CBG MEB

Public Assessment Report

Scientific discussion

Apulco CoHe 0.28%/9.5%, medicinal gas, compressed

Apulco CoHeMax 0.28%/14%, medicinal gas, compressed

(Carbon monoxide/Helium)

NL/H/2970/001-002/DC

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This module reflects the scientific discussion for the approval of Apulco CoHe 0.28%/9.5% and Apulco CoHeMax 0.28%/14%, 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.

A list of literature references is given on pages 15-17.

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
CO	Carbon monoxide
COHb	Carboxyhaemoglobin
COPD	Chronic obstructive pulmonary disease
DLCO	Lung Diffusion Capacity
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
ppm	Parts per million
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 CoHe 0.28%/9.5% and Apulco CoHeMax 0.28%/14% medicinal gas, compressed from Air Products Nederland B.V.

The product is for diagnostic use only. It is used for diagnostic testing of pulmonary function: determination of the diffusion capacity/transfer factor.

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 this gas cylinders for several patients, therefore the need for gas cylinders per year 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 CoHe 0.28%/9.5% and Apulco CoHeMax 0.28%/14% medicinal gas, compressed are colourless, odourless and tasteless gases.

The mixtures contain 0.28% of carbon monoxide, 9.5% or 14% of helium, 21% of oxygen and depending on the amount of helium, 69.22% or 64.72% of nitrogen.

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 bright green and the cylinder body in white.

II.2 Drug Substances

Carbon monoxide
The active substance carbon monoxide (CO) is described in the European Pharmacopoeia (Ph.Eur.). No Active Substance Master File (ASMF) or Certificate of Suitability (CEP) was submitted; full information on carbon monoxide is included in the dossier.

Manufacturing process
The MAH defines industrial carbon monoxide as starting material. It is regarded as drug substance as soon as it is tested according to the Ph.Eur. by the active substance manufacturer. In order to justify this approach, the MAH provided sufficient evidence that carbon monoxide can be regarded as industrial commodity used in non-pharmaceutical markets.

Quality control of drug substance
The proposed drug substance specification is in accordance with the Ph.Eur. monograph on carbon monoxide. The MAH confirmed that the Ph.Eur. monograph is suitable for the control of impurities originating from the manufacturing process.
Industrial carbon monoxide and the drug substance carbon monoxide are filled in dedicated and product specific aluminium cylinders. The pressure inside the cylinders is 200 bar. Sufficient information was provided on the standards according to which the cylinders are tested and on the valves.

Stability of drug substance
Bibliographic evidence is provided on the stability of carbon monoxide which is considered sufficient. The proposed re-test period of six months is granted, with the storage conditions “Shall not be exposed to extreme heat. If at risk of fire, move to a safe place. Handle carefully. Shall be returned with a minimum residual pressure. Cylinders shall be stored and transported with valves closed.”

Helium
The active substance helium is 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).

Premixes of carbon monoxide and nitrogen
For safety reasons, carbon monoxide is handled as premixes of carbon monoxide in nitrogen containing either 3% or 5% of carbon monoxide. The manufacturing process consists of filling of gaseous carbon monoxide and nitrogen by weight. The specifications of the premixes include the determination of the contents of carbon monoxide nitrogen. Impurities are tested in the individual gases and are not expected to increase in the premixes.
The premixes are packed in aluminium cylinders. The pressure inside the cylinders is 200 bar. Sufficient information was provided on the standards according to which the cylinders are tested and on the valves.
On the basis of bibliographic evidence and supportive 12 months stability data obtained from cylinders stored under cover and at room temperature, a shelf life of 18 months is applied for the premixes. Moreover, the MAH provided bibliographical evidence on the homogeneity of the premixes 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 18 months is justified. Storage conditions are “Shall not be exposed to extreme heat. If at risk of fire, move to a safe place. Handle carefully. Shall be returned with a minimum residual pressure. Cylinders shall be stored and transported with valves closed.”

II.3 Medicinal Product

Pharmaceutical development
The MAH has explained that mixing of the CO premix, helium, oxygen, and nitrogen results in a homogeneous product. Lung test gas 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 carbon monoxide and oxygen, because helium and nitrogen are inert gases, hence are compatible with all common materials.

Manufacturing process
The manufacturing process consists of filling of helium by pressure, followed by filling of the premix carbon monoxide in nitrogen, 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 CO premix, 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 carbon monoxide, helium, and oxygen (each cylinder), identification of nitrogen (one cylinder per batch), and pressure. The release and shelf life specifications are identical and are acceptable. 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 18 months for both mixtures in all container sizes. 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 CoHe 0.28%/9.5% and Apulco CoHeMax 0.28%/14% medicinal gas, compressed have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances 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

The components of the gas mixture, helium and oxygen are well known naturally occurring substances. The use of these gases in the diagnostic helium dilution test is clinically well-established. Besides the use as a diagnostic, carbon monoxide appears to have some cytoprotective, anti-inflammatory and neuroprotective effects in animal models. These effects have been investigated after prolonged exposure to CO, and are therefore likely not relevant for the current product.
With regard to safety pharmacology, although short term CO exposure is likely to increase COHb levels and therefore potentially induce hypoxia, adverse effects were only seen in animals after prolonged exposure or at COHb levels much in excess of clinically relevant levels for this diagnostic procedure (up to 3.2%).

III.2 Pharmacokinetics

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.
Diffusion of CO into erythrocytes and binding of CO to Hb is rapid. The half-time for saturation in rats was approximately 25-35 minutes at different concentrations of inhaled CO, with equilibrium reached between 60 and 120 minutes exposure. The majority of CO is measured in blood. A small proportion of inhaled CO undergoes oxidative metabolism, through mitochondrial cytochrome oxidase. In humans, the rate of oxidative metabolism has been estimated to be 14 µmol/day. The half-time for CO desaturation after removal from CO exposure is approximately 32-35 minutes.

III.3 Toxicology

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.
Toxicology studies in rats, mice, rabbits, dogs and monkeys reveal changes in respiratory system, cardiovascular effects, changes in haematological parameters, and to a lesser extent neurological effects, after subacute and chronic exposure to carbon monoxide. These effects are of little relevance for the clinical setting of a single breath application of Apulco CoHe and CoHeMax.
Carbon monoxide appears to have genotoxic potential when inhaled for 10 minutes or more at clinically relevant concentrations. The relevance of this finding for the clinical setting of 10 seconds inhalation is not known, but unlikely. Considering this genotoxic potential, a local carcinogenic effect after prolonged inhalation of CO is to be expected. However, the application of the single breath inhalation test resulting in exposure of 10 seconds is very unlikely to result in an increased carcinogenic risk.
A recent study in mice revealed a reduction in foetal growth and increased gestational deaths after exposure to carbon monoxide throughout pregnancy at the high dose resulting in COHb levels of 15.6% and 28.6% in maternal and foetal blood respectively. At the ‘no observed adverse effect level’ of 250 ppm, maternal and foetal blood COHb were around 13% and 23% respectively. As both duration of exposure and blood COHb are much in excess of those expected from clinical use of the product, there is a large safety margin, and no effect on the foetus is expected from the use of this diagnostic product.

III.4 Ecotoxicity/environmental risk assessment (ERA)

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

III.5 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 single breath diffusion test is a well-established procedure, and is widely used for diagnostic testing of pulmonary function, i.e. determination of the diffusion capacity/transfer factor.

The constituent gases have been selected on the basis of their ability or lack of ability to cross the alveolarcapillary barrier for diagnostic testing of lung function with determination of the lungs' diffusion capacity (or transfer factor) as the main parameter, and of lung volumes.

The concentrations of the individual test gases are standardised according to the American and European practice guidelines. The tracer gas should be relatively insoluble, chemically and biologically inert and the gaseous diffusivity should be similar to CO. Furthermore, it should not interfere with the measurement of CO concentration and the tracer gas should not ordinarily be present in alveolar gas or else be present at a known, fixed concentration (e.g. argon). Commonly used tracer gases are helium (He) and methane (CH4). The inspired CO should nominally be 0.3%. However, as ratios are more important than absolute values, exact concentrations are not critical.

Apulco CoHe 0.28%/9.5% and Apulco CoHeMax 0.28%/14% match well with the applied gases, as listed by MacIntyre et al (2005) and can be considered acceptable.

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.

CO is rapidly and extensively absorbed in the lung alveoli following inhalation. Because CO binds avidly to Hb, there is a relatively low free blood and cytosolic CO concentration in the erythrocyte and, therefore, a partial pressure gradient that drives CO transfer from alveolar air to blood.
The major factors that control absorption of CO include those that affect delivery of inhaled air to the alveolar region of the lung and those that affect the lung's CO diffusion capacity. Factors that may affect net CO absorption include health status (lung function), exercise, the supine position, age (increased in infancy and childhood, declines in adults with age), altitude, increasing the blood Hb concentration and decreasing the partial pressure of O_2 in inhaled air or blood and present COHb.

The adult human body is estimated to contain approximately 10 ml (448 mcmol) of CO. As a result of its affinity for hemoglobin and myoglobin the largest CO load after inhalation being found in blood, heart, skeletal muscle and spleen (Vreman et al, 2006).

Inhaled CO is eliminated from the body primarily by direct exhalation but also via oxidative metabolism. The mechanism of elimination of CO by exhalation is diffusion. The half-life for wash-out after exposure to CO was estimated to be 250-320 minutes (Peterson et al, 1975).

The metabolism of CO involves three major processes, (i) production of CO from endogenous and exogenous precursors, (ii) binding of CO to heme proteins, and (iii) oxidative metabolism of CO to CO_2. Endogenous CO is produced, primarily, from the enzymatic degradation of heme by the enzyme, heme oxygenase (HO).
A small proportion of inhaled CO undergoes oxidative metabolism, primarily due to the action of mitochondrial cytochrome oxidase (Young and Caughey, 1986). This is approximately 3% of endogenous carbon monoxide production.

IV.3 Pharmacodynamics

Carbon monoxide may have a physiological role in the body, such as a neurotransmitter or a blood vessel relaxant.
Carbon monoxide produces tissue hypoxia by binding to Hb, displacing O_2 from it, and forming COHb, which has less O_2-carrying capacity of blood and impairs release of O_2 from Hb in tissues.
The tissues that have the highest O_2 demand, such as brain and heart, are considered especially vulnerable because of the carbon monoxide-induced hypoxia. During exercise, increased cardiac work and O_2 consumption increases the vulnerability of the heart to CO-induced hypoxic injury, particularly in patients with underlying coronary artery or myocardial disease (US Department of Health and Human Services, 2009).

Brain hypoxia induced by CO can result in various symptoms of impaired central nervous system function, e.g. headache, dizziness, nausea, vomiting, confusion, disorientation, convulsions and coma (Dolan, 1985, Ernst and Zibrak, 1998). Delayed development of neuropsychiatric and neurological impairment may occur within 1-4 weeks of exposure (reviewed in US, 2009).
The treatment of carbon monoxide poisoning is removal from the environment and/or the supplemental oxygen until the carbon monoxide level is below 5%.

The pharmacodynamic process of the CO uptake to measure the diffusing capacity involves several steps of the physiological pathway and impairment in every step can result in a decrease of the CO diffusion (Brusasco et al, 2005).

Early studies using different low concentrations of CO showed different results on inflammatory responses. Also the results on COHb show differences.

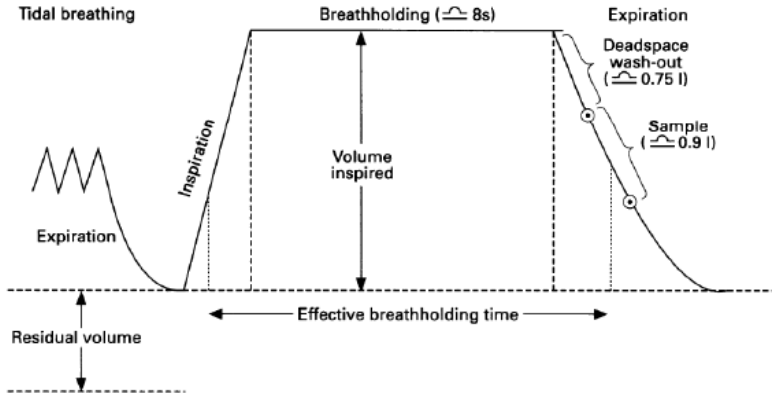
Regarding helium, the density of helium is much less than that of air and its viscosity is higher. Therefore, the work of breathing mixtures of helium and oxygen is less than with breathing air. The lower density of helium causes temporary voice changes.
In the lung function test, single breath helium test or multiple-breath washout test, helium mixes with air in the lungs. The inert properties of helium allows for measuring volumes after equilibrium is reached.

IV.4 Clinical efficacy

Measurements of lungs' diffusion capacity (or transfer factor) and of lung volumes is useful for the characterization of pathophysiological processes in lung disorders. The single breath diffusion test is indicated to distinguish various conditions of airway obstruction and restriction, which can disturb diffusion across the alveolarcapillary membrane (Vreman et al, 2000a). Measuring an "overall" CO uptake by the single-breath technique has proved useful in assessing a variety of lung abnormalities that impair alveolar capillary gas transport, such as obstructive lung diseases, parenchymal lung diseases, interstitial lung disease (e.g. asbestosis), pulmonary involvement in systemic diseases, cardiovascular diseases, etc.
The procedure has become a valuable tool in lung disease diagnostics (Aduen et al, 2007, Ates et al, 2006, Brunelli et al, 2006, Mohsenifar et al, 2003), in testing the efficacy of pulmonary disease treatments (Demedts et al, 2005, Taniguchi et al, 2010) and is used in clinical trials of inhaled drugs to monitor possible adverse effects on lung function (Muchmore et al, 2006, Norwood et al, 2007, Wise et al, 2007).

Single-Breath Inhalation Test
A combined task force of American Thorax Society (ATS) and European Respiratory Society (ERS) has listed the test criteria that are acceptable for measurement of D_{LCO} by the single-breath procedure (Macintyre et al, 2005).
The procedure is summarised in Figure 1 showing a spirogram.

Figure 1: Spirogram of the single-breath inhalation procedure for determining D_{LCO} (from Cotes et al, 1997)



The single-breath inhalation test measures the diffusing capacity for the lungs measured using carbon monoxide, also known as transfer factor (D_{LCO}).

The significant clinical value of measuring D_{LCO} has led to widespread and evidently successful efforts to improve instrumentation and to refine and standardise the procedures and performance of D_{LCO} measurements across laboratories (Crapo and Jensen, 2003, Jensen et al, 2009). Jensen and Crapo have outlined the essential elements of the single-breath CO inhalation test. The measurement of the lungs' diffusion capacity depends on the measurement of the diffusion rate of CO which, after inhalation, follows the same diffusion path of oxygen, namely from the alveoli across the alveolar-capillary membrane and on to Hb within the erythrocytes. From the concentration of expired CO, the D_{LCO} can be calculated.

The calculation requires that there is a non-absorbable carrier gas, such as helium, present in the inhaled mixture in order to allow calculation of (i) the degree of dilution of CO on inhalation and (ii) the alveolar CO concentration.
The procedure for measuring D_{LCO} for diagnostic purposes has been standardized in expert guidelines (Anon, 1987, Anon, 1999a) and recommendations (Cotes et al, 1993, Macintyre et al, 2005).
The updated recommendations (Anon, 1995) formed the basis of the American Association of Respiratory Care (AARC) Clinical Practice Guidelines (Anon, 1999a).

Elevated blood COHb causes a "back pressure" of CO across the alveolar-capillary barrier. Therefore, in the single-breath CO inhalation test, the possible presence of a CO "back pressure" needs to be taken into account and, if elevated basal COHb levels are suspected, blood COHb concentrations need to be measured before performing the test.
Reference equations for predicting the normal D_{LCO} values assume that blood COHb may be up to 2% (Macintyre et al, 2005). Corrections may be needed in case of increase in COHb values.

Clinical trials with Single-Breath Inhalation Test
An adequate review of clinical studies was provided to support the indication applied for. The use of carbon monoxide in combination with helium in single-breath diffusion test is described in many articles for more than one decade from the first systematic and documented use. Furthermore the use of carbon monoxide in combination with helium in single-breath test is implemented in clinical guidelines such as the ATS/ERS guidelines as part of the ''ATS/ERS Task Force: standardiasation of lung function testing", section "Standardisation of the single-breath determination of carbon monoxide uptake in the lung".

The clinical diagnostic value of the single-breath CO inhalation test is to show impaired transport between alveolar space and blood, thus being predictive for an impairment of $_2$ transport to alveolair blood. The CO single breath inhalation test is nowadays also used in trials for assessing safety of inhaled drugs, e.g. inhaled insulin.

Early studies already indicated that the single-breath CO inhalation test could indicate (severe) impairment to predict exercise-induced arterial oxygen desaturation (Epler (1980), Owens (1984)).
Additionally, more data became available (Nordenfelt and Svensson, 1987), showing that $D_{L,CO}$ values of ≤50% of predicted values correlates highly with exercise induced hypoxaemia (blood PO2 below 8-8.5 kPa).

These conclusions were confirmed in other studies all showing that $D_{L,CO}$ has predictive value for a diagnosing pulmonary disorder (Aduen et al (2007), Brunelli et al (2006), Mohsenifar et al (2003)).

$D_{L,CO}$ is used in the evaluation of the therapeutic effect in clinical practice as well as in clinical trials (Behr et al, (2009), Taniguchi et al, 2010)).

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 systematic and documented use of the single-breath CO inhalation test is described in many articles for several decades (i). Furthermore the use of $D_{L,CO}$ testing 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 (ii, iii) as well as the coherence of scientific assessments (iv). Therefore, the use of Apulco CoHe and CoHeMax for determination of the diffusion capacity/transfer factor is considered established.

Use in children

A body of literature supports the use of the single-breath carbon monoxide method to determine diffusion capacity in children. The use of the test for lung diffusion capacity (DLCO) has been mentioned for more than a decade in the literature (e.g. Rosenthal, 1993; Nyson, 1996). Furthermore, this test is considered clinically relevant in children with various diseases, e.g. cystic fibrosis (Fitzgerald, 2013), alpha 1-antitrypsin deficiency, juvenile systemic sclerosis (Torok, 2012), type I diabetes mellitus (impaired lung diffusion capacity (i.e. reduced DLCO) potentially being the first sign of microangiopathic involvement), pulmonary fibrosis, graft versus host disease after haematopoietic stem cell transplantation (e.g. Hoffmeister, 2006) and the assessment of lung toxicity in children undergoing chemotherapy with potentially toxic agents, such as bleomycin (Seed, 2012).
For the single-breath carbon monoxide (CO) method, there are published standard values for DLCO in healthy children for use as reference values for monitoring lung function in children with chronic lung disease: Cotes and colleagues derived standard normal values for lung diffusion capacity for normal healthy children (104 boys/108 girls) of mean age 8.3 years (range, 8-10 years) (Cotes et al, 1973) and a similar study by Rosenthal and colleagues (455 boys/317 girls; aged 4-19) established height relationships for lung diffusion capacity (DLCO) in healthy children (Rosenthal et al, 1993).
Since the use of lung test gas CO/He 0.28%/9.5% has been mentioned for more than a decade and the relevance and actual use of this test is confirmed coherently, its use can be considered established in children.

IV.5 Clinical safety

In the single-breath inhalation test, the 2 gases (CO and helium) in the mixture are inhaled at concentrations that provide no safety concerns to the test subjects.
The toxicity of CO is dependent on the concentration-dependent hypoxic effect of COHb formation following CO inhalation.
Levels of COHb are reported to be less than 3% in non-smokers and between 3 and 8% in smokers (Marshall et al, 1995). The single-breath test with 0.3% (3,000 ppm) CO has been reported to increase

COHb levels by less than 1% (Frey et al, 1987, Vreman et al, 2000a). A mean level of 3.2% COHb was reported in experimental studies of repeated (at 10 minutes intervals) single-breath inhalation of 0.3% CO (but with a duration of breath-holding that was longer than the standard 10 seconds). These data seem to indicate that the single breath inhalation of 0.3% CO generates comparatively low COHb levels and is unlikely to cause any adverse events. Furthermore, the MAH referred to Cotton et al (2005) who state that no adverse events were reported during several decades of extensive use of the single-breath inhalation test in pulmonary diagnostic laboratories throughout the world.

However, three 6-second breath-holding manoeuvres in healthy subjects inhaling 6% CO, which is over 10-times the concentration inhaled during the single breath inhalation test, transient symptoms of intoxication were reported (Fisher et al, 1969, Hyde et al, 1971).

Helium is also used in single-breath tests at a concentration of 9.5%. It is not absorbed and is biologically inert (Simon et al, 2006). Single-breath inhalation of helium is expected to be safe; inhalation of much higher concentrations of helium, in the form of Heliox, is reported with no significant safety concerns (Rodrigo et al, 2003).

Contra-indications for performing the single breath test are discussed by the MAH. Key contraindications for performing lung function test are described by the 1996 American Association for Respiratory Care (AARC):

- Haemoptysis of unknown origin: The forced inhalation maneuver during the test may aggravate the hemoptysis.
- Pneumothorax: The forced inhalation maneuver during the test may increase the air leak through the visceral pleura.
- Presence of CO toxicity: An increased HbCO may cause ST-segment change on ECG or may induce arrhythmias.
- Dangerous levels of oxyhemoglobin.
- Thoracic, abdominal (> 5 cm) or cerebral aneurysms: The forced inhalation maneuver during the test may cause rupture of the aneurysm.

Relative contraindications include:

- Patients with history of coronary artery disease may be at risk for ST segment depression induced by CO.
- 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: To avoid rupture site of injury, pain and discomfort.
- 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.
- Smoking within 24 hours of test administration.
- Reduced vital capacity not within the values needed to accurately interpret the gas transfer results.

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 CoHe 0.28%/9.5% and Apulco CoHeMax 0.28%/14%.

- Summary table of safety concerns as approved in RMP

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

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 single breath inhalation test for procedure for the diffusion of to measure D_{LCO} is described in the clinical guidelines such as the ATS/ERS task force 'standardisation of lung function testing'.
The composition of the mixture is compliant with the guidelines for single breath inhalation test. The gas mixture is intended for diagnostic use in clinical testing of the diffusion capacity of the lung (DLCO), in the widely-used single-breath inhalation test described in the guidelines.

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 CoHe 0.28%/9.5% and Apulco CoHeMax 0.28%/14% 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 diffusion capacity/transfer factor.

The use of carbon monoxide and 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 meeting of 2 October 2014, the application was discussed. The Board raised questions regarding the acceptability of industrial carbon monoxide as starting material. The MAH adequately justified that the starting material complies with ICH guideline Q11 'on development and manufacture of drug substances'. The substance is compliant to the European Pharmacopoeia monograph specification. Herewith the concern was adequately addressed.

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 CoHe 0.28%/9.5% and Apulco CoHeMax

0.28%/14% 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

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