CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Conoxia, 100% v/v, medicinal gas, compressed
Linde Gas Therapeutics Benelux 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/1669/001/MR
Registration number in the Netherlands: RVG 30355

11 January 2010

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 BE and LU
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 Conoxia, 100% v/v, medicinal gas, compressed, from Linde Gas Therapeutics Benelux 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 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 mutual recognition procedure concerns a bibliographical application based on well-established medicinal use of oxygen 100% v/v, medicinal gas, compressed. 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.

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 distillation of liquefied air. Sufficient information has been provided on the production process.

Specification
The drug substance specification is in line with the Ph.Eur.; this is acceptable. A batch is defined as the filling of one tank. This is acceptable as the production process is continuous. Batch analysis results of 3 batches of each manufacturing site have been provided, demonstrating compliance with the specification. The process is deemed sufficiently under control.

Stability
The drug substance is packaged 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 tests have been performed and a re-test has not been laid down. This is acceptable as the active substance is tested three times a day for compliance with Ph.Eur.

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

No excipients are used.

Container closure system
The medicinal gas is packed in gas cylinders. Cylinder/valve combinations which have been used in the gas industry for medicinal products for a long time are used. The gas cylinders are made of steel, aluminium or composite. The cylinder valves are made of brass, steel or aluminium. The materials in contact with the compressed gas mixture are compatible with oxygen. This is acceptable.

Pharmaceutical development
A historical overview of the development of oxygen as medicinal gas in cylinders has been provided. The packaging cylinders are usual and suitable for the product at issue, and have been used in the gas industry for medicinal products for many years. The critical steps in the filling process that can affect the quality of the product are vacuum pressure, leak checks, filling pressure and speed due to the development of heat during the filling of the cylinder, the target filling pressure will vary with the filling speed. The development of the product is satisfactorily performed and explained.

Manufacturing process
The manufacturing consists of filling gaseous oxygen into gas cylinders. All filling activities are performed on filling manifolds dedicated to filling of medicinal products only. Batch analysis results have been included for many batches, showing compliance with the specifications. The process has been adequately validated and is sufficiently under control.

Overages/Overfill
The manufacturing tolerances for filling pressure are 200 bar ± 4% so between 192 and 208 bar at 15 °C. This is acceptable.

Quality control of drug product
The product specification includes tests for appearance and labeling of the product, as well as for assay, water and filled quantity. The requirements are in line with the Ph.Eur. Analytical methods are according to Ph.Eur., and therefore do not require validation. Batch analysis results have been provided for 18 batches, demonstrating compliance with the Ph.Eur. requirements.

Stability tests on the finished product
Oxygen is a stable gas which has been used for a long time packaged in containers for which a long time of experience is available. Therefore, only a simple stability study has been performed. Five 10 L chrome-molybdenum steel cylinders were stored up to 48 months indoors in a non-controlled temperature area, where temperature could vary from -10°C to +30°C. There was no change in composition, neither in oxygen concentration, nor in level of impurities.
Also, results are available from a study in which gas cylinders were stored in a military depot for 17 years. The Ph.Eur. parameters were all within specifications. The only deviating parameters are pressure (>70% within 200 bar ±5%) and odour (only 40% passes test). The odour was rubber like, presumably originating from the sealing materials in the valve. The pressure deviation may result from the long storage time and is not considered to be a problem with regard to the quality of oxygen.
Based on the stability data provided, the claimed shelf-life of 3 years could be granted. The storage conditions are usual: *'Store between -20°C 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

Only limited non-clinical information is provided in the non-clinical overview, which was updated for the last time in 2003. Considering the existing extensive clinical experience with oxygen, a limited overview was accepted. Also, no update has been deemed necessary to reflect the changes due to the referral outcome for procedure NL/H/923 in preparation for the current MRP.

Pharmacology
No specific primary pharmacodynamics data were available. Instead, a short overview of the relevant physiology of oxygen transport by the blood is provided. In addition, the effects of administration of normobaric and hyperbaric oxygen on the fraction of oxygen dissolved in plasma is discussed.

Published studies of hyperoxia in laboratory animal species on mucociliary clearance in dogs and on

intratracheal mucous flow in cats, effects on rabbit, guinea pig and mouse alveolar macrophages were reviewed. The possible contribution of reactive oxygen species to lung damage caused by hyperoxia was discussed. The adverse effects of exposure to 100% oxygen for 7 days in baboons were described. A loss of pulmonary perfusion autoregulation was found in oxygen-injured primate lungs.

Pharmacokinetics
Clinical literature information was provided on pharmacokinetics/physiology of oxygen in plasma and its delivery to the tissues. The normal function of oxygen in metabolism is described, as well as the production of ROS (reactive oxygen species). The involvement of ROS in potential toxic reactions is shortly reviewed. The reversible binding of oxygen to haemoglobin is shortly described.

Toxicology
Single dose toxicity: The major clinical signs of death due to exposure to pure oxygen in rats is described. Death is due to pulmonary oedema and respiratory failure. However, after prior exposure to 85% oxygen, rats have been adapted and survive exposure to 100% oxygen for long periods of time.

Repeat dose toxicity: The pulmonary effects related to inhalation of different mixtures with oxygen (different fractions of inspired oxygen: FIO_2 of 0.6 – 1.0) in rats are described. Pathological pulmonary changes in baboons and squirrel monkeys exposed to 100% oxygen are described.

Special studies: details of pathological changes in animals exposed to high concentrations of inspired oxygen were reviewed.
- retinal pathology in rabbits
- lung pathology in monkeys (Macaca mulattta)
- lung pathology in rats and mice exposed to high concentratons of oxygen.

Overall it is concluded that based on literature, the pulmonary capillary endothelial is the first lung cell type to be seriously damaged by hyperoxia.

Under reproductive and developmental toxicity, the age-dependent resistance of neonatal rats to the pneumotoxic effects of prolonged hyperoxia compared with adult animals is described. Furthermore, the clinical manifestation of oxygen toxicity in intensive care units and in premature neonates is described.

Under genotoxicity it is agreed that no reports are available in the literature concerning this issue.

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 an expert report with 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 expert report is of good quality. No update has been deemed necessary to reflect the changes due to the referral outcome for procedure NL/H/923 in preparation of the current MRP.

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
As considered above, no clinical trial data have been submitted as the application is bibliographic. The use of gaseous oxygen is well established and it is used worlwide since a long time.
The expert report reflects and discusses all of the known indications applied for gaseous oxygen sufficiently. However, not all of these indications are included in section 4.1. of the proposed SPC, as the value of oxygen as adjuvans is debatable in certain treatment indications. Furthermore, oxygen may be administered above ambient pressure as auxilairy in the treatment of crush injuries, failing skin grafts and flaps, non-healing ischaemic wounds, burns, smoke inhalation, chronic refractory osteomyelitis, actinomycosis and intracranial abcesses. However, the MAH has not proposed to include these indications in the SPC.
Finally, the Guidelines of the Royal College of Physicians for Domicilliary Oxygen are considered in the expert report. These Guidelines include a detailed description of diseases and their severity that may be treated with gaseous oxygen at home.

Clinical safety
Safety aspects of the use of gaseous oxygen are considered and discussed adequately in the expert report. From post marketing data of 700,000 users of gaseous medicinal oxygen in Europe very few adverse events were reported:

- 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 central nervous system (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 entreocolitis. 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 it is known that in the UK per year about 4 cases of fires occur caused by patients smoking whilst receiving oxygen therapy. In the proposed SPC the risk of fire and 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.

<u>Risk management plan</u>
The safety profile of medicinal gaseous oxygen can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

<u>Pharmacovigilance system</u>

Several deficiencies were identified during the mutual recognition procedure in the pharmacovigilance system. The MAH therefore committed to ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

Product information

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 two rounds with 10 participants each. The age range and education level is considered to be representative for the indicated patient group. The user testing was performed thoroughly. Although the participants in general thought that the leaflet was too long, the general impression of the participants was positive. Testing resulted in many improvements to the leaflet. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Conoxia, 100% v/v, medicinal gas, compressed 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 presented an adequate overview of the available clinical and non-clinical data on the medicinal use of oxygen, supporting the well-established medicinal use of the product. The benefit/risk ratio is favourable for the proposed indications if oxygen is used correctly and under well-controlled circumstances.

Provided that the remaining deficiencies are rectified prior to the MAH placing the medicinal product on the market, the Pharmacovigilance System is considered to fulfil the requirements (see commitment below).

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other medicinal gaseous oxygen containing products.

The Board followed the advice of the assessors. Conoxia, 100% v/v, medicinal gas, compressed was authorised in the Netherlands on 31 January 2006.

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 12 November 2009.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from November 2009 to November 2012.

The date for the first renewal will be: 31 January 2011.

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

<u>Pharmacovigilance System</u>

- The MAH committed to submit an updated description of the Pharmacovigilance System. The following missing topics will be included under '*Procedures in place which are documented in writing':*
  - Detection of duplicate reports
  - Electronic reporting
  - Management and use of databases or other recording systems.

  The MAH will ensure that the system of pharmacovigilance is in place and functioning before the product is marketed in the CMSs.

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