CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Zuurstof medicinaal vloeibaar AIR PRODUCTS, 100% v/v, medicinal gas, liquefied Air Products Nederland B.V., the Netherlands

oxygen

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1986/001/MR
Registration number in the Netherlands: RVG 102874

18 August 2010

Pharmacotherapeutic group:	medical gases
ATC code:	V03AN01
Route of administration:	inhalation
Therapeutic indication:	normobaric oxygen therapy - treatment or prevention of acute or chronic hypoxia; hyperbaric oxygen therapy - treatment of serious carbon monoxide poisoning, 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).
Prescription status:	prescription only
Date of first authorisation (in BE):	19 January 1998
Date of authorisation in NL:	28 August 2009
Concerned Member States:	Mutual recognition procedure with BE, DE, CZ
Application type/legal basis:	Directive 2001/83/EC, Article 10a

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Zuurstof medicinaal vloeibaar AIR PRODUCTS, 100% v/v, medicinal gas, liquefied (Medicinal Liquid Oxygen) from Air Products Nederland B.V. The product was first registered on 19 January 1998 in Belgium. The date of authorisation in the Netherlands was on 28 August 2009 through MRP BE/H/0131/001. As a result of a RMS transfer after finalisation of this procedure, the Netherlands is now RMS for this product (assigned MRP number NL/H/1986/001).

Oxygen medicinal Air Products is indicated for:

Normobaric oxygen therapy
- Treatment or prevention of acute or chronic hypoxia.

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).

A comprehensive description of the indications and posology is given in the SPC.

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.

Since the "Note for Guidance on medicinal gases: Pharmaceutical documentation" (CPMP/QWP/1719/00) was adopted in 2002, it is mandatory in the European Union to register medicinal gases as medicine replacing the status of medical device. Hence, a number of medicinal gases have now received a marketing authorisation.

The marketing authorisation is granted based on article 10a (well-established medicinal use) of Directive 2001/83/EC.

This application concerns a bibliographical application based on well-established medicinal use of oxygen. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. ''Medicinal use'' does not exclusively mean ''use as an authorised medicinal product'', so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should

cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is oxygen, an established substance described in the European Pharmacopoeia (Ph.Eur.*). It has a molecular weight of 32.00 g/mol. Under atmospheric pressure, it is a colourless, odourless and insipid gas. In liquid form, it has a pale blue colour. The drug substance is obtained from a number of different manufacturers.

The Active Substance Master File (ASMF) procedure is used for two suppliers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Oxygen production is carried out in air separation units. It is an automatic and continuous manufacture process. Oxygen can be obtained both in the liquid and gaseous phase. There are no intermediates in the production process. All air separation plants use a similar manufacturing process. This process is considered well-established and has been sufficiently described. Process validation data have been provided for each site.

Quality control of drug substance
The drug substance specifications are fully in accordance with the Ph.Eur. This is considered suitable for control of oxygen drug substance from the different sites. The container closure system for the drug substance is appropriately documented. Correct reference to the relevant legislation and standards is made. Batch analytical data have been provided for each supplier. All results meet the requirements.

Stability of drug substance
No stability data are required for liquid oxygen drug substance; the CHMP guideline on medicinal gases considers bibliographic data sufficient to document drug substance stability. Bulk medicinal liquid oxygen is a very stable gas that has been used for a long time and packaged in containers of established quality.
No formal shelf life or retest period was requested for the drug substance since the finished product specifications fully reflect the requirements of the Ph.Eur. monograph.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Medicinal Liquid Oxygen AIR PRODUCTS contains as active substance 100% v/v oxygen (O_2) and is a colourless, odourless and tasteless gas. Liquefied oxygen is light blue in colour.

The liquefied gas is packed in vacuum isolated receptacles made of stainless steel alloys or aluminium alloys. These receptacles are mounted with a wide variety of accessories for filling and emptying and for pressure build up and pressure relief. Other accessories are mounted for pressure and level indication.
The capacities of the cryogenic vessels range from 30 litres to 40.000 litres

No excipients are present.

Pharmaceutical development
Oxygen has been used as a medicinal product for many years. The development of the product has been described. Several relevant physico-chemical properties are discussed and compatibility of the gas with the applied containers is also sufficiently guaranteed. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is standard for oxygen and has been sufficiently described. As process only consists of transferring liquid oxygen between tanks and/or tankers, process validation focused on the maintenance of product purity in accordance with Ph.Eur. during the different transfilling steps. The manufacturing process has been sufficiently validated for each manufacturing site.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is in full accordance with the Ph.Eur. monograph and includes tests for identification, assay and purity.
Batch analytical data from the proposed production sites have been provided, demonstrating compliance with the specification.

Package
The container closure system is fully in compliance with the legislation of Transport of Dangerous Goods, *i.e.* “ADR” for transport tanks. More recently manufactured transport tanks comply with the European Transportable Pressure Equipment Regulations 99/36 EC, while stationary tanks comply with the European Pressure Equipment Regulations 97/23 EC.
Compliance with the ADR (chapter 6) guarantees compatibility between oxygen and the containers. In addition, compatibility of receptacle and valve and accessory materials is standardized, for cryogenic oxygen in EN 1797:1998 or in ISO 21010:2004 and for all other cryogenic gases EN ISO 11114-1: 1997 for metallic materials and in EN ISO 11114-2 for non-metallic materials are applicable.

Stability of drug product
No formal stability study has been carried out on this medicinal air. Experience over the last decades has shown that there is no change in medicinal air when stored. Based on bibliographic grounds and by experience there is no reason for any interaction to be expected between the product and the material of the container within the shelf life of the product. A shelf life of 6 months was granted under the claimed storage conditions, as stated in section 6.4 of the approved SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

Elements relating to the safety of old medicinal gases in the context of compiling the non-clinical documentation for Module IV (Safety) of the dossier are specified in the SWP Recommendation for Nonclinical Safety Requirements for Old Medicinal Gases (EMEA/CHMP/SWP/283223/2005), see also the Annex of the CHMP Draft Quality Guideline on medicinal gases: pharmaceutical documentation. (CPMP/QWP/1719/00 Rev 1).

In general, the principles applied under the "Note for Guidance on the Non-Clinical Documentation for Mixed Marketing Authorisation Applications (CPMP/SWP/799/95)" should be applied. Further non-clinical investigations may be needed if safety aspects or concerns are not addressed by available non-clinical data or cannot be justified based on available literature and/or clinical data, especially when these effects are very difficult to detect clinically.

Pharmacology
The MAH describes the basic role of oxygen in anaerobic and aerobic metabolism and energy supply.
The use of *supplemental* oxygen is to reverse the effects of hypoxia. The hypoxia is commonly a result of an underlying disease and rarely a result of a primary deficiency of oxygen in the inspired gas. Oxygen alone will not cure an underlying disease.
No non-clinical in vitro or in vivo primary pharmacodynamic data have been included.
Effects of oxygen inhalation on the core-battery of safety pharmacology studies (CNS, cardiovascular system and respiratory system) are well known in humans.
A reference to the clinical expert report is made for pharmacodynamic drug interactions. No pharmacodynamic interactions are included in section 4.5 of the SmPC.
The MAH considered the potential for effects on lung function and gas exchange.

Pharmacokinetics
Pharmacokinetic properties of medicinal oxygen are well known. The MAH presented a description of clinical ADME, no comparison to ADME in laboratory animal species was included. The metabolism within the lungs has been addressed.

Toxicology
Non-clinical toxicology studies performed should use the intended clinical route of administration, i.e. inhalation and should be conducted in compliance with the principles of Good Laboratory Practices (GLP) and also include toxicokinetic evaluations.
The GLP status of the referenced articles is unknown, but it is acknowledged that for many bibliographic applications this can be accepted, considering the well-established knowledge on the safety of the product under consideration.
The MAH describes the effect of oxygen at different pressures on retinal vascularisation and lung damage in mice and rats. Oxygen toxicity at different concentrations and pressures has also been described in humans. Depending on the oxygen pressure mainly retinal toxicity, lung lesions and neurological symptoms occur.

Oxygen has shown mutagenic effects in *in vitro* tests with mammalian cells. Reactive oxygen species (ROS) are clearly genotoxic. The formation of ROS takes place at substantially lower levels under normobaric conditions or under normal (air) breathing conditions. Although a cancer -inducing effect of therapeutic oxygen was not found to date, oxygen toxicity and possible cancer-promoting effects of hyperbaric oxygen therapy have been a matter of serious concern.
The risk of genotoxicity is negligible as long as the anti oxidative defense mechanism is not affected.
The idea is receiving increased support that ROS-mediated processes of carcinogenesis have practical thresholds. Since ROS are genotoxic in principle, questions arise whether increased ROS exposure will superimpose to an endogenously produced background level of DNA lesions, related to mechanisms that may result in non-linear dose-effect relationships (Bolt et al., Toxicol Lett. 2004, 151, 29-41).
Since high internal doses of ROS are clearly genotoxic, the exposure to ROS should be limited. The anti oxidative status of the patient might be improved by anti-oxidant supplementation.
Although available data do not suggest a tumor promoting effect for hyperbaric oxygen, conventional carcinogenicity studies are not known.

The dangers of hyperoxia to the fetus have been demonstrated in animal models. In animal experiments, oxidative stress has led to fetal dysmorphogenesis, abortions, and intrauterine growth restriction. Excess oxygen during pregnancy may induce abnormalities in the development of the neural tube.
However, careful review of animal studies and human clinical experience indicates that the short duration of hyperoxic exposure attained during hyperbaric oxygen therapy can be tolerated by the fetus (Van Hoesen et al., JAMA 1989, 261(7):1039-43).

The MAH claims that it is unlikely that materials extracted or leaching from valves and gaskets can occur.

Environmental risk assessment
No environmental risk assessment has been performed, which is acceptable for this application.

II.3 Clinical aspects

To support this application, the MAH submitted an expert report with a review of the literature. Since the medicinal use of oxygen is considered 'well established', a bibliographic application is acceptable. There have been many publications over the years concerning both its safety and efficacy. The safety and efficacy sections are based on clinical experience of the use of synthetic air as published in the literature.

Pharmacokinetics
Oxygen moves down a stepwise series of partial pressure gradients from the inspired air to the body's cells and their mitochondria where it is used in aerobic metabolic pathways to produced biological energy from food. The pharmacokinetic properties of oxygen are influenced by the absorption, distribution, metabolism and excretion.

Absorption
The partial pressure of oxygen in air is around 159 mmHg at normal barometric pressure. As the air is inhaled to the distal airways and alveoli the pressure drops (due to dilution and by uptake into the blood) to 110 mmHg. The oxygen then diffuses into the pulmonary capillary bed driven by the gradient between the partial pressure in pulmonary mixed venous blood and that in the alveolar gas. Under normal circumstances the percentage of oxygen in atmospheric air is constant at 21% and does not change with altitude. Ventilation of the alveoli is essential if alveolar oxygen pressure is to be maintained and carbon dioxide removed. Alveolar ventilation depends on the rate of breathing and the tidal volume. The PaO_2 provides the driving pressure for diffusion into the pulmonary capillary blood and in normal conditions is the main determinant of PaO_2. The capillary blood is usually fully oxygenated before it has traversed one third of the distance of the alveolar-capillary interface. Efficient gas exchange requires matching of alveolar ventilation and perfusion. Inadequate ventilation of perfused alveoli or reduced perfusion of well-ventilated alveoli impairs reoxygenation of pulmonary arterial blood and is termed ventilation-perfusion mismatch.

Distribution
The human tissues have no long-term storage system for oxygen. This means that the tissues rely on a continuous supply at a rate that precisely matches changing metabolic requirements. Oxygen is delivered by the circulation (following a gradient out of the blood and into the cells). The delivery of oxygen to the tissues depends on arterial oxygenation, cardiac output, regional perfusion, local oxygen carriage systems and oxygen utilisation. As a result of the loss to the tissues, the PO2 of venous blood is about 55 mmHg lower than that of in arterial blood. Most oxygen is carried in the blood attached to haemoglobin with only a small amount (typically less than 2%) dissolved in plasma. Haemoglobin is a tetrameric protein that transports H+ and CO_2 in addition to O_2. The affinity of haemoglobin for oxygen is regulated by specific molecules in its environment such as H+ and CO_2 and organic phosphate compounds. Typical concentration in arterial blood for a subject at sea levels breathing air would be of 19.8ml of oxygen per 100ml of blood. Haemoglobin is a tetrameric protein that transports H+ and CO_2 in addition to O_2. The affinity of haemoglobin for oxygen is regulated by specific molecules in its environment such as H+ and

CO2 and organic phosphate compounds. The major function of the central circulation is to transport oxygen from the lungs to the peripheral tissues at a rate that satisfies overall oxygen consumption.

Metabolism
Cytochrome C oxidase is nowadays thought to be responsible for about 90% of the total oxygen consumption of the human body. There are some 200 oxidases responsible for the metabolism of oxygen.

Excretions
Oxygen, which has been absorbed into the body's metabolic processes, is excreted almost entirely as water and carbon dioxide.
Finally it should be noted that oxygen transport could be affected by numerous conditions, such as newborns, sickle-cell anaemia and thalassemias.

Pharmacodynamics
Oxygen is an element vital to living organisms. It is involved in all metabolic processes in tissues and cells. The oxygen required for those processes is exchanged through the alveoli in the lungs after inhalation of air, which has an oxygen content of approximately 20.9%. After being transferred to the blood, the oxygen is bonded to the haem group of the haemoglobin molecule and transported to the tissues where it is needed. The arterial oxygen tension can be quantified, and is expressed as the partial pressure of oxygen in kilo Pascal (kPa) or millimetres of mercury (mmHg).

Normal values for the arterial pressure of oxygen at sea level are:

PaO_2: normally between 10 and 14.5 kPa (or 74 and 108 mmHg)

When PaO_2 values are lower than the above minimum value, the patient may suffer from hypoxemia.

Oxygen is the main oxidant used by the cell to convert nutrients, such as glucose and fatty acids, to energy. The NADH and $FADH_2$ formed in glycolysis, fatty acid oxidation and the citric acid cycle are energy rich molecules, which contain a pair of electrons that have a high, transfer potential. When these electrons are transferred to molecular oxygen by a series of electron carriers (flavins, iron-sulphur complexes and quinones), a large amount of energy is liberated. This released energy is converted to a proton gradient across the inner mitochondrial membrane. As protons flow back to the mitochondrial matrix through a proton channel, adenosine diphosphate is phosphorylated to adenosine triphosphate (ATP), a molecule that can be considered as the universal currency of energy in biological systems. This process in which ATP is formed as electrons are transferred from NADH to $FADH_2$ to O_2 is called oxidative phosphorylation. This is the major source of ATP in aerobic organisms.

Two different pathways are involved in the metabolism of glucose: one anaerobic and one aerobic. The first one occurs in the cytoplasm and is only moderately efficient. The latter takes place in the mitochondrial matrix and results in the greatest release of energy. As its name implies, it requires oxygen.

Anaerobic pathway: Glucose in the bloodstream diffuses into the cytoplasm and is locked there by phosphorylation. A glucose molecule is then rearranged slightly to fructose and phosphorylated again to fructose disphosphate. These steps all actually require energy, in the form of 2 ATPs per glucose. The fructose is then cleaved to yield 2 glyceraldehyde phosphate (GPs). In the next steps, energy is finally released, in the form of 2 ATPs and 2 NADHs.

Aerobic pathway: Pyruvate is the starting molecule for oxidative phosphorylation via the Kreb's or citric acid cycle. In this process all of the C-C and C-H bonds of the pyruvate will be transferred to oxygen. Basically, the pyruvate is oxidized to acetyl coenzyme A, which can then bind with the four carbons oxaloacetate to generate a six-carbon citrate. Carbons and hydrogens are gradually cleaved from this citrate until all that remains is the four-carbon oxaoacetate we started with. In the process, 4 NADHs, one FADH2 and one GTP are generated for each starting pyruvate. The aerobic metabolism generates much more ATPs than the anaerobic counterpart.

Clinical efficacy

The medicinal product is intended for the pulmonary administration of oxygen and aerosol therapy after evaporation. Scientific evidence has shown the efficacy of Medicinal Liquid Oxygen in the treatment of various clinical entities. Hereby a division should be made between normobaric oxygen therapy and hyperbaric oxygen therapy.

Normobaric oxygen therapy

- Hypoxemia and Hypoxia, irrespective of origin (acute or chronic)
  a. Indications include pneumonia, acute severe asthma, and acute exacerbations of chronic bronchitis, acute exacerbations 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 many of these conditions high oxygen concentration (up to 100%) should be used. The exceptions to this rule are chronic bronchitis and emphysema. Patients with chronic bronchitis and emphysema may benefit from long-term oxygen therapy. A recent review of 5 randomised controlled trials comparing domiciliary long-term oxygen therapy with control treatment in a total of 539 patients with COPD and hypoxemia found that long-term oxygen therapy improved survival in patients with severe hypoxemia but few co-morbidities. However, it did not improve survival in patients with moderate hypoxemia or those with mild to moderate hypoxemia and nocturnal oxygen desaturation.
  b. This use of normobaric oxygen therapy for hypoxemia as a causal therapy has been established through many clinical studies, clearly indicating that the potential benefits outweigh the risks in this specific clinical indication.

- Mechanical ventilation
  a. Mechanical ventilation is a method to mechanically assist or replace spontaneous breathing when patients cannot do so on their own. This can be due to different clinical conditions, such as resuscitation anaesthesia, acute respiratory insufficiency or coma). In many cases, mechanical ventilation is applied in acute settings during serious illness. Positive end-expiratory pressure and increased inspired oxygen fraction are the primary means of improving oxygen saturation during mechanical ventilation.
  b. Ventilated patients are at higher risk for complications (such as pneumothorax) and a prolonged stay in the hospital intensive care unit. The usefulness of oxygen has been studied in different ventilation modes. Oxygen has been adequately studied in conditions of resuscitation anaesthesia, acute respiratory insufficiency and coma.

- Aerosol therapy vector
  a. Inhalation has become the mainstay of respiratory care and became known as aerosol therapy. Its scientific base developed rapidly late, after 1974. Despite some initial practical problems, scientific evidence accumulated that supported the advantages of the inhalation route over other drug-administration routes. Inhaled drugs are localized to the target organ, which generally allows for a lower dose than is necessary with systemic delivery, and thus fewer and possibly less severe adverse effects. Currently, there exist 3 types of aerosol devices that are clinically considered equivalent: metered-dose inhaler, dry powder inhaler and nebulizer.
  b. Only one study (with 8 healthy subjects) using oxygen as aerosol therapy vector was included in the dossier.

- Extracorporeal circulation during cardiovascular surgery
  a. The principle behind this technique involves obtaining access to drain blood from the venous circulation into the extracorporeal circuit where it is oxygenated and cleaned of carbon dioxide before being returned to the patient's circulation. Long-term studies have confirmed its benefits, in improved survival without severe disability. In addition, the value of extracorporeal life support in paediatric and adult respiratory failure is becoming clearer.
  b. Several studies have investigated the clinical experience with extracorporeal circulation. In addition, some recent studies (three of them included in the dossier) focused on the use of extracorporeal membrane oxygenation (ECMO) during paediatric cardiopulmonary resuscitation and for the treatment of severe haemodynamic instability after cardiac arrest in adults. These

results indicate that ECMO is an effective strategy to salvage (leading to improved survival) patients with extreme haemodynamic instability and multiorgan failure, but a risk of technical complications still exists.

- Neonatal hypoxia
  a. The clinical indications consist mainly of hyaline membrane disease or patent ductus arteriosus. Prehospital care for preterm infants with respiratory distress syndrome (RDS) or a suspected patent ductus arteriosus consists of supplement oxygen for any hypoxia and supportive care.
  b. Preterm infants with RDS or hyaline membrane disease often require a period of assisted ventilatory support. The aim is to treat hypoxemia and hypercarbia associated with respiratory distress syndrome while minimising ventilator associated lung trauma and oxygen toxicity. Oxygen dependence is common in prematures with patent ductus arteriosus. In addition, increased oxygen tension is also a potent stimulator of ductal closure after birth. The response to oxygen is very closely related to gestational age. Infants with severe respiratory disease requiring high ventilation pressure and high oxygen concentration will rarely show short-term improvement in pulmonary disease as a result of closure of a patent ductus. Earlier treatment of a patent ductus arterious could reduce the ventilation period and the possible risk of developing chronic lung disease.

- Carbon monoxide poisoning
  a. After carbon monoxide poisoning, and removal from the soured, a significant amount of recovery is to be expected from patients receiving 100% oxygen and appropriate cardiovascular support. Emergency care will start as soon as possible by providing 100% oxygen by either non-rebreather mask or endotracheal tube. The immediate effect of oxygen will be to enhance the dissociation of COHb.
  b. Volunteer studies have shown that administration of 100% oxygen reduces the half-life of COHb from a mean of 5 hours (range between 2 and 7 hours) in room air to a mean of approximately 1 hour in 100% oxygen at normal atmospheric pressure. It should be added that this type of patients often requires hyperbaric oxygen treatment.

<u>Hyperbaric oxygen therapy (HBO)</u>
HBO is administered intermittently, usually one to two times a day, to treat a variety of conditions. Many different clinical entities can be treated through the use of HBO, although the level of evidence is quite different for the various conditions. It can be used in first instance for the treatment of air embolism

- Treatment of air embolism (exogenous or endogenous)
  a. In the case of air/gas embolism hyperbaric oxygen reduces bubble size in accordance with Boyle's law – at 3 ATA bubble volume is reduced by about 2/3. Hyperoxia increases the diffusion gradient with the embolized gas, moving gas into solution where it can be metabolized.
  b. Until date no randomised controlled clinical trials have investigated the use of HBO in air embolism. Only a case series (consisting of 19 patients) has been published. Patients with iatrogenic cerebral arterial gas embolism showed significant improvement in symptoms with HBO. It should be mentioned that this study lacked the presence of a control group! Additional case reports indicate good results (e.g. survival rates) in patients with systemic air embolism, when treatment is early initiated.
  c. Clinical experience suggests maximal benefit with 100% oxygen at 2.8 ATA and repeated treatments until no further improvement is seen, typically after no more than 5 – 10 treatments.

- (supporting) Treatment of gas gangrene (*clostridial myonecrosis*)
  a. A recent review compared published retrospective comparison studies and case series reporting results with HBO. Number of patients in these studies were relatively small (ranging from 9 to 139), but included both adults and children. Most authors commented that adjunctive HBO was beneficial, when considering mortality as an outcome measure along with rates of clinical improvement, infections and amputation. Some adult case series showed significant reduction in morbidity and mortality by the addition of HBO to antibiotic therapy and surgical debridements.
  b. Another recent review publication considers hyperbaric oxygen therapy currently as a useful adjunct to the standard medical and surgical management of gas gangrene. Although no

adequately controlled trials exist, its use if widely accepted. In addition, the jury of the European Committee for Hyperbaric Medicine Consensus did conclude, "*HBO therapy should be integrated in a treatment protocol comprising adequate surgical and antibiotic therapy – type 1 recommendation with a level C scientific evidence*".

- Carbon monoxide poisoning
  a. As stated previously, oxygen should be given in high concentrations (up to 100%) as soon as possible following carbon monoxide poisoning until the carboxyhaemoglobin concentration has fallen below dangerous levels (+/- 5%). Although starting this treatment with 100% oxygen at ambient pressure is crucial in the healing process, randomized controlled trials have shown HBO as an efficacious therapy for acute CO poisoning if delayed neurological sequelae are to be minimized.
  b. The results of several randomized controlled trials showed some mixed results, although they were generally in favour of the use of hyperbaric oxygen treatment. Studies showed that hyperbaric oxygen therapy decreased the incidence of delayed neurological sequelae, indicating that HBO often benefits the brain more than normobaric oxygen (improvement of energy metabolism, prevention of lipid peroxidation and decrease of neutrophil adherence). Hyperbaric oxygen therapy also reduces the time of initial recovery.

Finally, some additional clinical indications should be mentioned, such as treatment of cluster headache (oxygen treatment of choice for attacks, although evidence from large scale clinical trials is still lacking), osteoradionecrosis (no proper clinical trials have been performed in this indication, but its use in clinical practice seems to be of overriding importance) and vascular problems in skin transplants and skin reconstruction (only case reports available, showing significant improvements in skin grafts and flaps but there still is clearly a lack of adequate clinical data).

Most scientific evidence exists for the treatment of cluster headache. Oxygen therapy is hereby considered as the treatment of choice for attacks. The sumatriptan cluster headache study group has used oxygen for more than 16 years as rescue medication in their trials on the effectiveness of intranasal zolmitriptan in acute cluster headache.

Clinical safety
Hereby several types of safety issues and adverse effects should be considered. Before the application of oxygen therapy some special warnings and precautions should be considered:

Oxygen therapy must be given with the utmost care in cases of hypercapnic chronic respiratory insufficiency, which call for low oxygen flow rates, constant monitoring of the patient's clinical condition and regular measurement of arterial blood gases.

Given the toxicity of pure oxygen when administered for longer periods of time at high flow rates, the FiO_2 level in breathing support should as a rule not exceed 60-70%.

In the literature a number of adverse events are mentioned of which the underlying mechanisms and environmental triggers are now sufficiently known. The three most important side effects described in the literature are:

- Pulmonary toxicity and cardiac disorders
  a. Pulmonary lesions are probably caused by increased production of free radicals due to hyperoxia, but can also lead to morphological changes in the epithelium and changes in local vascularisation. Currently there are no effective means to prevent or lessen pulmonary oxygen toxicity, other than decreasing the oxygen concentration and providing supportive measures.
  b. In general oxygen therapy causes only minor effects on pulmonary and cardiovascular function. Heart rate and cardiac output are reduced when 100% oxygen is administered for short periods (less than 6 hours) and under normobaric conditions.

- Central nervous system toxicity

a. Some excitation-related disorders have been documented, most of which are associated with high oxygen concentrations (FiO_2) and occur particularly with hyperbaric oxygen. This CNS oxygen toxicity seems only to occur when partial pressure of inspired oxygen is over 2 atmospheres.
b. CNS toxicity occurs before pulmonary toxicity at these oxygen pressures.

- Retinal damage
  a. Exposure of neonates to high concentrations of oxygen may cause retrolental fibroplasia (retinopathy of prematurity). Additionally, overexposure of oxygen in neonates may lead to bronchopulmonary dysplasia, subependymal and intraventriclar haemorrhage and necrotic entreocolitis. Hence, this patient population should not be exposed to high concentrations of oxygen as is included in the appropriate SPC section.
  b. Temporary loss of eyesight may be a possible risk of hyperbaric oxygen therapy. However, these side effects of hyperbaric oxygen therapy tend to be mild and reversible.

- Oxygen radical disease (in prematurity)
  a. Retinopathy is perhaps but one manifestation of the potential oxygen radical disease of prematurity. Others include bronchopulmonary displasia, subependymal and intraventricular haemorrhage and necrotising enterocolitis.
  b. The advice must remain to avoid over-exposure of oxygen in the neonate.

- Hyperbaric oxygen therapy
  a. Patients scheduled for HBO therapy need a careful pre-examination and monitoring. Possible complications during HBO therapy include barometric lesions to the middle ear, nasal sinuses, inner ear, lung and teeth. However, the predominant complication is presented by pressure equalization problems within the middle ear. Next to barotraumas and CNS toxicity, musculoskeletal and connective tissue disorders, including myalgia, may be provoked by HBO.
  b. Side effects of hyperbaric oxygen therapy tend to be mild and reversible.

- Miscellaneous
  a. Haemolysis has been described, as has lipid peroxidation and membrane damage in potentially any metabolising cell.

There are no known cases of interaction with other medicinal products and oxygen.

Available published data do not contraindicate the product during pregnancy. Available data do not contraindicate breast-feeding. This product may be taken during pregnancy and lactation.

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

Pharmacovigilance plan
The Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Minimisation Plan
Concerning the need for a risk minimisation plan the MAH declares no such plan is deemed necessary. The application concerns a product for which no safety concerns requiring additional risk minimisation activities have been identified. This is considered acceptable.

Product information

SPC
The MAH committed to harmonise the content of the SPC with that accepted for Gaseous Medicinal Oxygen (NL/H/923/01/MR), established through a CMD(h)-referral.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. The test was performed on the Dutch PIL. Improvements to the PIL were made while preparing the leaflet for the pilot test and as a result of the pilot test.

The results in both test rounds showed that 100% of the questions were answered correctly. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Based on the submitted dossier and further literature, Zuurstof medicinaal vloeibaar AIR PRODUCTS, 100% v/v, medicinal gas, liquefied can be considered effective in the approved indications as normobaric oxygen therapy and hyperbaric oxygen therapy. These are consistent with the spectrum of activity reported in standard references and published literature.

The liquid form of oxygen is extremely volatile. The medical applications of liquid oxygen come from the fact that oxygen is vital to the human body for respiration. Medicinal liquid oxygen is a well-known active substance with established efficacy and tolerability. For this application, no original clinical study data nor clinical trials were conducted nor presented. The dossier contains detailed references to published scientific literature.

The risk of oxygen is low when oxygen is used short term and with concentrations lower than 60%. Longer exposure and use at higher concentrations may lead to pulmonary and/or CNS toxicity, as well as retina toxicity. Patients whose respiratory centre is depressed, who are dependent on hypoxic drive for their respiration, and neonates are at particular high risk from exposure to high concentrations of oxygen. The problem may be prevented by careful titration of oxygen concentrations to prevent over-exposure. In conclusion, as oxygen has been on the market for many years, the efficacy and safety of oxygen is well established. The benefit/risk ratio can be regarded as positive if the substance is used correctly and under well-controlled circumstances.

The medicinal product is manufactured in a standard, well-established process and its quality is sufficiently guaranteed.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates.

On the basis of the data submitted, adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile has been demonstrated for Zuurstof medicinaal vloeibaar AIR PRODUCTS, 100% v/v, medicinal gas, liquefied. BE granted a marketing authorisation on 19 January 1998.

As a result of the MRP there was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, have granted a marketing authorisation. The mutual recognition procedure was finished on 16 October 2008. Zuurstof medicinaal vloeibaar AIR PRODUCTS, 100% v/v was authorised in the Netherlands on 28 August 2009.

The PSUR submission cycle is 3 years. The first PSUR covers the period from October 2008 to July 2009, in line with the data lock point for oxygen.

The date for the first renewal will be: 23 October 2010.

The following post-approval commitment has been made during the procedure:

Product information

- The MAH committed to harmonise the content of the SPC with that accepted for Gaseous Medicinal Oxygen (NL/H/0923/001/MR), established through a CMD(h)-referral.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HBO	Hyperbaric oxygen therapy
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
ROS	Reactive Oxygen Species
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached