form two molecules of water. The energy formed is bound by the formation of adenosine triphosphate (ATP).

Excretion
Oxygen is excreted almost entirely as carbon dioxide, via the lungs.

Drug Interactions with oxygen
Despite being a naturally occurring gas, interactions between oxygen and other substances have been reported.

Amiodarone
There is a high incidence of lung complications, including adult respiratory distress syndrome, when patients treated with amiodarone are given 100% oxygen. This has been listed in the SmPC for Medical Oxygen, 100% inhalation gas.

Bleomycin
The use of oxygen in high concentrations in bleomycin-treated patients can cause adult respiratory distress syndrome. The incidence of this can be reduced by limiting oxygen concentrations to less than 30% and carefully monitoring fluid replacement. This has been listed in the SmPC for Medical Oxygen, 100% inhalation gas.

Patients with pre-existing oxygen radical damage to the lung may have this damage exacerbated by oxygen therapy e.g. in the treatment of paraquat poisoning. Supplemental oxygen should, therefore, be kept to the minimum feasible in such conditions.
This has been listed in the SmPC for Medical Oxygen, 100% inhalation gas.

**Alcohol**
Alcohol can cause respiratory depression, potentiating that caused by oxygen. This has been listed in the SmPC for Medical Oxygen, 100% inhalation gas.

**PHARMACODYNAMICS (PD)**
The administration of supplemental oxygen will improve tissue oxygen delivery in patients with arterial hypoxaemia, provided that:
- The hypoxaemia is not due to a true right-to-left heart shunt.
- The oxygen therapy does not, itself, reduce tissue blood flow.
Oxygen therapy may decrease ventilation, heart rate and cardiac output. 100% oxygen at atmospheric pressure does not alter oxygen consumption, carbon dioxide production or the respiratory quotient in normal subjects at rest.

**Pharmacokinetic and Pharmacodynamic Conclusion**
The pharmacokinetics and pharmacodynamics of oxygen are well-known and it has been used in clinical practice for many years. The applicant did not present or claim any new information on the pharmacokinetics and pharmacodynamics of Medical Oxygen, 100% inhalation gas, and none are required. The information provided is relevant and sufficient.

**EFFICACY**
Medical oxygen can be used for the following conditions:

**Acute hypoxaemia**
Indications include pneumonia, acute severe asthma, acute exacerbations of chronic bronchitis and of emphysema, pulmonary embolism, pulmonary oedema, adult and neonatal respiratory distress syndromes, fibrosing alveolitis and diseases of the chest wall or of a neuromuscular nature. In all of these indications, except for chronic bronchitis and emphysema, high oxygen concentrations (up to 100%) are used.

**Chronic hypoxaemia**
Patients with chronic bronchitis and emphysema may benefit from long-term oxygen therapy. Ambulatory oxygen can be used to increase exercise tolerance in patients with chronic obstructive pulmonary disease (COPD).

A recent review of five randomised, controlled trials comparing domiciliary long-term oxygen therapy with control treatment in a total of 539 patients with COPD and hypoxaemia found that long-term oxygen therapy improved survival in patients with severe hypoxaemia.

**Interstitial / intracavity gas**
Oxygen gas does not show much clinical efficacy in this unless there is also hypoxaemia. Breathing high concentration oxygen will decrease the arterial oxygen tension and aid resorption of gas that has escaped to body cavities (e.g. pneumothorax).

**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%). The mortality rate in severe cases is 13.5% when oxygen above ambient pressure is initiated within 6 hours, but 30.1% when initiated later than 6 hours. Thus, the sooner oxygen above ambient pressure is initiated the better.
Anaesthesia
Oxygen is also widely used as a diluent or carrier gas to allow the creation of gas mixtures (e.g. anaesthetics) that contain no less oxygen than atmospheric air.

Oxygen can be used for many other conditions including: Chronic hypoxaemia (in patients with resting hypoxia), shock, severe anaemia, arterial gas embolism and decompression sickness, sleep apnoea, cluster headaches, severe anaerobic infections, risperatory distress syndrome and many others.

The indications listed in Section 4.1 of the SmPC for Medical Oxygen, 100% inhalation gas are:

1. At high concentrations in the treatment of acute severe asthma, pulmonary thrombo-embolism, pneumonia and fibrosing alveolitis.
2. For the treatment of carbon monoxide poisoning.
3. To reduce the volume of air trapped in body cavities, as for example, in patients with pneumothorax and air embolism. Inhalation of air containing a high concentration of oxygen (and hence low concentration of nitrogen) enhances removal of trapped nitrogen.
4. As a diluent or carrier gas in anaesthesia.

This is satisfactory.

Overall Conclusions on Clinical Efficacy
The information presented regarding the efficacy of oxygen in the proposed indications is sufficient. The use of oxygen in the proposed indications is well established and described in literature.

SAFETY
Fire
Fire risk is enormously increased by the use of high concentrations of oxygen. The risk of fire and serious burns should always be stressed to patients receiving oxygen therapy. Whilst oxygen is non-flammable, it strongly supports combustion. Thus smoking is prohibited when oxygen is in use and no naked flames should be allowed near the container. It is also very important that the reducing valve, which controls the flow rate, is free from all traces of oil and grease; otherwise there is a risk of spontaneous combustion and a violent explosion may occur.

Both of these points are listed in section 4.4 Special warnings and precautions for use in the SmPC for Medical Oxygen, 100% inhalation gas.

Adverse events
Suppression of hypoxic drive
Hypoxic drive is when the respiratory centre is depressed and ventilation is maintained by stimulation of carotid and aortic chemo-receptors, e.g. patients with severe chronic obstructive airways disease such as bronchitis and emphysema. In such patients, an acute rise in PaO₂ as a result of oxygen inhalation may further depress ventilation. This has been included in Section 4.8 Undesireable effects in the SmPC for Medical Oxygen, 100% inhalation gas.

Careful titration and monitoring of oxygen is needed to provide sufficient oxygenation without hypoventilation. High dose oxygen given to patients with chronic obstructive pulmonary disease who have type II respiratory failure can reduce the hypoxic drive to breathe and increase ventilation-perfusion mismatching. This causes carbon dioxide retention and a respiratory acidosis that may be lethal. In these patients initial treatment with low oxygen concentrations (24-28%) should be progressively increased.
This has been included in Section 4.2 Posology and method of administration, in the SmPC for Medical Oxygen, 100% inhalation gas. High concentrations of oxygen are contra-indicated in chronic severe airways disease in the SmPC for Medical Oxygen, 100% inhalation gas.

Toxicity
The two areas most affected are the central nervous system (CNS) and the lungs. Exposure to high concentrations of inspired oxygen increases the production of highly reactive metabolites of oxygen, including free radicals and hydrogen peroxide. The metabolites therefore lead to death and lysis of cells.

**Pulmonary Oxygen Toxicity**
Toxicity is likely to occur sooner as the inspired oxygen pressure (PO2) increases. Below 0.5 atmospheres, no harm appears to occur with indefinite exposure. Between 0.5 and 2 atmospheres, pulmonary toxicity occurs after prolonged exposure. After constant exposure for over 24 hours, death can follow a week later from pulmonary oedema and hypoxia. There are no current effective means to prevent or lessen pulmonary oxygen toxicity, other than decreasing the oxygen concentration and providing supportive measures. Segmental collapse associated with paediatric bronchography has also been reported [0]. This is thought to be due to the rapid absorption of anaesthetic gases (halothane and oxygen) combined with partial bronchial block caused by the contrast medium (particularly, aqueous medium).
This has been included in Section 4.9 Overdose, in the SmPC for Medical Oxygen, 100% inhalation gas.

**CNS Oxygen Toxicity**
Above 2 atmospheres CNS toxicity occurs. Mood changes, nausea, dizziness and convulsions resembling grand mal fits have been associated with breathing 100% oxygen at pressures over 2 atm. When 80,679 patient-treatments for 9 clinical indications were retrospectively evaluated, only 2 seizures attributable to CNS oxygen toxicity were documented, yielding an incidence of 2.4 per 100,000 patient-treatments. This concluded that the risk of seizures due to CNS oxygen toxicity during hyperbaric oxygen therapy is very low as long as appropriate exclusion criteria and treatment profiles are used.
This has been included in Section 4.8 Undesirable effects, in the SmPC for Medical Oxygen, 100% inhalation gas.

**Toxicity in premature infants**
Oxygen causes tissue injury through the formation of reactive oxygen intermediates and peroxidation of membrane lipids. Premature infants, who have severely reduced antioxidant defences, are particularly sensitive to the toxic effects of oxygen. Overexposure to oxygen in premature infants contributes to the development of chronic lung disease (bronchopulmonary dysplasia), subependymal and intraventricular haemorrhage and necrotising enterocolitis. Exposure of neonates to high concentrations of oxygen may cause retrolental fibroplasia (retinopathy of prematurity) and if continued, may lead to blindness. The problem may be prevented by careful titration of oxygen concentrations. These conditions have been included in Section 4.8 Undesirable effects in the SmPC for Medical Oxygen, 100% inhalation gas.
High concentrations of oxygen are contra-indicated in this patient population in the SmPC for Medical Oxygen, 100% inhalation gas.
Generally, two situations cause adverse effects whilst using Medical Oxygen, 100% inhalation gas.
  • Where exposure is to a high concentration of oxygen for a prolonged period.
  • Where exposure is to oxygen above ambient pressure.

Patients with chronic obstructive airways disease and neonates are at particular risk from exposure to high concentrations of oxygen. There is also a risk of fire. Warnings regarding all of these have been included in the SmPC for Medical Oxygen, 100% inhalation gas.

Post Marketing
Very few adverse events with Medical Oxygen have been reported. However, about 4 fires per year in the UK are caused by patients smoking whilst receiving oxygen therapy. The risk of fire has been included in the SmPC for Medical Oxygen, 100% inhalation gas.

The applicant does not propose any additional measures for risk management following Marketing Authorisation nor any additional post marketing surveillance measures. Oxygen has a well known safety profile and no additional measures are expected. The proposed approach is acceptable.

Overall Conclusions on Safety Efficacy
The supplied description of the potential side-effects in the SmPC is comprehensive and in-line with the published literature. The applicant did not make any new safety related claims. Oxygen is a substance with well known safety profile. The presented information is acceptable.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
These are clinically satisfactory.

APPLICATION FORM (MAA)
This is satisfactory.

DISCUSSION
In view of the literature review submitted, the benefits of Medical Oxygen, 100% inhalation gas outweigh the risks.

CONCLUSION
It is recommended that a Marketing Authorisation is granted for this application from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Medical Oxygen, 100% inhalation gas are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
The pharmacology, pharmokinetics and toxicology of oxygen are well-known. No new or unexpected safety concerns arise from this application.

EFFICACY
Oxygen is a well-known substance and has been used for many years. The information presented regarding the efficacy of oxygen in the proposed indications is sufficient. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The data submitted supports the claim that the applicant’s product is of a well-known substance. Extensive clinical experience with oxygen is considered to have demonstrated its therapeutic value. The benefit/risk for the indications proposed is, therefore, considered to be positive.
# STEPS TAKEN FOR ASSESSMENT

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<td>The MHRA received the marketing authorisation application on 16th August 2005.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 24th November 2005.</td>
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<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the quality dossier on 8th March 2006, 30th November 2007 and 14th January 2009.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 14th January 2009, 30th June 2010 and 20th December 2010 for the quality section.</td>
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<td>The application was determined on 1st July 2011.</td>
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Medical Oxygen, 100% inhalation gas

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Oxygen Ph Eur 100%v/v
Consists solely of compressed oxygen conforming to the requirements of the monograph of the European Pharmacopoeia.
There are no other ingredients

3 PHARMACEUTICAL FORM
Inhalation Gas
A colourless, odourless and tasteless gas supplied under pressure in cylinders

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
At high concentrations in the treatment of acute severe asthma, pulmonary thrombo-embolism, pneumonia and fibrosing alveolitis.
For the treatment of carbon monoxide poisoning.
To reduce the volume of air trapped in body cavities, as for example, in patients with pneumothorax and air embolism. Inhalation of air containing a high concentration of oxygen (and hence low concentration of nitrogen) enhances removal of trapped nitrogen.
As a diluent or carrier gas in anaesthesia.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Posology
High concentration oxygen therapy, with concentrations up to 60% for short periods is safe for conditions like pneumonia, pulmonary thrombo-embolism and fibrosing alveolitis. Low concentration (controlled) oxygen therapy should be used in patients with ventilatory failure due to chronic obstructive airways disease and other causes. The concentration should not exceed 28% and even 24% may be excessive in some patients.

Oxygen may be administered at concentrations of up to and including 100% though with most delivery systems inspired concentrations over 60% (80% in children) are unlikely to be achieved. In practice 30% is usually taken as the lower limit, with allowance for a safety margin. The dosage is adapted to the patient on the basis of the clinical course of the illness and generally ranges from 1 to 10 litres of gas per minute.

Systems for longer-term oxygen therapy usually rely on a mixture of air and additional oxygen being supplied.

Care should be taken to prevent rebreathing of expired carbon dioxide. With vented face masks and flow rates over 4 litres/minute this should rarely be a problem.

In an emergency a doctor may need to administer doses considerably higher to patients with severe breathing difficulties. Such doses may be up to 60 litres per minute, controlled by special flowmeters.

Other systems of administration include face tents, headboxes, cot hoods and supply to a tracheostomy. In severe hypoxia the use of a positive pressure mask may be valuable. This technique should only be used by experienced practitioners.

Method of administration
Medical Oxygen is administered via inspiratory air.
Masks, nasal cannulae, etc. can provide fixed or variable mixtures depending on their design. In circumstances where oxygen is not being mixed with air, but is mixed with other gases (e.g. anaesthetics and analgesics) then it is essential that the proportion of oxygen in the inspired mixture never falls below the concentration in air. In practice 30% is usually taken as a lower limit, with allowance for a safety margin.
Instructions for Use

GENERAL
- All personnel handling gas cylinders or being responsible for pipeline gas supplies should have adequate knowledge of the properties of the gas, precautions to be taken, actions in the event of any emergency and the correct operating procedures for their installation.
- If you own your own cylinders, you must be aware of and discharge your statutory obligations with regard to maintenance and testing.
- Ensure that when cylinders are collected the driver has been properly instructed in the method of handling cylinders and in dealing with any emergency.

STORAGE OF CYLINDERS
- Cylinders should be stored under cover, preferably inside, kept dry and clean and not subjected to extremes of heat or cold.
- Cylinder should not be stored near stocks of combustible materials or near sources of heat.
- Warning notices prohibiting smoking or naked lights should be posted clearly.
- Emergency services should be advised of the location of the cylinder store.
- Medical cylinders containing different gases should be segregated within the store.
- Full and empty cylinders should be stored separately. Full cylinders should be used in strict rotation.
- Medical cylinders should be stored separately from industrial and other non-medical cylinders.
- Cylinders must not be repainted, have any markings obscured or labels removed.
- Precautions should be taken to protect cylinders from theft.

PREPARATION FOR USE
- Cylinder valves must be opened slowly.
  1. Cylinder valves should be opened momentarily prior to use to blow any grit or foreign matter out of the outlet.
     a. Ensure that the connecting face of the pin index yoke, or regulator is clean and the sealing washer or ‘O’ ring where fitted is in good condition.
  2. Where an integral valve is not used only the appropriate regulator should be used for the particular gas concerned.
- Pipelines for medical gases should be controlled in accordance with the conditions set out in HTM 02.
- Cylinder valves and any associated equipment must never be lubricated and must be kept free from oil and grease.

LEAKS
1. Should leaks occur, this would usually be evident by a hissing noise.
2. Leaks can be found by brushing the suspected area with an approved leak detection solution
3. Sealing or joining compounds must never be used to cure a leak.
4. Never use excessive force when connecting equipment to cylinders.

USE OF CYLINDERS
1. Cylinders should be handled with care and not knocked violently or allowed to fall.
2. Cylinders should only be moved with the appropriate size and type of trolley.
3. When in use, cylinders should be firmly secured to a suitable cylinder support.
4. Medical gases must only be used for medicinal purposes.
5. Smoking and naked lights must not be allowed within the vicinity of cylinders or pipeline outlets.
6. After use, cylinder valves should be closed using moderate force only and the pressure in the regulator or tailpipe released.
7. When empty, the cylinder valve must be closed.
8. Immediately return empty cylinders to the empty cylinder store for return to Medical Gas Solutions Ltd.

4.3 CONTRAINDICATIONS
1. High concentrations of oxygen are contra-indicated in chronic severe airways disease and premature neonates
2. Patients should not smoke while on oxygen therapy because of the fire risks

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Patients with chronic severe obstructive airways disease rely on hypoxic drive for respiration. When such patients are given oxygen therapy it must be administered at a relatively low concentration and must be accurately metered and titrated against arterial concentrations and clinical observation. Connections for hoses, valves etc. must be clean and dry. If necessary, clean only with plain water. Do not use solvents. Use clean, lint free cloths for cleaning and drying off. Use no oil or grease on valve or associated equipment. Do not allow naked flames near the container. Do not smoke when using oxygen. Do not breathe oxygen at pressures in excess of atmospheric.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
Interactions with amiodarone have been reported. Relapse of bleomycin-induced lung disease may be associated with a fatal outcome. Patients with pre-existing oxygen radical damage to the lung may have this damage exacerbated by oxygen therapy e.g. in the treatment of parquat poisoning. Respiratory depression due to alcohol may potentiate that caused by oxygen.

4.6 PREGNANCY AND LACTATION
There are no contraindications for oxygen therapy during pregnancy or breast-feeding or any effect on fertility that is known.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Oxygen therapy at ambient pressure has no adverse effect on the ability of the patient to drive and operate machinery.

4.8 UNDESIRABLE EFFECTS
In patients with chronic severe airway disease who rely on hypoxic drive of respiration, the administration of high levels of oxygen will result in further under-ventilation and further accumulation of carbon dioxide and acidosis. In the premature infant exposure to excessive oxygen concentrations may be associated with the following conditions: retrolental fibroplasia, bronchopulmonary dysplasia, subependymal and intraventricular haemorrhage and necrotising enterocolitis. CNS oxygen toxicity only occurs when the partial pressure of inspired oxygen exceeds 2 atmospheres (203 kPa), that is in hyperbaric oxygen therapy. Hyperbaric oxygen treatment has been shown in some studies to be linked with hyperbaric Oxygen-induced oxidative DNA damage that can lead to gross genetic alterations and chromosome aberrations after hyperbaric oxygen under therapeutic conditions. It has also been shown that a single hyperbaric oxygen exposure induced adaptive protection against further induction of oxidative DNA damage. Cases must be assessed individually and the therapy protocol may consider a shortened treatment before the standard protocol is applied.

4.9 OVERDOSE
Prolonged hyperoxygenation can result in lung injury. Cases must be assessed individually, but experience from healthy volunteers would suggest that prolonged exposure, over periods of months, to concentrations up to 30% whilst producing sub-clinical pathologic changes has not been proven to cause specific lung injury. Similarly for exposures up to 60% for up to one week. However administration of 100% oxygen for more than 24 to 30 hours will result in substernal chest pain and mild dyspnoea. Symptoms may progress, become systemic and include malaise, nausea and transient paraesthesia. See section 4.8 for the effects of overdose in specific patient groups.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic Group - Medical Gas. ATC Code - V03AN01.

The characteristics of medical oxygen are: odourless, colourless gas.
Oxygen is present in the atmosphere at 21% and is an essential for life. Oxygen must be supplied continuously to all body tissues in order to maintain the cells’ energy production. Oxygen is transported via the airways to the lung with the inspired air. Gas exchange takes place in the alveoli through the difference in partial pressure from the inspired air/gas mixture to the capillary blood. The oxygen is transported in the blood, mainly bound to haemoglobin, to the capillary bed in tissue where it is transported by the pressure gradient to the difference cells. In the mitochondria in the individual cells the oxygen is consumed in an enzymatic chain reaction forming energy. By increasing the oxygen fraction in inspired air the partial pressure gradient transporting oxygen to the cells is increased.

5.2 PHARMACOKINETIC PROPERTIES
The inhaled oxygen is taken up by a pressure dependent gas exchange between alveoli gas and the capillary blood that passes the alveoli. The oxygen is transported to all tissues in the body. A partial pressure dependent transport of the oxygen to the individual cells takes place. Oxygen is a vital component in the cell’s intermediate metabolism for the creation of energy (the aerobic ATP production in the mitochondria).

5.3 PRECLINICAL SAFETY DATA
The published toxicological-pharmacological data indicates that medical oxygen is not harmful to humans.

6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
There are no excipients.

6.2 INCOMPATIBILITIES
There are no known incompatibilities with oxygen.

6.3 SHELF LIFE
36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Storage area to be free from oil or grease. Segregate from flammable gases and other flammable materials in store. Keep container below 50°C and not subject of temperature extremes, in a well ventilated place. Keep storage area free from debris. Medical cylinders containing different gases to be segregated and identified. Medical cylinders not to be stored with other types of cylinders. Full cylinders should be used in strict rotation and full and empty cylinders separated.

6.5 NATURE AND CONTENTS OF CONTAINER
Medical Oxygen Ph Eur 100% is a compressed gas that is held within a pressure vessel made of a limited list of materials. These can include steel, aluminium, aluminium liners with carbon wrap on either the sides of the cylinder or all over. The cylinders conform to the requirements set out in the current Carriage of Dangerous Goods and the Transportable Pressure Equipment Regulations 2004 control these cylinders. All cylinders used for Medical Oxygen are designed and tested to conform to these regulations.

Medical Oxygen cylinders are fitted with a valve, the valve can be a pin-index valve conforming to BS EN 407, a bullnose valve that complies with BS341 or an integral pressure regulator valve that is CE marked for Medical Device regulations.

The cylinders have a variety of water capacities ranging from 0.5 to 68 litres and are filled to either 137, 200 or 300 bar.

This gives the following range of nominal oxygen content in litres of the cylinders at 15°C and 1013.2 mbar:

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Contact Medical Gas Solutions to refill the cylinder. Any cylinders that are no longer required should be returned to Medical Gas Solutions.
7  MARKETING AUTHORISATION HOLDER
Medical Gas Solutions Ltd
Unit 19 Manor Industrial Park
Bagillt
Flint. CH6 5UY

8  MARKETING AUTHORISATION NUMBER(S)
PL 17872/0002

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
01/07/2011

10  DATE OF REVISION OF THE TEXT
01/07/2011
Medical Oxygen 100% Inhalation Gas - Patient Information Leaflet

Read all of this leaflet carefully because it contains important information for you. Keep this leaflet, you may need to read it again. Ask your pharmacist or doctor if you need more information or advice.

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1. What is Medical Oxygen 100% Inhalation Gas and what it is used for?

Medical Oxygen 100% Inhalation Gas is a breathed in (inhalation) gas. It is colourless, odourless and tasteless. It is supplied under pressure in a cylinder with a valve to control the flow of gas. A variety of cylinder sizes are available.

What Medical Oxygen 100% Inhalation Gas is used for?

Medical Oxygen 100% Inhalation Gas is used to increase levels of oxygen in the body's tissues. It may be used in the following circumstances:

- at high concentration when there is a reduced amount of oxygen being taken into the body through the lungs due to acute or severe asthma or lung diseases such as pulmonary thrombo-embolism (a blockage of one of the arteries in the lung), pneumonia fibrosing alveolitis (inflammation and scarring of the air sacs of the lungs) and pulmonary oedema (a disease affecting the heart)
- in low concentrations when there are breathing difficulties due to conditions such as chronic obstructive airways disease (COPD) (a collection of lung diseases caused by damage to the lungs)
- in the treatment of acute and severe asthma, sleep apnoea (a sleep disorder in which a person has irregular breathing at night and is excessively sleepy during the day), cluster headaches (attacks of severe, one sided headaches over several weeks), shock (a dramatic reduction in blood flow that, if left untreated, can lead to collapse, coma and even death) and in other situations where localised blood supply is poor
- for resuscitation purposes by trained persons, where oxygen supply to the body is reduced due to medical emergency
- when the oxygen capability of the blood is reduced such as in carbon monoxide poisoning or severe anaemia (a condition which occurs when there is a reduced number of red blood cells or haemoglobin concentration)
- when gas is trapped in body spaces such as in pneumothorax (air that is trapped next to a lung resulting in collapse of the lung) or air embolism or other gas disturbances such as decompression sickness (associated with diving)
- as a carrier gas or as a diluent for anaesthetic gases or vapours.

2. Before you use Medical Oxygen 100% Inhalation Gas

Interactions with other medicines, medical conditions or diseases

Interactions with other medicines are unlikely when used as directed. However, it is important that you tell your doctor if you are taking, or have recently taken, any other medicine – even those not prescribed. Unless specially advised by your doctor to do so, do not use Medical Oxygen 100% Inhalation Gas if:

- you are taking or have recently taken aminodarone (used to treat irregular heart beat) or bleomycin (given as an injection or drip to treat some types of cancer)
- you have a Chronic Obstructive Pulmonary Disease (COPD) (a collection of lung diseases caused by damage to the lungs).

Take special care with Medical Oxygen 100% Inhalation Gas

Care is needed in the handling and use of Medical Oxygen 100% Inhalation Gas. You must follow your doctor’s instructions.

Fire Risks:

- do not smoke or allow those near you to smoke during treatment with Medical Oxygen 100% Inhalation Gas smoking during oxygen treatment has caused serious injuries and can prove fatal.
- do not allow naked flames in the area where you are using your Medical Oxygen 100% Inhalation Gas, since even the smallest spark can cause violent ignition; electrical equipment capable of sparking (including toys which may produce sparks) must not be used where you are using your Medical Oxygen 100% Inhalation Gas.

Medical Risks:

- if oxygen is being used for a premature or newborn infant, they must receive a carefully monitored dose of oxygen. Giving too much oxygen can damage their sight
- if you have a chronic obstructive airway disease you must receive a carefully monitored dose of oxygen
- although Medical Oxygen 100% Inhalation Gas is necessary for patients with lung damage due to poisons such as paracetamol (a type of weed killer), it may worsen the lung injury; the dose must be monitored carefully

Taking Alcohol and Other Risks

- a slowing down in your breathing caused by drinking alcohol may be made worse by the use of Medical Oxygen 100% Inhalation Gas
- do not breathe Medical Oxygen 100% Inhalation Gas at pressures higher than atmospheric pressure.

Special Circumstances:

Pregnancy

Medical Oxygen 100% Inhalation Gas can be used if you are pregnant, however, seek medical advice before taking any medicine.

Premature/Newborn Babies

Medical Oxygen 100% Inhalation Gas for premature or newborn babies should only be taken under the direction of a qualified medical person.

Breast-feeding

Medical Oxygen 100% Inhalation Gas can be used if you are breast-feeding, however, seek medical advice before taking any medicine.

Driving and using machines
Non-continuous use of Medical Oxygen 100% Inhalation Gas at atmospheric pressure will not affect your ability to drive or operate machinery. However, if you are using oxygen continuously you must be assessed by your doctor.

3. How to use Medical Oxygen 100% Inhalation Gas

Medical Oxygen 100% Inhalation Gas will be administered via inhalation and you will be given a facemask, mouthpiece or nasal cannula (prongs) to use which are connected to Medical Oxygen 100% Inhalation Gas via a suitable medical device. The device must be operated in the manner described by the manufacturer. The amount of oxygen you will receive is controlled by the type of equipment that you are supplied with and the flow rate. You must use the flow rate prescribed by your doctor and the equipment provided.

The flow rate of oxygen used in your treatment will depend on the conditions it is being used to treat. Your doctor will tell you how much oxygen you should use per day and how long your treatment with Medical Oxygen 100% Inhalation Gas is likely to last.

Other systems used to administer oxygen include face tents, headboxes, cot hoods, a positive pressure mask or supply to a tracheotomy. These systems will only be used to give you oxygen under the direct supervision of attendant and suitably trained medical personnel.

Connections for hoses, valves etc. must be kept clean and dry. If necessary clean only with plain water. Do not use solvents. Use clean, lint free cloths for cleaning and drying off. Do not use oil or grease on any oxygen equipment.

Premature/Newborn Babies

Medical Oxygen 100% Inhalation Gas for premature or newborn babies should only be taken under direction of a qualified medical person.

If you use more Medical Oxygen 100% Inhalation Gas than you should:

If you may have used more Medical Oxygen 100% Inhalation Gas than you should, talk to a doctor or pharmacist as soon as possible. However, it is very unlikely that an over dose will occur.

Using 100% Medical Oxygen 100% Inhalation Gas continuously for more than a day may produce chest pain and difficulties in breathing. Such a concentration is likely only to be achieved using specialised (hospital) equipment.

Using Medical oxygen 100% Inhalation Gas at pressure higher than atmospheric may lead to convulsions. This is only likely to occur in specialised circumstances when using decompression units, high altitude mountaineering or diving.

Withdrawal

There are no additional side-effects from withdrawal of oxygen.

4 Possible side effects.

Like all medicines Medical Oxygen 100% Inhalation Gas can have side effects. The toxicity of Medical Oxygen 100% Inhalation Gas depends upon both the pressure (concentration) of Medical Oxygen 100% Inhalation Gas that is breathed in and the amount of time that it is used for. The higher the pressure that Medical Oxygen Inhalation Gas is breathed in at, the shorter the time that it can safely be used for.

Side-effects may include:

- giving too much oxygen in newborn and premature infants can damage their sight and may be associated with other damage (these conditions have more than one cause and can occur even in the absence of oxygen therapy)
- lung damage from prolonged giving too much oxygen – symptoms include shortness of breath, cough and chest discomfort
- central nervous system toxicity if Medical Oxygen 100% Inhalation Gas is breathed in at pressures of twice atmospheric pressure or more as in hyperbaric oxygen therapy. This would normally only occur in specialist hospital treatment. Symptoms could include nausea, mood changes, vertigo, twitching, convulsions and loss of consciousness.

If you notice any side effects not mentioned in this leaflet please inform your doctor or pharmacist.

5. How to Store Medical Oxygen Inhalation Gas

Check the date given on the batch label attached to the cylinder. Do Not Use Medical Oxygen 100% Inhalation Gas after the expiry date given on the label.

Medical Oxygen 100% Inhalation Gas is supplied in cylinders as a gas

1. Keep Medical Oxygen 100% Inhalation Gas out of the reach and sight of children.
2. Medical Oxygen 100% Inhalation Gas should be stored securely in a well-ventilated place, under cover and kept clean and dry.
3. Medical Oxygen 100% Inhalation Gas must be stored at temperatures below 50°C and they should preferably be stored between 10°C and 30°C.
4. Medical Oxygen 100% Inhalation Gas must be stored separately from other medical gases and non-medical gases.

6. Further information

The name of your medicine is Medical Oxygen 100% Inhalation Gas, commonly named as Oxygen Inhalation Gas.

The active substance is Oxygen Ph. Eur., Minimum Purity 99.5% v/v.

Medical Oxygen 100% Inhalation Gas is supplied as a gas in cylinders. These contain compressed gas. The cylinder label gives the amount of oxygen provided by the cylinder when it is used at normal atmospheric pressure.

Further information on handling and using Medical Oxygen Inhalation Gas is available from Medical Gas Solutions

The Manufacturer and Marketing Authorisation holder is:
Medical Gas Solutions Ltd. Unit 19, Manor Industrial Estate, Bagilith, Flintshire, CH6 5UY
Manufacturing Authorisation Number MIA No. 17872
Marketing Authorisation Number PL 17872/0002

This leaflet was prepared for approval June 2011
Medical Oxygen, 100% Inhalation Gas
Oxygen Ph. Eur.

1072. OXYGEN, COMPRESSED, 2.2 (5.1)

- STRONGLY SUPPORTS COMBUSTION
- STORE CONTAINER UNDER COVER IN A WELL VENTILATED PLACE AWAY FROM EXTREMES OF HEAT AND COLD
- KEEP CLEAN AND DRY
- KEEP AWAY FROM COMBUSTIBLE MATERIAL

Special Precautions
Care is needed in the handling and use of medical oxygen gas cylinders. Do not smoke or allow those near you to smoke during treatment with medical oxygen. Smoking during oxygen treatment has proved fatal (due to fire and burns) to more than one patient.
Do not breathe medical oxygen at pressures higher than atmospheric.
If you have a chronic obstructive airway disease you should only receive a carefully monitored dose of oxygen. Carefully follow your doctor’s instructions.
Medical oxygen may increase any depression of respiration caused by alcohol- making it more difficult for you to breathe.
Although oxygen is necessary for patients having lung damage due to poisons such as paraquat, it may worsen the lung injury. The dose should be monitored carefully.

Storage Instructions
Cylinders should be stored under cover, preferably inside, kept dry and clean and not subjected to extremes of heat or cold.
Cylinders should not be stored near stocks of combustible materials or near sources of heat.
Warning notices prohibiting smoking and naked lights must be posted clearly.
Emergency services should be advised of the location of the cylinder store.
Medical cylinders containing different gases should be segregated within the store.
Full and empty cylinders should be stored separately. Full cylinders should be used in strict rotation.
Medical cylinders should be stored separately from industrial and other non-medical cylinders.
Cylinders must not be repainted, have any markings obscured or labels removed.
10 litre size cylinders and larger should be stored vertically. 5 litre size cylinders and smaller should be stored horizontally.
Precautions should be taken to protect cylinders from theft.

Volume of Product: .......... litres @ 15°C 1 atm