CBG MEB

Public Assessment Report

Scientific discussion

Apulco He 9%, medicinal gas, compressed
Apulco HeOxy 9%, medicinal gas, compressed

(Helium)

NL/H/2969/001-002/DC

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This module reflects the scientific discussion for the approval of Apulco He 9% and Apulco HeOxy 9% medicinal gas, compressed. The procedure was finalised on 23 January 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AARC	American Association for Respiratory Care
ASMF	Active Substance Master File
ATS	American Thorax Society
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CF	Cystic fibrosis
CMS	Concerned member state
COPD	Chronic obstructive pulmonary disease
ERS	European Respiratory Society
FRC	Functional residual capacity
GTN	Glyceryl Trinitrate
He	Helium
MAH	Marketing authorisation holder
MBW	Multiple breath washout (method)
O_2	Oxygen
Ph.Eur.	European Pharmacopoeia
PL	Package leaflet
RMS	Reference member state
SmPC	Summary of product characteristics
TLC	Total lung capacity
VC	Vital capacity

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Apulco He 9% and Apulco HeOxy 9% medicinal gas, compressed from Air Products Nederland B.V.

The product is for diagnostic use only. It is for use in the determination of the lung volumes during multiple breath helium diagnostic testing of lung function.

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

Lung function gases are always administered through a lung function gas machine. The machines can work with gas mixtures which slightly differ in the range of the individual components within the gas mixture composition, but the type and number of gas components in the gas mixture is defined by the machine manufacturer.
In addition to this variety of gases, the doctor can also decide to use slightly different lung function gas mixtures, within the tolerances allowed by the machine. The demand for lung function gas mixtures is therefore changing constantly.
Each lung function gas mixture is a stable mixture and is filled and supplied in dedicated high pressure cylinders. The doctor can use these gas cylinders for several patients, therefore the need for gas cylinders is very low, typically 2 to 10 cylinders per year, per mixture depending on the application.

This decentralised procedure concerns an application under Article 10(a) of Directive 2001/83/EC, well established use. This is according to current EU directives (EU, 2001a) on what defines a medicinal product, which includes “Any substance or combination of substances (...) administered to human beings (...) with a view (...) to making a medical diagnosis”.

Also, inhaled gases for lung function tests should be considered as medicinal products of well established medicinal use as they meet the defining qualifications (EU, 2001b) relating to:

(i) ”the time over which a substance has been used”, which “must not be less than one decade from the first systematic and documented use”,
(ii) “quantitative aspects of the use of the substance”,
(iii) “the degree of scientific interest in the use of the substance (reflected in the published scientific literature)”
(iv) “the coherence of scientific assessments”.

Therefore, the application is solely based on scientific literature data, and no new non-clinical or clinical studies were conducted.

The concerned member states (CMS) involved in this procedure were Germany and Spain.

II. QUALITY ASPECTS

II.1 Introduction

Apulco He 9% and Apulco HeOxy 9% medicinal gas, compressed are colourless, odourless and tasteless gases.

Apulco He contains 9.0% helium, 21% oxygen and, as balance, nitrogen. Apulco HeOxy contains 9.0% helium, 35% oxygen and, as balance, nitrogen. The products consist of essentially similar mixtures with the concentration of oxygen differing between the two.

The medicinal product is packed in gas cylinders made of aluminium, equipped with a brass valve with a specific outlet connector. Gas cylinders are identified also by colour: the shoulder is painted in light blue and the cylinder body in white.

II.2 Drug Substance

The active substance is helium, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Helium is a colourless, odourless, tasteless, and inert gas. Helium is extracted from natural gas.

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.

Manufacturing process
Upon liquefaction of natural gas, helium is concentrated in the gaseous phase. Helium is purified from this phase and liquefied. At the transfilling site, helium is vaporised and filled in cylinder bundles. The manufacturing process was sufficiently described.

Quality control of drug substance
The drug substance specification is in accordance with the Ph.Eur. monograph on helium. Batch analysis data demonstrating compliance with the release specification were provided for three batches, each consisting of a pack of 23 cylinders with a water capacity of 50 litres.
The drug substance is packed in cylinder bundles made from steel. Each bundle has one valve. Valves are of the NEVOC (New European Valve Outlet Connections) type. The pressure inside the cylinders is 300 bar. Sufficient information was provided on the standards according to which the cylinders are tested and on the valves.

Stability of drug substance
No stability studies have been carried out on the drug substance as it is a stable, inert gas. The claimed re-test period of 36 months is justified. The cylinder bundles are stored according to GMP Annex 6 (stored under cover, protected from adverse weather conditions).

II.3 Medicinal Product

Pharmaceutical development
The two mixtures differ in the amounts of oxygen and nitrogen. The mixtures contain 9% of helium, 21% or 35% of oxygen and depending on the amount of oxygen, 56% or 70% of the excipient nitrogen. Lung volume mixtures have been used as a medicinal gas for more than 10 years.
The manufacturing steps do not result in any change of state. The choice of aluminium or aluminium hoopwrapped cylinders is based on the specific wishes of the customer/user of the final product. The choice of cylinder material and the valve is based on their specific compatibility for use with oxygen, because helium and nitrogen are inert gases, hence are compatible with all common materials. Pharmaceutical development has been adequately described.

Manufacturing process
The manufacturing process consists of filling of helium by pressure, followed by filling of oxygen and nitrogen by weight. The manufacturing process was adequately described. A batch is defined as all cylinders filled during an uninterrupted filling operation, via a multi-cylinder manifold and using the same batch of the materials helium, oxygen, and nitrogen, respectively.
The manufacturing process was successfully validated with a sufficient number of batches of both mixtures covering all cylinder sizes. The provided process validation data demonstrate reproducibility of this process.

Control of excipients
The excipients oxygen and nitrogen are tested according to the Ph.Eur. CEPs are available for both excipients.

Quality control of drug product
The drug product specification includes acceptance criteria for the content of helium and oxygen (each cylinder), identification of nitrogen (one cylinder per batch), and pressure. The release and shelf life specifications are identical. The drug product specification is acceptable. Sufficient batch analysis data have been provided for each mixture.

Stability of drug product
On the basis of bibliographic evidence, the MAH claims a shelf life of 36 months for the drug product. In addition, supporting stability data have been provided covering 24 months of all container sizes of the mixture containing 35% of oxygen and 18 months for all container sizes of the mixture containing 21% of oxygen. No trends are seen in these stability data. Moreover, the MAH provided bibliographical evidence on the homogeneity of the drug product under various conditions of use (e.g., extreme temperatures, cooling and heating cycles, cylinder utilisation, abrupt opening). Based on the provided bibliographical evidence and the supporting stability data, the claimed shelf life of 36 months is justified. Appropriate storage conditions have been laid down, which are included in section 6.6 of the SmPC.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Apulco He 9% and Apulco HeOxy 9% medicinal gas, compressed have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:
- The MAH committed to continue the stability studies up to the shelf life of 36 months.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

The components helium and oxygen are well known naturally occurring substances. The use of these gases in the diagnostic helium dilution test is clinically well-established.
The pharmacokinetics of O_2 in this product will follow the normal physiological kinetic properties of O_2.
Helium is not absorbed after inhalation, and exhaled without modification. Helium and oxygen are not generally toxic, genotoxic, carcinogenic or toxic to reproduction at the concentrations in which they are present in the current product.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since lung function tests are well-established medicinal products that have been used for decades, approval of Apulco He 9% and Apulco HeOxy 9% will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

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 member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

The application is based purely on bibliographic clinical evidence that the helium dilution test is a well-established procedure, and is widely used in lung function diagnostics for measuring static lung volumes.

Helium is the only constituent of the gas mixture that is required for measuring lung volumes. The oxygen and nitrogen are normal air constituents and are required, respectively, as vital physiological substrate and as inert “filler” to provide an equilibrium pressure at room temperature.

Inhaled helium is non-toxic at room temperature and is essentially physiologically inert.

The MAH declared that the concentrations of the lung test gas, He 9%, and O_2 21% or 35%, are standardised according to the American and European practice guidelines (AARC 1999[1], Macintyre et al, 2005[2], Wanger et al, 2005[3]). Since its introduction, helium has been used at the concentration close to 10% or even higher for dilution test, for measuring lung volumes.

The gases are used in the helium dilution test which is a closed-circuit, multiple-breath procedure and, for this reason, oxygen is present at a concentration that is higher than normal atmospheric concentration of 21% in order to ensure normal oxygenation as oxygen is consumed during the procedure (the gas detection systems need to be calibrated across the range of expected change in the concentration of oxygen).
For that reason the test gas has to consists of air with added oxygen at 25–30% or possibly higher, (and helium at 10% or less) according to the recommendations of the American Thorax Society (ATS) and European Respiratory Society (ERS). Apulco He has oxygen content of 21%, which is lower than recommended. In many pulmonary function laboratories, total lung capacity is routinely measured with the multiple-breath closed-circuit helium dilution technique. The MAH has justified the lower content of oxygen than stated in the ATS/ERS recommendations, arguing that at the beginning of the test, the oxygen level in the spirometer should be adjusted to 25-30% and that, during the multiple breath helium dilution test, oxygen is added, to compensate for oxygen absorption.

IV.2 Pharmacokinetics

Helium is physiologically inert and does not leave the lung via the bloodstream and, therefore, there are no clinically-relevant pharmacokinetic considerations.

IV.3 Pharmacodynamics

Because the density of helium is much less than that of air and its viscosity is greater, adding helium to air reduces turbulence in the airways (Simon et al, 2006[4]). Therefore, the work of breathing mixtures of helium and oxygen is less than with breathing air. The lower density of helium causes temporary voice changes.
In the lung function test, single breath helium test or multiple-breath washout test, helium mixes with air in the lungs. The inert properties of helium allow for measuring volumes after an equilibrium is reached.

[1] American Association for Respiratory Care (AARC) Clinical Practice Guideline Single-Breath Carbon Monoxide Diffusing Capacity, 1999 Update. RESPIRATORY CARE • May 1999 Vol 44 No 5
[2] MacIntyre N et al.. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005; 26: 720–735
[3] Wanger J et al. Standardisation of the measurement of lung volumes, Eur Respir J 2005; 26: 511–522.
[4] Simon B, Moody E & Johns R (2006) Therapeutic Gases:oxygen, carbon dioxide, nitric oxide and helium. In:Goodman & Gilman`s The Pharmacological Basis of Therapeutics (Ed: L. Brunton, J. Lazo and K. Parker) p. McGraw-Hill 0-07-146804-8

IV.4 Clinical efficacy

Lung function testing starts with spirometry. Additional testing measuring lung volumes (total lung capacity (TLC) and functional residual capacity (FRC)) might be necessary for the characterization of pathophysiological processes in lung disorders and is indicated for confirming or exclusion of a restrictive pattern in a patient with a reduced vital capacity (VC) (restrictive disorder). Restrictive lung disorders include interstitial lung diseases. They also include diseases, in which there is decreased chest wall compliance, i.e. kyphocscoliosis. Neuromuscular diseases also cause a restrictive ventilatory disorder, mainly due to inspiratory muscle weakness.
Measurement of lung volumes is also valuable in patients with COPD for selection of candidates most likely to benefit from lung volume reduction.

Lung volumes can be measured by the multiple breath helium dilution method, nitrogen washout, body plethysmography or radiographic imaging. The first two methods are used extensively in hospital pulmonary function laboratories, but they may underestimate the TLC in patients with moderate to severe COPD. The gold standard for measurement of TLC, particularly in the setting of significant airflow obstruction, is body plethysmography.
Apulco He 9% and Apulco HeOxy 9% are to be used for the determination of TLC and FRC during multiple breath helium diagnostic testing.
The method is based on the principle of gas equilibration. Gas containing a known concentration of He, as an indicator, is equilibrated between an unknown lung volume and a closed system, which has an in-line reservoir of known volume, by rebreathing. When equilibration has been achieved, the He concentration is the same in all parts of the system, and the final concentration of He in the reservoir can be determined. Assuming mass balance, the total volume of its distribution can, thus, be calculated from the initial concentration and volume of distribution of the He, and its final concentration. Subtracting apparatus volume from total volume gives lung volume (TLC). The test takes about 8-10 minutes, and rarely exceeds 10 min, even in patients with severe gas-exchange abnormalities.
At the beginning of the test, the oxygen level in the spirometer should be adjusted to 25-30% and, during the multiple breath helium dilution test, oxygen is added, to compensate for oxygen absorption. The volume of air contained in the lung at end-tidal expiration is defined as functional residual capacity and, in healthy adults, this volume is usually determined by the passive balance between the elastic forces of the lung and chest wall. FRC is measured by helium dilution (FRCHe).

Assessment of established use criteria

(i) ”the time over which a substance has been used”, which “must not be less than one decade from the first systematic and documented use”,
(ii) “quantitative aspects of the use of the substance”,
(iii) “the degree of scientific interest in the use of the substance (reflected in the published scientific literature)”
(iv) “the coherence of scientific assessments”.

The use of helium in the multiple-breath helium dilution test is described in many articles longer than one decade from the first systematic and documented use (i, ii) . Furthermore the use of helium in the helium dilution method is implemented in clinical guidelines such as the ATS/ERS guidelines as part of the ‘‘ATS/ERS Task Force, confirming a high degree of scientific interest (iii) as well as the coherence of scientific assessments (iv): Standardisation of lung function testing (Wanger et al, 2005[3]).

Children

In infants and very young children, clinical measurements of lung volumes are performed for a variety of reasons: to assess growth and development of the lung, to determine the efficacy of therapeutic interventions and to evaluate the effect of lung injury early in life and chronic lung disease.
In this population, the helium dilution procedure is mostly used to measure FRC. For pre-school children (95-125 cm in height) Pauwels et al (1996[5]) have derived reference values. The authors concluded that FRC measurements can be routinely performed in pre-school children using the helium dilution test.

[5] Pauwels JH, Van Bever HP, Desager KN, Willemen MJ, Creten WL, Van Acker KJ & Vermeire PA (1996) Functional residual capacity in healthy preschool children. Eur Respir J 9: 2224-30.

Beydon et al (2007)[6] concluded in their report that the multiple breath washout (MBW) test can be performed successfully in the vast majority of children between the ages of 3 to 6 years because it involves only normal tidal breathing. In patients with cystic fibrosis (CF), this test may be more sensitive to airway involvement than spirometry or airway resistance measurements.
Knowledge about the usefulness of the MBW for monitoring the progression of disease or the response to treatment remains limited. The MBW test may be particularly suitable when screening for post-transplant bronchiolitis obliterans.
In conclusion, the use of helium in single-breath or multiple-breath washout test is also investigated and described for specific population groups. Specifically in young children not many pulmonary function tests are possible, while this test can be performed. The helium dilution test is considered to be well established for all groups including young children.

IV.5 Clinical safety

Contra-indications for performing the helium dilution test are discussed by the MAH, mainly referring to a recent overview article (Cooper, 2010[7]). Absolute contraindications include:

- Haemoptysis as the forced inhalation maneuver during the test may aggravate the hemoptysis
- Pneumothorax as the forced inhalation maneuver during the test may increase the air leak through the visceral pleura
- Thoracic, abdominal (> 5 cm) or cerebral aneurysms as the forced inhalation maneuver during the test may cause rupture of the aneurysm.

In addition, relative contraindications include:

- Unstable cardiovascular status:
  - Recent Myocardial infarction – waiting time 1 week: Safety data on exercise testing post myocardial infarction show that most patients are stable after 7 days so it is reasonable to perform lung function test safely after this time.
  - Angina pectoris – administration of sublingual glyceryl trinitrate (GTN) prior to test is recommended: The need to perform lung function testing preoperatively in a patient with chronic angina is a common request on lung function departments. The administration of GTN prior to testing is often sufficient to avoid symptoms and permit useful lung function testing to be performed.
- Recent eye surgery – waiting time 2-3 weeks, but longer waiting times may be appropriate depending on the type of eye surgery. Increase of intraocular pressure might occur.
- Presence of acute illness or symptoms that might interfere with the test.
- Recent thoracic or abdominal surgery - waiting time 4 weeks: because of increased pressure on the surgical wound
- Inadequacy of the patient to follow the instructions for the specific test communicated by the technician due to mental or physical disorder
- Large meal or vigorous exercise immediately before the test
- Morbid obesity may be a condition in which the test result cannot be interpreted properly (slow VC is usually reduced). Body plethysmography is the proper alternative.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Apulco He 9% and Apulco HeOxy 9%.

- Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	Safety in paediatric population

[6] Beydon N et al. American Thoracic Society Documents An Official American Thoracic Society/European Respiratory Society Statement: Pulmonary Function Testing in Preschool Children. Am J Res Crit Care Med 2007; 175;1304.
[7] Cooper BG. An update on contraindications for lung function testing. Thorax (2010, doi:10.1136/thx.2010. 139881)

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

Reviews of the clinical literature provided evidence that the helium dilution test is a well-established procedure, and is widely used in lung function diagnostics. The procedure is described in the clinical guidelines such as ATS/ERS task force 'standardisation of lung function testing'.
Helium is an inert gas that does not cause adverse events. However, adverse events may occur due to the lung function manoeuvre when oxygen supply to the equipment is insufficient to compensate for the breathing use of oxygen. When the recommended procedure is followed, and the oxygen level in the spirometer is adjusted to 25-30% to compensate for oxygen absorption, the risk of hypoxia should be negligible.

V. USER CONSULTATION

The package leaflet (PL) 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. During the two test rounds, with 10 participants each, 100% of the requested information in the patient information leaflet was found and understood without any problem. This means that the formal success criteria are met: more than 90% of the participants were able to find the requested information, and of those, more than 90% were able to understand the information that was found and would act appropriately. Therefore, the conclusion of this readability test is that the PL can enable the patient to use the medicinal product safely and effectively.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Apulco He 9% and Apulco HeOxy 9% medicinal gas, compressed have a proven chemical-pharmaceutical quality. The products can be considered effective and safe in diagnostic use, i.e. for determination of the lung volumes during multiple breath helium diagnostic testing of lung function.
The use of helium in this indication has been described in many articles for more than one decade. For this application, no original clinical trials or clinical study data were conducted or presented.

In the Board meetings of 30 January and 2 October 2014, the application was discussed. In the first meeting, the Board raised questions regarding the oxygen content in the Apulco He 9% mixture, which is lower than stated in the ATS/ERS recommendations. The MAH properly justified this lower oxygen content. At the beginning of the multiple breath helium dilution test, the oxygen level in the spirometer should be adjusted to 25-30%. During the test oxygen is added to compensate for oxygen absorption. Herewith the concern was adequately addressed; the Board concluded that the benefit-risk profile of both mixtures is positive.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for Apulco He 9% and Apulco HeOxy 9% based on literature, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 January 2015.

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