CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Lucht medicinaal Air Products, 22% v/v, medicinal gas, compressed
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/1074/001/MR
Registration number in the Netherlands: RVG 29452

26 August 2009

Pharmacotherapeutic group:	medical gases
ATC code:	V03AN01
Route of administration:	inhalation
Therapeutic indication:	prevention of hypoxia
Prescription status:	non prescription
Date of first authorisation in NL:	5 March 2007
Concerned Member States:	Mutual recognition procedure with BE, CZ, DE, ES, PT, UK
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 Lucht medicinaal Air Products, 22% v/v, medicinal gas, compressed, from Air Products Nederland B.V.. The date of authorisation was on 5 March 2007 in the Netherlands.

Lucht medicinaal Air Products is considered a drug, i.e. it is used for medicinal purposes. The indication of Lucht medicinaal Air Products is prevention of hypoxia. The deprivation of oxygen (hypoxia) leads to death within minutes. This application concerns synthetic air in cylinders for medicinal use only and does not cover compressed ambient air or the use of air for non-medicinal purposes.

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

Air medicinal synthetic AIR PRODUCTS provides an alternative air source that can be of use if special requirements are to be met with regard to purity; synthetic air is a mixture of pharmaceutical oxygen and pharmaceutical nitrogen and therefore does not contain any impurities and contaminations, as in compressed environmental 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 Air medicinal synthetic AIR PRODUCTS. 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 is a colourless, odourless and insipid gas. In solid and liquid form it has a pale blue colour.

Manufacture
Oxygen is prepared in air separation plants from atmospheric air. It is produced by mechanical separation of the components of air using cryogenic distillation of liquefied air. Contaminants in the air (water, CO, CO_2 and the hydrocarbons) must be removed prior to introduction into the cryogenic part of the process. The complete process takes place in a closed system. Sufficient information has been provided on the production process.

Specification
The drug substance specification is in line with the Ph.Eur., except for an identification test for oxygen. Furthermore, the specification is acceptable. A batch is defined as the filling of one tank. This is acceptable as the production process is continuous. Analytical results of 3 batches of each manufacturing site show compliance with the specification. The process is deemed sufficiently under control.

Stability
The drug substance is packed in insulated containers dedicated for the storage of oxygen. The pressure in storage and transport vessels is always above atmospheric pressure. The complete tank content is regularly checked on purity. No stability test has been performed. The claimed shelf life of six months can be granted based on the bibliographic data provided.

** 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
Lucht medicinaal Air Products 22% v/v contains as active substance 21-22.5% of oxygen, and is a colourless, odourless and tasteless gas.

The medicinal gas is packed in a high-pressure cylinder, constructed from chromium molybdenum steel or aluminium. The cylinder has a conventional isolating valve, which is used to open and close the cylinder, or an integral valve (integral pressure regulator coupled with an isolating valve). The valves are made of brass. The colour of the cylinder body is white and for the shoulder it is blackband on white. The packaging cylinders are usual and suitable for the product at issue. The capacity ranges between 0.5 and 50 litres.

The product contains 77.5-79% nitrogen as excipient. The specification of nitrogen complies with the current version of the Ph.Eur.. The mixture of nitrogen and oxygen is a very stable gas mixture. There is no reaction between the oxygen and nitrogen at the temperatures and pressures the medicinal air is exposed to.

Pharmaceutical development
Air has been used for many years and supplied by Air Products for more than 30 years. The choice for the cylinder is based on the pressure requirements of the final product. The choice for the material and the valve is based on their compatibility for use with mixtures containing oxygen. No development data are included, but there is no objection to that as the product has already been used for a long time.

Manufacturing process
The cylinders are filled by pressure. As the gas is compressed into the cylinders the temperature of the cylinders increases. The pressure and the temperature are monitored to ensure that the cylinders are filled to the correct fill pressure. The gas enters the cylinder through a small orifice, which causes significant mixing within the cylinder. Once mixed, the mixture remains mixed under all normal ambient conditions without separation. Validation data for three batches of each manufacturing site have been included and a separate risk analysis was also provided.

Product specification

The product specification includes tests for appearance and labelling of the product and for assay, identity of nitrogen and water. The analytical methods of the Ph.Eur. monograph were used. Therefore, no separate validation was deemed necessary.
Batch analysis data have been provided on three batches of each manufacturing site. Compliance with the proposed release requirements was demonstrated.

Stability tests on the finished 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 mixture and the material of the container within the shelf life of the product.
The end of shelf life specification is identical to the release specification.
The MAH submitted two documents providing bibliographic evidence for the claimed shelf life, i.e. the stability and compatibility in accordance with Framework Directive on Transport of Dangerous Goods by Road and stability as a product characteristic in accordance with the EMeA NfG on Medicinal Gases. The identification, assay and impurities do not change during storage. Small leakages through the valve may occur, but these are always from the container towards atmosphere.
Based on the data submitted, a shelf life of 3 years 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

Air has been used in Europe for many years and supplied by Air Products for more than 30 years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment is necessary.

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

II.3 Clinical aspects

Since the use of synthetic air 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
Inhaled oxygen is absorbed by a pressure-dependent gas exchange between alveolar gas and the capillary blood passing through the alveoli.
The oxygen is transported to all tissues of the body (mainly bound to haemoglobin) by the systemic circulation. Only a very small portion is free oxygen (dissolved in plasma). Oxygen is an essential component of the intermediate metabolism of the cell for the creation of energy – aerobic ATP production in de mitochondria. The oxygen that is absorbed by the body is almost entirely excreted in the form of carbon dioxide that is produced in this intermediate metabolism.

Clinical efficacy
Air is essential for life. The deprivation of oxygen (hypoxia) leads to death within minutes. Lucht medicinaal Air Products may be supplied for the prevention of hypoxia.

The main components of ambient air are around 20.9% v/v oxygen (depending on the height above sea level) and nitrogen. However, there are many other components in ambient air including argon, carbon dioxide, helium, methane, hydrogen, nitrous oxide and water vapour. Ambient air also contains many pollutants e.g. carbon monoxide, which can be natural or man-made in origin. Lucht medicinaal Air

Products is a synthetic mixture of oxygen Ph.Eur. 22% v/v and nitrogen 78% v/v. It is a colourless, odourless, tasteless gas and is used as a source of oxygen and as a source of clean air. Since the amount of oxygen in Lucht medicinaal Air Products is around 22% v/v, there is really no difference with ambient air.

According to the MAH Lucht medicinaal Air Products can be used for a variety of applications as a source of oxygen and a source of clean air. These applications are no medical indications. It should be noted that the utilizations mentioned below from the list of possible utilizations were not proposed to be included in the SPC.

- to maintain a near physiological gas in the lung
- breathing if there is a suspicion of, or possibility of, contamination of the normal atmosphere e.g. contamination of the atmosphere with noxious gases, fumes or vapours
- pollution of the atmosphere (including pollution with particulate matter)
- to prevent collapse of marginally ventilated alveoli
- anaesthesia, if it is desired to avoid the use of nitrous oxide
- to prevent oxygen toxicity
- situations where a pharmaceutically controlled air supply is desired (such as the supply of incubators)
- where it is desired to control air flow (by use of a pressurised supply through a flow meter) and to provide motive power e.g. driving 'air drills'.
- resuscitation of asphyxiated newborns when 100% oxygen is not appropriate
- dyspnoea in cancer patients
- brain-injured patients

The MAH was requested to delete the following mentioned utilizations from the list of possible utilizations mentioned in their clinical overview, as scientific evidence for its beneficial use is lacking:

- *Resuscitation of asphyxiated newborns when 100% oxygen is not appropriate*
  The scientific evidence is not evident. There has to be more evidence to apply air in stead of oxygen.

- *Dyspnoea in cancer patients*
  Breathlessness in cancer patients remains a devastating symptom, which is difficult to control successfully at present. A careful assessment of the patient with the best diagnosis of the possible cause(s) of breathlessness, reversal or improvement of the symptoms, and pharmacological palliation is a first step. This approach needs to be allied to a strategy to increase the patient's mastery of the symptom and reduce the distress. There is no evidence that Lucht Medicinaal gas has a specific place in these patients.

- *Brain-injured patients*
  The mentioning of the utilization in brain injured patients lacks a solid base. In reference to the article mentioned by the MAH, Andrews and others concluded that there were no clinically relevant or statistically significant reductions in brain temperature measured in the frontal lobe in the trial with air flow of humidified air at room temperature through the upper respiratory tracts of intubated brain-injured patients. Therefore this utilization cannot be considered established.

<u>MEB's overall conclusions on clinical efficacy</u>
Based on the submitted dossier and further literature Lucht medicinaal Air Products can be considered effective in situations of prevention of hypoxia.
Except for nitrogen, there are no other excipients and there are no known incompatibilities.

Clinical safety
The safety of Lucht medicinaal Air Products is determined by the two components of air oxygen and nitrogen. The concentration of oxygen in Lucht medicinaal Air Products remains fixed at around 22% v/v and thus the toxicity seen with oxygen given at higher concentrations does not occur with Lucht medicinaal Air Products. Lucht medicinaal Air Products does not have the specific safety issues of oxygen and nitrogen when these are administered at high concentrations.

Toxicity of oxygen
Oxygen given at high concentrations has several complications, such as suppression of hypoxic drive in patients whose respiratory centre is depressed, retrolental fibroplasia (retinopathy of prematurity) in neonates at exposure to high concentrations.
Exposure to high concentrations of inspired oxygen increases the production of free radicals and hydrogen peroxide. These metabolites lead to damaging of cells. The two areas most affected are the CNS and the lungs, the occurrence of toxicity being dependent on the inspired oxygen pressure (PO2) and the duration of exposure. Toxicity is likely to occur sooner as the inspired PO2 increases. Below 0.5 atmosphere no harm appears to occur with indefinite exposure. Between 0.5 and 2 atmosphere pulmonary toxicity occurs after prolonged exposure. Above 2 atmosphere CNS toxicity occurs (Eckenhoff & Longnecker, 1996). Mood changes, nausea, dizziness and convulsions have been associated with breathing 100% v/v oxygen at pressures of over 2 atmosphere. The convulsions (the Paul Bert effect, (Nunn, 1993)) resemble grand mal fits. Whilst full recovery is usual, those in compromised positions (e.g. divers) may succumb to the dangers of their environment (e.g. drowning).
CNS oxygen toxicity only occurs when the partial pressure of inspired oxygen is over 2 atmosphere. CNS toxicity occurs before pulmonary toxicity at these oxygen pressures.

Nitrogen toxicity
Nitrogen is an asphyxiant but the composition of the mixture with oxygen in air obviously avoids this problem. Detrimental effects can occur if nitrogen is replaced by some other gas within the body (e.g. if gas spaces become overpressurised or overdistended if nitrogen is replaced by nitrous oxide). Nitrogen narcosis has been reported from nitrogen breathed at high pressure such as in deepwater diving.

Oxygen and nitrogen toxicity is not a problem with Lucht medicinaal Air Products if used properly. Lucht medicinaal Air Products should not be used for treatment of hypoxia, not used above normal athmosphere pressure and not for diving. This information is clearly included in the SPC.

Burns
The risk of fire and serious burns should always be mentioned to patients receiving Lucht medicinaal Air Products, although it is the same risk as with ambient air. Whilst Lucht medicinaal Air Products is non-flammable it will support the combustion of flammable materials. Thus, smoking is prohibited when air is in use and no naked flame should be allowed near cylinder or pipeline outlet. It is very important that the isolating valve (that opens and closes the cylinder) or integral valve (integral pressure regulator coupled with isolating valve) is free from all traces of oil and grease since rarely spontaneous combustion and a violent explosion may occur (British Pharmaceutical Codex, 1954). However, the risk is no higher than with ambient air.
Although there is a risk of fire with air this risk is not as high as with pure oxygen. Rapid venting of gas from a cylinder may result in its chilling. Cold burns, due to contact with chilled metalwork of the valve are a potential hazard for operators. These points are all noted in the SPC for Lucht medicinaal Air Products

Mixing with other gases
Lucht medicinaal Air Products must not be given mixed with other gases if the resulting mixture will contain less than 21% v/v oxygen. In practice, this means that if it is to form a component of a gas mixture, oxygen must be one of the other components.

Humidification
Lucht medicinaal Air Products does not contain as much water vapour as ambient air. Thus, for prolonged inhalation exposure, humidification should be considered. A statement has been added to the SPC.

Patient exposure
With appropriate use and avoiding risk situations like hyperbaric applications Lucht medicinaal Air Products is safe. There are no other excipients and there are no known incompatibilities. With regards to special groups, no special precautions are required for children, women who are pregnant or breast-feeding or the elderly.

Assessor's overall conclusions on clinical safety

Lucht medicinaal Air Products is used as a source of oxygen and a source of clean air in prevention of hypoxia. There is no dose as such for air therapy. Except for nitrogen, there are no other excipients and there are no known incompatibilities.

With regard to special groups, no special precautions are required for children, women who are pregnant or breast-feeding or the elderly.

There are no specific undesirable effects of breathing air. Overdose cannot occur but Lucht medicinaal Air Products must not be administered at pressure as it may cause decompression sickness and oxygen toxicity.

The SPC contains sufficient information to inform physicians and patients about the occurrence of potentially severe adverse drug reactions and to warrant the safe use of Lucht medicinaal Air Products used under the conditions stipulated.

Pharmcovigilance plan

The member states consider that 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 management plan

The application concerns a product for which no safety concerns have been identified. There is no need for a risk minimisation plan.

Product information

Readability test

The MAH refers to the leaflet of Gaseous Medicinal Oxygen Air Products, that was assessed and approved during NL/H/0923/001/MR. Lucht medicinaal Air Products has the same active substance, the same route of administration and the same leaflet lay-out and design as Gaseous Medicinal Oxygen Air Products. Based on the Guidance for the Pharmaceutical Industry on the use of Bridging Studies it can be concluded that a bridging study can be accepted based on the following condition: the same key messages for safe use are applied within the range of medicinal gases as a group of medicines.

Two tests were performed with 10 participants each. An even spread of ages ranging from 20 up to 71 years, an even proportion of both genders and a more or less even spread of educational level were taken into account when recruiting the respondents.

The overall outcome of the readability testing indicates that the potential users (patients) are able to locate, understand and act appropriately upon the information in the resulting leaflet. This means that the package leaflet is fully in compliance with the requirements of Directive 2001/83/EC as amended by Directive 2004/27/EC and of the Readability Guideline.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Based on the submitted dossier and further literature, Lucht medicinaal Air Products, containing 22% v/v and nitrogen 78% v/v can be considered effective in situations of prevention of hypoxia. Except for nitrogen, there are no other excipients and there are no known incompatibilities. With regard to special groups, no special precautions are required for children, women who are pregnant or breast-feeding or the elderly.

The method of manufacture is a standard method used by Air Products for a number of years in Europe.

There are no specific undesirable effects of breathing air. Overdose cannot occur, but Lucht medicinaal Air Products must not be administered at pressure as it may cause decompression sickness and oxygen toxicity.

The SPC contains sufficient information to inform physicians and patients about the occurrence of potentially severe adverse drug reactions and to warrant the safe use of Lucht medicinaal Air Products used under the conditions stipulated. The SPC adequately warns of the problems that can occur with air therapy, including the risk of burns. The SPC, package leaflet and labelling are in the agreed templates.

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

In the Board meeting of 4 September 2003 and 8 July 2004, a discussion was held regarding the proposed indication and the prescription status of Lucht medicinaal Air Products. The MEB, on the basis of the data submitted, considered that Lucht medicinaal Air Products, 22% v/v, medicinal gas, compressed demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation. Lucht medicinaal Air Products, 22% v/v, medicinal gas, compressed was authorised in the Netherlands on 5 March 2007.

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 24 May 2009.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from March 2007 to March 2010.

The date for the first renewal will be: 5 March 2012.

There were no post-approval commitments made during the procedure.

References

Andrews PJD, Harris B and Murray GD. Randomized controlled trial of effects of the airflow through the upper respiratory tract of intubated brain-injured patients on brain temperature and selective brain cooling. British Journal of Anaesthesia 2005; 94 (3): 330–335.

British Pharmaceutical Codex. Oxygen. 1954. 528-529.

Eckenhoff RG & Longnecker DE. The Therapeutic Gases. Oxygen, carbon dioxide, nitric oxide, helium and water vapour. Goodman and Gilman 's The Pharmacological Basis of Therapeutics 1996. Ninth Edition. Editors: JG Hardman et al, 16: 349-359. New York, USA: McGraw-Hill.1996

Nunn JF. Hyperoxia and oxygen toxicity. Nunn's Applied Respiratory Physiology 1993 32: 537-555.

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
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
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