

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Airapy, 21.5% 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/1661/001/MR
Registration number in the Netherlands: RVG 34694**

6 December 2010

Pharmacotherapeutic group:	medical gases
ATC code:	V03AN05
Route of administration:	inhalation
Therapeutic indication:	prevention of hypoxia
Prescription status:	non prescription
Date of first authorisation in NL:	28 November 2007
Concerned Member States:	Mutual recognition procedure with BE, 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 Airapy, 21.5% v/v medicinal gas, compressed from Linde Gas Therapeutics Benelux B.V. The date of authorisation was on 28 November 2007 in the Netherlands.

Airapy is considered a drug, i.e. it is used for medicinal purposes. The indication of Airapy, 21.5% v/v medicinal gas, compressed 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.

Airapy 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 Airapy, 21.5% v/v medicinal gas, compressed. 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 liquid form it has a pale blue colour.

Manufacturing process

Oxygen is prepared in air separation plants from atmospheric air. It is produced by distillation of liquefied air. The process is described in literature and it is common for the production of oxygen. Sufficient information has been provided on the production process.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. This 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 nine batches show compliance with the specification. The process is deemed sufficiently under control.

Stability of drug substance

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 tests have been performed and a re-test has not been laid down. This is acceptable as the active substance is tested 3 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

Airapy contains as active substance 20.4-22.6 % v/v of oxygen, and is a colourless, odourless and tasteless gas.

The product contains 77.4-79.6% nitrogen as excipient.

The medicinal gas is packed in cylinders or cylinder bundles as a compressed gas to a pressure of 200 bar. This is common for medicinal gases. The product is packaged in seamless cylinders made of steel or aluminium. Valves are made of brass.

Pharmaceutical development

The development of the product is satisfactory performed and explained. The product is intended to replace air. The packaging cylinders are usual and suitable for the product at issue. 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. No overage is used. The manufacturing tolerances for filling pressure are 200 bar \pm 4% so between 192 and 208 bar at 15 °C. This is acceptable.

Manufacturing process

The product is manufactured by adding oxygen and nitrogen to the gas cylinders one after another. Standard filling equipment is used. The cylinders are filled by weight; first oxygen is added, followed by nitrogen. The cylinder is placed on rotation equipment to homogenize the mixture. The pressure and the temperature are monitored to ensure that the cylinders are filled to the correct fill pressure. Proper in-process controls were laid down. Sufficient validation data have been provided on the different stages of the manufacturing process.

Control of excipients

Nitrogen complies with Ph.Eur. requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance and labeling of the product and for assay, identity of nitrogen, water. The requirements are in line with the Ph.Eur. Results of batch analysis have been provided on 18 batches, demonstrating compliance with Ph.Eur. requirements.

Stability of drug product

The product is packaged in gas cylinders complying with current regulations. Stability studies at ambient temperature, 30°C and 60°C have been performed with oxygen covering the whole shelf life of 36 months at 30°C. These studies are justified to be used to substantiate a shelf-life of 3 years for the product at issue with the usual storage condition '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

Air has been used in Europe for many years. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment is necessary. A combined non-clinical and clinical expert report has been submitted. This is briefly discussed in section II.3 'Clinical aspects'.

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.

According to the MAH Airapy can be used for a variety of applications as a source of oxygen and a source of clean air. These applications for air are discussed. Some of these were however considered non-applicable for a medicinal product; they were assessed as being applications for a medical device. The RMS however has agreed to summarise these applications to one acceptable indication: prevention of hypoxia. The MAH has accepted this summary.

Airapy 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 Airapy must not be administered at pressure as it may cause decompression sickness and oxygen toxicity.

Product information

SPC

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 Airapy used under the conditions stipulated.

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 1 round with 5 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. There was a sufficient number of questions on critical sections 2 and 3.

The three stages of testing resulted in small adaptation of the PIL. The latest QRD was the reason for the most adaptations. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Based on the submitted dossier and further literature, Airapy, 21.5% v/v medicinal gas, compressed, containing 21.5% v/v and nitrogen 78.5% 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.

There are no specific undesirable effects of breathing air. Overdose cannot occur, but Airapy 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 Airapy used under the conditions stipulated. 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.

The Board followed the advice of the assessors. Airapy, 21.5% v/v medicinal gas, compressed was authorised in the Netherlands on 28 November 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, considered that Airapy 21.5% 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.

A first six-month's PSUR was submitted after registration and covered the period from 28 November 2007 to 27 May 2008. The MAH state that in the PSUR covering period no new safety issues have been identified. For this reason and because medicinal air has been in use in medical practice for a long time, a 3-yearly PSUR cycle was accepted.

The date for the first renewal will be: 28 November 2012.

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
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 _{1/2}	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