CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Medicinal Gaseous Oxygen AIR PRODUCTS, 100% 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/0923/001/MR
Registration number in the Netherlands: RVG 29459

Date of first publication: 9 May 2008
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Pharmacotherapeutic group:	all other therapeutic products, medical gases
ATC code:	V03AN01
Route of administration:	inhalation
Therapeutic indication:	Normobaric oxygen therapy: treatment or prevention of acute or chronic hypoxia, treatment of cluster headache 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 NL:	31 January 2006
Concerned Member States:	Mutual recognition procedure with CZ, DE, and PT; second wave- SK
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 concerned member states have granted a marketing authorisation for Medicinal Gaseous Oxygen AIR PRODUCTS, inhalation gas 100% v/v, from Air Products Nederland B.V. The date of first authorisation was on 31 January 2006 in the Netherlands.

The product is indicated for:

normobaric oxygen therapy

- treatment or prevention of acute or chronic hypoxia
- treatment of cluster headache

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).

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.

This application concerns a bibliographical application based on well-established medicinal use of Medicinal Gaseous Oxygen AIR PRODUCTS. This type of application does not require submission of the results of preclinical 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.

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

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 these product types 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 and excipients
The active substance is oxygen, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data of liquid oxygen samples demonstrating compliance with this specification have been provided for 3 batches from one site and at least 2 batches for the other 6 sites. One batch is defined as one filled tanker.

The Active Substance Master File (ASMF) procedure is used for 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.

A re-test period of 6 months can be granted. No formal stability study has been carried out on liquid oxygen by the MAH. The MAH refers to stability information in the literature. This is acceptable, considering that oxygen is a naturally occurring element, which is a highly stable diatomic gas, and also considering the Note for Guidance on medicinal gases: pharmaceutical documentation.

No excipients are used, which is common for medicinal gas.

**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 Gaseous Oxygen AIR PRODUCTS, 100% v/v, medicinal gas, compressed, consists of oxygen. Oxygen is a colourless, odourless and tasteless gas.

The packaging cylinders are usual and suitable.
-Cylinder: high-pressure cylinder, constructed from chromium molybdenum steel or aluminium.
-Valve: conventional isolating valve used to open and close the cylinder or integral valve (integral pressure regulator coupled with an isolating valve).
The MAH has laid down the sizes of cylinders with the pressure to be used, and the material and the valves, in accordance with the Note for Guidance on medicinal gases: pharmaceutical documentation.

Medicinal oxygen is administered through inhaled air, preferably using dedicated equipment, e.g. nasal cannulae or facial mask to spontaneously breathing patients. Other methods include anaesthetic circuits (using masks or endotracheal tubes), resuscitator devices, hoods, cots, tents and incubators.
There is no dose as such for oxygen therapy. Gaseous oxygen is administered in many various situations at different concentrations and different pressures, e.g. normal concentration of oxygen at normal atmospheric pressure, higher concentrations at normal atmospheric pressure and oxygen above ambient pressure.

Pharmaceutical development
Since the “Note for Guidance on medicinal gases: Pharmaceutical documentation” (CPMP/QWP/1719/00) was adopted in 2002, it is mandatory in the EU to register medicinal gases as medicine replacing the status of medical device. In this case, AIR Products/NL has supplied oxygen 100% v/v for several decades. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice for the cylinder is based on the pressure requirements of the final product.

Manufacturing process and quality control of the medicinal product
No process validation report has been submitted. This is acceptable, since the manufacturing of the finished product is a well-established method that has been used by Air Products/NL for several decades in Europe for the production of gaseous medicinal oxygen. Besides, a specification for filling pressure is included. The MAH has submitted a validation report on the reproducibility of the filling process at one of the sites according to the Note for Guidance on medicinal gases: pharmaceutical documentation. Validation results of at least 20 consecutive batches showed that the requirements of the Ph.Eur. are met, all batches are filled to >200 bar, and that the vacuum levels are in line with the GMP requirements.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for oxygen in the Ph.Eur. and includes tests for identification, oxygen purity, carbon dioxide, carbon monoxide and water. The finished product specification for the package includes nominal filling charge pressure, filling charge pressure tolerance, appearing and labelling. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

The normal analytical methods used are those specified by the Ph.Eur.

Batch analytical data from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
No formal stability study has been carried out, which is acceptable for this oxygen containing product. Gaseous oxygen contained within the high-pressure cylinder is in its most stable state. A shelf life of 3 years can be granted, based on bibliographical data. The stability is in accordance with framework Directive on transport of dangerous goods by road, and with the Note for Guidance on medicinal gases. The labelled storage conditions are between -20 and +65 degrees Celsius. Further special precautions are mentioned in the 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

This active substance has been available on the European/Dutch market for several decades. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

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

II.3 Clinical aspects

Medicinal gaseous oxygen is a well-known active substance with established efficacy and tolerability.

For this bibliographical application, the MAH has not conducted clinical trials or presented original clinical study data. The MAH has submitted detailed references to published scientific literature, which is in

accordance with current regulations. This is acceptable, since the current application concerns a product that is essentially similar to those already on the market in the Netherlands.

The following indications were acceptable for all concerned member states: *'normobaric oxygen therapy: treatment or prevention of acute or chronic hypoxia', 'normobaric oxygen therapy: treatment of cluster headache', 'hyperbaric oxygen therapy: treatment of serious carbon monoxide poisoning', hyperbaric oxygen therapy: treatment of decompression sickness, or of air/gas embolism of a different origin'* and *'hyperbaric oxygen therapy: as supporting treatment in cases of clostridial myonecrosis (gas gangrene)'*.

However, during the procedure a potential serious risk to public health was raised regarding two proposed indications in the SPC: *'hyperbaric oxygen therapy: for the support treatment of blood circulation problems in skin transplants and skin reconstruction'* and *'hyperbaric oxygen therapy: supporting treatment in cases of osteoradionecrosis'*. Therefore, a referral to the CMD(h) was started. The opinion of the MEB was discussed in the Board meeting of 11 October 2007 regarding the two indications, which were not approvable for all concerned member states.

In the CMD(h) meeting of 12-13 November 2007, the following was discussed:
A concern was raised regarding the clinical evidence for the indications *'Hyperbaric oxygen therapy: for the support treatment of blood circulation problems in skin transplants and skin reconstruction'*, and *'Hyperbaric oxygen therapy: supporting treatment in cases of osteoradionecrosis'*.
At the CMD(h) meeting the RMS presented its view and the applicant's written response was discussed. The indications approved in another Mutual Recognition Procedure (SE/H/0607/001-002/MR, including DK, EE, FI, IS, LT, LV and NO) were also taken into account during the discussion. Following the discussion, agreement was reached to <u>remove the indication</u> *'Hyperbaric oxygen therapy: for the support treatment of blood circulation problems in skin transplants and skin reconstruction'* because of the lack of adequate clinical data.
It was also agreed to <u>maintain the indication</u> *'Hyperbaric oxygen therapy: supporting treatment in cases of osteoradionecrosis'* as the established use of hyperbaric oxygen in daily clinical practice is considered to be of overriding importance, even though there is a lack of data from adequate clinical trials.

Oxygen is essential for life. Ambient air consists of around 20.9% v/v oxygen (depending on the height above sea level) and nitrogen. As one of the three basic essentials of life (oxygen, water and food) there is no substitute for oxygen. The deprivation of oxygen (hypoxia) leads to death within minutes. Oxygen is usually given as a source of extra oxygen in patients with hypoxia of various origins to restore, or at least improve, tissue oxygen levels, and thus prevent death. Oxygen therapy has also been shown to be effective in the treatment of cluster headache. The use of oxygen at pressure greater than atmospheric pressure increases the amount of oxygen in the blood above that of normal levels, and thus increases tissue oxygen levels. Hyperbaric oxygen therapy is the primary therapy in patients with severe CO intoxication, decompression sickness and arterial gas embolism and as adjuvant therapy for osteoradionecrosis, and clostridial myonecrosis.
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. 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 good if the substance is used correctly and under well-controlled circumstances.

<u>Risk Management Plan</u>
A risk management plan is not necessary, because of the age of the product group. The safety profile of medicinal gaseous oxygen can be considered to be well established and no product-specific pharmacovigilance issues were identified pre- or post authorisation, which are not adequately covered by the current SPC. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European risk management plan is not necessary for this product.

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 readability test has been adequately performed. The test process involved two rounds with 10 participants each.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Medicinal Gaseous Oxygen AIR PRODUCTS, 100% v/v, inhalation gas is essentially similar to many other medicinal oxygen products considering the same pharmaceutical form, the same route of administration, the consistent manufacturing as required according to the European Pharmacopoeia and the similar impurity profile.

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. Braille conditions are met by the MAH.

The following indications were acceptable for all concerned member states: *'normobaric oxygen therapy: treatment or prevention of acute or chronic hypoxia', 'normobaric oxygen therapy: treatment of cluster headache', 'hyperbaric oxygen therapy: treatment of serious carbon monoxide poisoning', hyperbaric oxygen therapy: treatment of decompression sickness, or of air/gas embolism of a different origin'* and *'hyperbaric oxygen therapy: as supporting treatment in cases of clostridial myonecrosis (gas gangrene)'*. However, during the procedure a potential serious risk to public health was raised regarding two proposed indications in the SPC: *'hyperbaric oxygen therapy: for the support treatment of blood circulation problems in skin transplants and skin reconstruction'* and *'hyperbaric oxygen therapy: supporting treatment in cases of osteoradionecrosis'*. Therefore, a CMD(h) referral was started. The opinion of the MEB was discussed in the Board meeting of 11 October 2007 regarding the two indications, which were not approvable for all concerned member states.

Following the discussion in the CMD(h) of 12-13 November 2007, agreement was reached to remove the indication *'Hyperbaric oxygen therapy: for the support treatment of blood circulation problems in skin transplants and skin reconstruction'* because of the lack of adequate clinical data. It was also agreed to maintain the indication *'Hyperbaric oxygen therapy: supporting treatment in cases of osteoradionecrosis'* as the established use of hyperbaric oxygen in daily clinical practice is considered to be of overriding importance, even though there is a lack of data from adequate clinical trials.

On the basis of the data submitted, the concerned member states have granted a marketing authorisation.

The PSUR submission cycle is 3 years. The first PSUR will therefore cover the period from January 2006 till January 2009.

The renewal date is 31 January 2011.

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

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
CMS	Concerned member state
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
MRP	Mutual Recognition Procedure
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RMS	Reference member state
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 procedure	Approval/ non approval	Assessment report attached
Repeat use procedure with SK	NL/H/0923 /001/E/001	E	2-3-2010	3-5-2010	Approval	Y, Annex I

ANNEX I – Repeat use procedure (NL/H/0923/001/E/001)

The Repeat use procedure started on 2 March 2010. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state (SK), on the basis of the data submitted, considered that Medicinal Gaseous Oxygen AIR PRODUCTS, 100% v/v, inhalation gas is essentially similar to many other medicinal oxygen products considering the same pharmaceutical form, the same route of administration, the consistent manufacturing as required according to the European Pharmacopoeia and the similar impurity profile. The CMS has therefore granted a marketing authorisation. The repeat use procedure was finished on 3 May 2010.

The date for the first renewal will be: 31 January 2011. This is five years after national approval in the Netherlands.

A three-yearly PSUR cycle has been agreed upon in accordance with the agreed scheme during the initial MRP.

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