CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Mediox, inhalation gas 100% v/v
Medidis 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/2297/001/MR
Registration number in the Netherlands: RVG 30851

22 April 2013

Pharmacotherapeutic group:	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 BE, DK
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 Mediox, inhalation gas 100% v/v from Medidis B.V. The date of 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. (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 of vital importance to life and all tissues should receive a continuous oxygen supply in order to maintain cellular energy production. Oxygen in inhaled air reaches the lungs and diffuses over the walls of the alveoli and surrounding blood capillaries. It then reaches the blood which (mainly bound to haemoglobin) then transports it through the body. This is a normal physiological process, essential for survival.
The administration of additional oxygen in the case of hypoxia improves oxygen supply to the tissues.
By the administration of oxygen under pressure (hyperbaric oxygen therapy) the amount of oxygen that can be absorbed by blood (including the fraction not bound to haemoglobin) can be significantly increased. As a result the amount of oxygen that can be supplied to tissues also increases. With the use of hyperbaric oxygen therapy in the treatment of gas or air embolisms the high pressure reduces the volume of the gas bubbles. The gas can then be absorbed faster from the gas bubble in the blood, and be exhaled via the lungs.

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.

In this mutual recognition procedure 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 medicinal, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). Full details regarding the production process are included in the dossier.

Manufacturing process
The manufacturing process of oxygen for medical purposes complies with the technical state of the art for cryogenic air separation. The production of oxygen by cryogenic air separation is a physical process; the oxygen is not subject to any chemical reactions. A validation protocol has been submitted and results of the validation are provided. The included batch analysis results of three batches show compliance with the Ph.Eur. monograph.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur.; this specification is acceptable. Results have been provided on three batches showing compliance with the specification. The process is sufficiently under control.

Stability of drug substance
Reference is made to the Note for Guidance on medicinal gases, which states that in case of highly stable gases with a long history of utilisation, bibliographic data is sufficient (e.g. for oxygen). A literature reference is given. Furthermore, it is noted that in the daily production of liquid oxygen it is continuously pumped into the storage container which results in continuous mixing of freshly produced oxygen with residual oxygen. Samples obtained from the transport tankers are consistently in compliance with the release specification. The stability of the liquid oxygen is considered sufficiently guaranteed.

** 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
MEDIOX contains as active substance 100% v/v oxygen (O_2) and is a colourless, odourless and tasteless gas.

The oxygen gas is packed in pressurized gas cylinders. The gas cylinders are made of steel, aluminium or composite material. The valves are made of brass. The gas cylinder body and shoulder (the curved part at the top of the cylinder) are painted white. The compressed gas is available in different unit volume sizes of single cylinders of nominal water capacities from 0.3 L to 50 L and cylinder bundles of 800 L (or 16 x 50 L).

No excipients are present.

Pharmaceutical development
The development of the product is satisfactory performed and explained.
The filling process used is well established and has been used by the drug product manufacturer for many years. The oxygen is stored in liquid form in a bulk tank. The liquid oxygen is pressurized, becomes gaseous after passing through an evaporator and is filled in cylinders. No overfill is used.
The packaging cylinders are usual and suitable for the product at issue. Reference is made to ISO 11114-1 and ISO 11114-2 regarding the compatibility of the gas cylinder and valve materials with the gas content. All packaging and valve materials used comply with this standard.

Manufacturing process
The phase of the oxygen is first changed from liquid to gaseous and then filled into suitable gas cylinders. The process has sufficiently been described. To demonstrate the reproducibility of the filling process, data of several batches were evaluated. It may be concluded that the filling process is suitable and that Ph.Eur. and GMP requirements are safeguarded by various measuring points. Validation data of cylinders filled to 300 bar have been provided.

Quality control of drug product
The product specification complies with the Ph.Eur. 0417 (oxygen for medicinal use) requirements. Since the analytical methods used are those described in the Ph.Eur. monograph for oxygen and since the drug product does not contain any excipients, validation of test methods is not required. Batch analytical results have been submitted from five full-scale batches with filling pressure of 200 bar and 300 bar.

Stability of drug product
Formal shelf life testing on the drug product has not been conducted since oxygen is highly stable in its gaseous state with no degradation pathway and when held in an inert container. The product is packaged in gas cylinders complying with current regulations. A shelf-life of 3 years can be granted based on bibliographic documentation. Storage conditions are set between -20 and +65 °C.

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

Medical gases containing 100% v/v oxygen have been available on the European market for many years. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the Board agreed that no further non-clinical studies are required.

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

II.3 Clinical aspects

Oxygen is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. As the use of medicinal oxygen is well established and supported by many publications over the years concerning both its safety and efficacy, the Board agreed that no further clinical studies are required.

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 produce biological energy from food fuel (e.g. glucose metabolism).

Pharmacodynamics
In cases of arterial hypoxia, the administration of supplemental oxygen will improve tissue oxygen delivery. Oxygen therapy may decrease ventilation, heart rate and cardiac output. 100% oxygen at atmospheric pressure does not alter oxygen consumption, carbon dioxide production or the respiratory quotient in normal subjects at rest.

Clinical efficacy
No clinical trial data have been submitted as the application is bibliographic. The use of gaseous oxygen is well established and it has been used worldwide for decades.

Clinical safety
Safety aspects of the use of gaseous oxygen are considered and discussed adequately in the provided Expert Report. From post marketing data of 700,000 users of Gaseous Medicinal Oxygen in Europe very few adverse events were reported.
The most important identified risks are:

- Suppression of hypoxic drive. In patients whose respiratory centre is depressed by long term retention of carbon dioxide, injury or drugs, ventilation is maintained by stimulation of carotic and aortic chemoreceptors. In patients with such a hypoxic drive, e.g. in severe chronic obstructive disease, an acute rise in PaO2 as a result of oxygen inhalation may further depress ventilation. Hence, careful oxygen titration is needed as stated clearly in the SPC.
- Pulmonary and CNS toxicity. Exposure to high concentrations of inspired oxygen increases the production of toxic metabolites (free radicals and hydrogen peroxide) more than endogeneous enzymes can detoxify them resulting in accumulation of toxic metabolites. The most susceptible sites for toxic oxygen metabolites are CNS and the lungs. As a result neurological symptoms, severe pulmonary oedema, hypoxia and finally death may occur. Paragraphs about CNS and pulmonary toxicity are included in the SPC.
- Retinal damage. 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 entereocolitis. Hence, this patient population should not be exposed to high concentrations of oxygen as is included in the appropriate SPC section.
- Fire. From post- marketing data about 4 cases of fires caused by patients smoking whilst receiving oxygen therapy occur per year in the UK. In the proposed SPC the risk of fire and the appropriate precautions are included. Beside no smoking, warnings and an equipment instruction are incorporated in the SPC/PIL.
- Contaminants. The main contaminants of oxygen are argon and methane. None of them may cause any toxic effects at the present levels.

Clinical conclusion
Based on the broad experience and literature data, oxygen is considered to have a well established efficacy and safety profile. The benefit/risk ratio is favourable if the substance is used correctly and well-controlled.

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 management plan
The application concerns a product for which no safety concerns requiring additional risk minimisation activities have been identified. Routine pharmacovigilance activities will be sufficient to ensure safe use of the product. This is considered acceptable.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with those accepted for other gaseous oxygen products approved in the Netherlands.

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 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The two rounds of testing showed that, for each question, at least 99.5% of participants were able to find the correct information, and at least 99.5% of participants were able to answer the questions correctly. No revisions were made based on the results.
Based upon evaluation and analysis presented the package information leaflet for Mediox 100% v/v meets the necessary conditions for readability testing.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

MEDIOX, inhalation gas 100% v/v 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.

Medicinal 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 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, patients 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.

The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that well-established use has been demonstrated, and has therefore granted a marketing authorisation. MEDIOX, inhalation gas 100% v/v was authorised in the Netherlands on 31 January 2006. The other member states mutually recognised the Dutch evaluation for the marketing authorisation. The mutual recognition procedure was finished on 10 December 2012.

The date for the first renewal will be: 13 July 2017.

The following post-approval commitments have been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to specify temperature and pressure stabilisation time after filling
- The MAH committed to describe the nature of leak testing.
- The MAH committed to provide validation data on the filling procedure of cylinder bundles.
- The MAH committed to provide the Notified Body certificates for all marketed cylinders and valves.

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
CNS	Central Nervous System
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