IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1075/001/001
Case No: 2062990

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Air Products Ireland Limited

Unit 950, Western Industrial Est, **Killeen Road**, **Dublin 12**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Medical Oxygen. Inhalation Gas. Minimum Purity 99.5%v/v

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **10/09/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Medical Oxygen. Inhalation Gas. Minimum Purity 99.5 % v/v

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Oxygen. Minimum Purity 99.5% v/v.

3 PHARMACEUTICAL FORM

Inhalation Gas
A colourless odourless gas.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

- At high concentrations in the treatment of acute severe asthma, pulmonary thrombo-embolism, pneumonia and fibrosing alveolitis.
- At low concentrations in the treatment of ventilatory failure due to chronic obstructive airways disease and other causes.
- For the treatment of carbon monoxide poisoning.
- To reduce the volume of air trapped in body cavities, as for example, in patients with pneumothorax, air embolism and decompression sickness. Inhalation of air containing a high concentration of oxygen (and hence low concentration of nitrogen) enhances removal of trapped oxygen.
- Pulmonary oedema.
- As a diluent or carrier gas in anaesthesia.
- Other indications include cystic fibrosis, shock, severe anaemia, sleep apnoea, cluster headaches and anaerobic infections.

4.2 Posology and method of administration

High concentration oxygen therapy, with concentrations up to 60% for short periods is safe for conditions like acute severe asthma, pulmonary thrombo-embolism, pneumonia 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%.

Oxygen may be administered at concentrations of up to and including 100% although with most delivery systems inspired concentrations over 60% (80% in children) are unlikely to be achieved. In practice 24% 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. 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 bellow the concentration in air. In practice 30% is usually taken as a lower limit, with allowance for a safety margin.

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.

4.3 Contraindications

Oxygen supports combustion and smoking should be prohibited when oxygen is in use and no naked flames should be allowed.

4.4 Special warnings and precautions for use

There are no absolute contraindications to the use of oxygen but inspired concentrations should be limited in the case of premature infants and those patients with chronic airways disease.

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.
There is need to limit inspired oxygen concentrations in premature infants because of the risk of retinopathy of prematurity.

High concentrations of oxygen should always be reduced as soon as possible to the lowest concentrations needed to correct hypoxia, in order to prevent the development of any associated oxygen toxicity.

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 the cylinder 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.

In spite of the various hazards associated with oxygen the benefits of treatment will often far outweigh the risks. Those risks can be minimised by titrating oxygen supply to the needs of the individual patient.

The danger of oxygen and fire cannot be over-emphasied. 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 flame should be allowed. Since even the smallest spark can cause violent ignition, electrical equipment capable of sparking (including even toys which may produce sparks) should not be used in the vicinity of patients receiving oxygen.

It is very important also that the reducing valve that controls the flow rate is free from all traces of oil and grease since otherwise there is a risk of spontaneous combustion and a violent explosion may occur.

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 paraquat 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.

4.7 Effects on ability to drive and use machines

In normal circumstances, oxygen does not interfere with conscious level but patients who require continuous oxygen support will require individual assessment as to their ability to drive or 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 intraventicular haemorrhage and necrotising enterocolotis.

In hyperbaric chambers in the management of conditions such as cabon monoxide poisoning, anaerobic infections and acute ischaemic diseases, convulsions and other central nervous system (CNS) effects may occur at 2 atmospheres or more, after a few hours exposure to pure oxygen. At higher pressures more rapid onset of CNS symptoms will occur.

Oxygen toxicity depends upon both the inspired pressure (a function of concentration and barometric pressure) and the duration of exposure, the safe duration decreasing as the pressure increases.

At lower pressures of up to 2 atmospheres absolute, pulmonary toxicity occurs before CNS toxicity; at higher pressures the reverse applies. Symptoms of pulmonary toxicity include a decrease in vital capacity, cough and substernal distress. Symptoms of CNS toxicity include nausea, mood changes, vertigo, twitching, convulsions and loss of consciousness. Retinopathy of prematurity (retrolental fibroplasia) has been associated in some premature infants with excessive oxygen therapy.

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

The characteristics of oxygen are:

Odourless, colourless gas.
Molecular weight 32.00

Boiling point	-183.1 degrees Celsius (at 1 bar)
Density	1.355kg/m3 (at 15° Celsius)

Oxygen is present in the atmosphere at 21% and is an absolute necessity for life.

The basal oxygen consumption in man is about 250ml/min for a body surface of 1.8sq metres. It is reduced by about 10% during anaesthesia and natural sleep and by about 50% for a 10 degree Celsius fall in body temperature.

Alveolar air contains about 15% oxygen at 14 kpa (105mm Hg) and arterial blood has an oxygen tension of 13 kpa (97mm Hg).

The difference, known as the alveolar-arterial oxygen tension gradient, increases with age. The difference may be as great as 4kpa (30mm Hg) in a healthy, elderly individual.

Oxygen in the blood is mostly combined with haemoglobin. Normally, haemoglobin in arterial blood is 97% saturated and the oxygen content of the blood is 19.8 vol%, 0.3ml of this being carried in solution. The remainder is held in chemical combination with haemoglobin.

The concept of oxygen availability can be expressed as the product of the cardiac output and the oxygen content of the blood.

The average healthy individual with a basal oxygen consumption has no more than 4 minutes supply of oxygen in the blood.

5.2 Pharmacokinetic properties

The uptake of oxygen by the blood in the lungs and discharge to the tissues is determined by the oxygen dissociation curve. The characteristic sigmoid shape ensures that, at tensions between 5kpa (40mm Hg) and 2kpa (15mm Hg) the oxygen carried in the blood from the lungs can readily be given up to the tissues.

The uptake from the lungs is rapid because blood flow through the capillaries, where the exchange takes place, occurs in about 0.5 seconds. The uptake of oxygen is favoured by the simultaneous loss of carbon dioxide which is then excreted in the expired air. Conversely, the entry of carbon dioxide into the blood from the tissues facilitates oxygen transfer to the cells.

At rest, mixed venous blood returning to the lungs contains 13-14ml of oxygen per 100ml, but with severe exercise, the oxygen content may fall to 3-4ml. In very active tissue, almost complete extraction occurs.

5.3 Preclinical safety data

Experience of oxygen therapy has largely derived from experience in man. Thus, whilst there obviously have been laboratory studies, there are no formal ‘pre-clinical’ observations to report.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

There are no known incompatibilities with oxygen.

6.3 Shelf Life

Three years.

6.4 Special precautions for storage

1. Medical oxygen should be stored securely in a well-ventilated place, under cover and kept clean and dry.
2. Cylinders should be stored where they will not be exposed to extremes of temperature.
3. Cylinders should be stored at temperatures below 50^{o}C, they should preferably be stored between 10^{o}C and 30^{o}C.
4. Full cylinders should be stored separately from empty cylinders.
5. Medical oxygen cylinders should be stored separately from non-medical cylinders and from other medical cylinders containing different gases.
6. Cylinders up to 5 litres in size should be stored horizontally; larger cylinders should be stored vertically.
7. Cylinders should be used in strict rotation with the oldest cylinder being used first.

6.5 Nature and contents of container

Cylinder

The base materials of the cylinder are steel or aluminium.

Steel cylinder

This is of high strength chromium molybdenum steel alloy construction. The quality and heat treatment of this metal is such that the cylinder can withstand greater pressure than a cylinder of inferior steel of the same weight.

Aluminium cylinder

This is of high strength aluminium alloy construction. Cylinders of this material, due to its relatively lightweight, are preferred for ambulatory uses and applications where portability is required. There are two variations:

a. A cylinder entirely of aluminium alloy.
b. A cylinder of aluminium alloy over wrapped with windings of high strength fibre on the parallel section of the basic aluminium cylinder, the additional strength provided by the additional wrapping reduces the cylinder weight further. In either variation the oxygen product is only in contact with the aluminium alloy of the cylinder.

Cylinders are colour coded in accordance with BS 1319C.

The valve

a. Pin index.
b. Bull nose.
c. Integral valve combining the functions of isolation of the cylinder contents, provision of a 3 bar regulated outlet pressure, provision of a range of calibrated flow rates, qualitative indication of the cylinder content, relief valve for the protection of low pressure equipment in the event of a regulator failure.

The guard

Cylinders with a nominal water capacity of greater than 5 litres are fitted with a valve guard. The function of the guard is to protect the valve from being inoperable or shearing of in the event of an impact to the valve.

The following is a list of the nominal oxygen content in litres of the cylinders at 15 C and 1013.2 mbar:
74, 81, 88, 97, 103, 107, 113, 118, 129, 132, 145, 147, 150, 154, 161, 162, 171, 176, 177, 184, 185, 191, 193, 201, 206, 210, 214, 216, 221, 226, 235, 236, 242, 247, 250, 257, 258, 265, 268, 274, 277, 279, 290, 294, 300, 306, 308, 309, 322,

323, 338, 339, 343, 353, 355, 364, 368, 370, 371, 382, 385, 386, 387, 397, 401, 403, 407, 412, 419, 426, 429, 432, 435, 441, 450, 451, 456, 462, 467, 470, 472, 484, 485, 493, 500, 514, 515, 516, 524, 529, 532, 536, 544, 548, 555, 557, 559, 564, 573, 579, 580, 586, 588, 596, 600, 603, 613, 617, 622, 629, 632, 643, 645, 647, 661, 662, 665, 676, 677, 678, 686, 691, 693, 706, 707, 709, 720, 725, 729, 735, 740, 741, 750, 758, 764, 771, 772, 774, 779, 790, 793, 794, 802, 806, 809, 815, 822, 823, 832, 836, 838, 853, 854, 857, 863, 867, 870, 879, 882, 887, 894, 897, 900, 903, 911, 919, 922, 925, 926, 935, 941, 943, 951, 956, 965, 967, 970, 983, 985, 986, 987, 999, 1000, 1007, 1014, 1015, 1017, 1029, 1032, 1044, 1048, 1050, 1058, 1064, 1072, 1073, 1079, 1080, 1088, 1093, 1096, 1103, 1110, 1112, 1115, 1117, 1128, 1132, 1136, 1141, 1144, 1147, 1158, 1161, 1172, 1176, 1177, 1179, 1191, 1193, 1200, 1202, 1205, 1209, 1220, 1222, 1225, 1233, 1235, 1241, 1243, 1250, 1257, 1264, 1265, 1273, 1279, 1286, 1290, 1294, 1295, 1306, 1308, 1322, 1323, 1326, 1329, 1338, 1350, 1352, 1354, 1357, 1367, 1370, 1372, 1382, 1386, 1387, 1393, 1397, 1402, 1411, 1415, 1418, 1426, 1435, 1436, 1441, 1449, 1451, 1455, 1458, 1467, 1470, 1479, 1480, 1483, 1499, 1501, 1511, 1515, 1520, 1522, 1531, 1542, 1543, 1547, 1564, 1565, 1572, 1580, 1586, 1596, 1603, 1608, 1612, 1629, 1634, 1651, 1665, 1672, 1693, 1696, 1715, 1727, 1736, 1757, 1758, 1779, 1788, 1801, 1819, 1822, 1844, 1850, 1865, 1881, 1886, 1908, 1912, 1929, 1942, 1951, 1972, 1973, 1994, 2004, 2015, 2021, 2035, 2036, 2058, 2066, 2079, 2097, 2101, 2122, 2127, 2144, 2158, 2189, 2220, 2251, 2281, 2312, 2343, 2374, 2405, 2436, 2466, 2497, 2528, 2559, 2590, 2621, 2651, 2682, 2713, 2744, 2775, 2806, 2836, 2867, 2898, 2907, 2929, 2960, 2991, 3021, 3052, 3083, 3469, 3804, 5059, 6939, 7276, 7608, 10118, 14552.

The following is a list of the actual range of container sizes. The nominal cylinder size is stated in litres:

0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.1, 4.2, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9, 9.0, 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 23.6, 47.2.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Use in accordance with the doctor's instruction.

GENERAL

1. 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.
2. 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

See Section 6.4.

PREPARATION FOR USE

1. Cylinder valves should be opened momentarily prior to use to blow any grit or foreign matter out of the outlet.
2. Ensure that the connecting face of the yoke, manifold or regulator is clean and the sealing washer or 'O' ring where fitted is in good condition.
3. Cylinder valves must be opened slowly.
4. Only the appropriate regulator should be used for the particular gas concerned.
5. Pipelines for medical gases should be controlled in accordance with the conditions set out in HTM 2022.
6. 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 test solution.
3. The gland packing around the valve spindle may become loose and can be cured by tightening the gland nut clockwise. Do not overtighten.

4. Sealing or joining compounds must never be used to cure a leak.
5. 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.

Immediately return empty cylinders to the empty cylinder store for return to Air Products.

7 MARKETING AUTHORISATION HOLDER

Air Products Ireland Limited
Unit 950
Western Industrial Estate
Killeen Road
Dublin 12

8 MARKETING AUTHORISATION NUMBER

PA 1075/1/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 September 2004
Date of last authorisation: 10 September 2009

10 DATE OF REVISION OF THE TEXT

September 2009