VI.2 ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 OVERVIEW OF DISEASE EPIDEMIOLOGY

Indication: cluster headache

Demographics

The male to female ratio is between 2.5:1 and 7.1:1. Cluster headache can be seen in children and elderly patients. On average, the headache starts at the age of 28 – 30 years and before 20 years in 35% of cases.

In men, cluster headache starts before 40 years in 75% of patients while there are two major periods of appearance of cluster headache in women: one period earlier than men and a second period after the age of 50 years.

Risk factors for the disease

A genetic background for cluster headache has not been described but is likely. There is a familial occurrence in 2 – 7%.

There seems to be an association with smoking. However, a causative link to smoking seems unlikely.

Natural history

Long-term relief period may occur after the age of 50 years.

Depressive symptoms and suicidal ideations are frequent in patients with cluster headache.

Indication: correction of hypoxia

Medicinal oxygen is used in the clinical treatment of disorders arising from, or resulting in, hypoxia, which is defined as a lack of oxygen delivery to the cells.

Acute hypoxia

Hypoxia can arise in numerous environmental and clinical situations and can be provoked by many different causes that can be summarized as:

- Exogenous causes (e.g. altitude or toxic substance);
- Oxygen uptake disorders within the lungs;
- Oxygen transport impairment (e.g. anaemia, heart or circulatory failure);
- Problems in oxygen extraction and/or consumption;
- Disorders in the central control of ventilation.

Hypoxia can be generalized to the entire organism or restricted to one or several organs.

Chronic hypoxia

Chronic obstructive pulmonary disease (COPD) is the main cause of chronic hypoxia. Other causes are: interstitial lung disease, cystic fibrosis, pulmonary hypertension, neuromuscular or chest wall disorders, advanced cardiac failure and pulmonary malignancy.

Indication: osteoradionecrosis

Osteoradionecrosis is as an area of necrotic bone within an irradiated area that persists without healing for 3 months or more in the absence of local neoplastic disease. Osteoradionecrosis of jaws is most frequently linked with radiation-induced damage in patients with head and neck cancer or oral cancer. Osteoradionecrosis of the ribs may also occur after whole-breast radiation therapy, however it is very rare.

Radiotherapy induces hypoxia, fibrosis and endarteritis, resulting in capillary loss, creating unfavourable conditions for wound healing.

Demographics

Osteoradionecrosis may occur in all patients treated with radiotherapy for head and neck cancer and especially in people over age 50 years.

Risk factors for the disease

In addition to radiotherapy, contributing factors are trauma (including dental extractions), the state of the dentition, radiation dosage, alcohol and tobacco use, and concomitant surgery and chemotherapy.

Natural history

Clinical findings can range from asymptomatic bone exposure to severe necrosis.

Indication: Clostridium perfringens myonecrosis

Clostridial myonecrosis is an infection that destroys muscle tissue. As clostridia are anaerobic bacteria, the development of this disease necessitates the conjunction of two factors: bacterial contamination and the presence of tissue hypoxia.

Infection can occur through contamination of wounds or when bacteria enter from the gut by way of breaks in the digestive mucosa.

Hyperbaric oxygen is used as adjunctive treatment to the standard medical and surgical management of clostridial myonecrosis.

Natural history

Clostridial proliferation is associated with the release of various toxins that play important role in the spread of infection by decreasing blood supply in neighbouring tissues. Hypoxic conditions favour tissue destruction by anaerobic bacteria.

In the absence of therapeutic intervention, clostridial myonecrosis therefore progresses unchecked. Once the clostridial toxins reach the arterial circulation, systemic shock and multiorgan failure rapidly ensue which may culminate in death.

Indication: gas embolism

Gas embolism occurs as a consequence of the entry of gas into the vasculature (arteries or veins).

It is principally of iatrogenic origin during invasive procedures. In most cases, gas embolism is air embolism, although other medical gases can also be responsible.

Arterial gas embolism

The surgical procedures carrying the greatest risk are craniotomy, hip replacement, caesarian section and cardiac surgery.

Hyperbaric oxygen therapy is the first-line treatment of choice.

Venous gas embolism

Air may be introduced into veins during placement, use or removal of a central venous catheter or a haemodialysis catheter, during surgical procedures and in the context of pregnancy and delivery.

It also occurs after compressed-gas diving, rapid exposure to altitude, rapid rates of decompression during flight and in a hypobaric chamber or accidental loss of pressure during flight in commercial aircraft.

Hyperbaric oxygen therapy is not a first-line treatment for venous air embolism, but may be a useful adjunct.

Indication: Carbon monoxide poisoning

Tissue hypoxia in CO poisoning affects all organs and systems, and involvement of the major organs worsens prognosis.

Any people exposed to sources of exogenous toxic CO such as gasoline engines in motor vehicles, small engines and boats; carbon-fuelled appliances such as furnaces, water heaters and boilers, and charcoal and propane heating and cooking sources, as well as from methylane chloride without proper ventilation may suffer from carbon monoxide poisoning.

People who are most at risk from CO poisoning complications include those with coronary heart disease, cardiovascular disease, or anaemia; pregnant women and their foetus; infants; patients with pulmonary and heart disease, and elderly people.

Neurological sequelae, such as poor concentration and memory problems, may develop in people recovering from CO-poisoning.

Indication: Decompression sickness

Decompression sickness is caused by the formation of inert gas bubbles in the tissues and/or blood when the partial pressure of tissue inert gas exceeds ambient pressure causing supersaturation and release of inert gas from solution.

Gas bubbles may cause direct mechanical disruption of tissue, occlusion of blood flow, platelet deposition and activation of the coagulation cascade.

Decompression sickness occurs most commonly in divers ascending from a minimum depth of 20 feet (6 meters) of sea water, but can also occur during rapid decompression in aviators after rapid ascent from sea level to altitude (typically >17,000 feet / 5,200 meters), in astronauts participating in "space walk" or during cabin decompression.

VI.2.2 SUMMARY OF TREATMENT BENEFITS

Indication: cluster headache

Recommendations for the use of oxygen therapy in acute attacks of cluster headache are based on the results of three consistent clinical trials (Cohen 2009, Fogan 1985, Kudrow 1981):

- In the Kudrow study, 50 patients were randomly selected to receive as first treatment either oxygen treatment (n=25) or a sublingual ergotamine tartrate tablet (Ergomar®, n=25), both treatment starting at the onset of 10 episodes of cluster headache attack. At the end of the first treatment period, patients were given the other treatment for another ten-attack treatment period. Treatment was considered as successful when complete or almost complete pain relief was obtained within the 15 min treatment in at least seven attacks. A total of 41 patients (82%) had successfully aborted cluster headache attacks with oxygen inhalation and 35 patients (70%) were successfully treated with ergotamine, the difference being not significant. Amongst responsive patients, headache relief was more rapid with oxygen treatment, 46% of oxygen-treated patients being relieved within 6 min compared with 28.6% in the ergotamine-treated group.
- In a double-blind, randomized, crossover, controlled study (Fogan 1985), the efficacy of oxygen, versus air, inhalation treatment was studied in the relief of pain provoked by cluster headache attacks in 19 patients. Inhalation treatments were selected randomly and consisted in 100% oxygen or air. The 19 patients experienced a total of 76 attacks treated with 100% oxygen and 62 attacks treated with air. A complete or a substantial relief in 80% or more attacks was reported by 9 out of 16 patients (56%) with the use of oxygen, compared with 1 out of 14 patients (7%) when inhaled air. The average relief score with oxygen treatment was 1.93 ± 0.22 and it was 0.77 ± 0.23 with air ($p<0.01$).
- Cohen et al. designed a double-blind, randomized, crossover and placebo-controlled trial evaluating the efficacy of inhaled pure oxygen, versus air, in pain relief during cluster headache attacks in 76 patients. Pain was rated as 0 for pain free, 1 for mild, 2 for moderate, 3 for severe and 4 for very severe pain. A reduction in the pain scale was considered positive if the pain scale at each time point was at least 1 category less severe than the start of the headache. Pain relief was observed in 78% of attacks when patients received oxygen compared with 20% of attacks when they received air ($p<0.001$).

Indication: correction of hypoxia

- Acute hypoxia: the rationale for controlled oxygen supplementation in acute hypoxemic hypoxia is well established, although evidence of efficacy from randomized controlled trials is limited, as the performance of such trials raises several ethical issues in such clinically unstable conditions.
- Chronic hypoxia: supplemental long-term oxygen therapy (LTOT) has been shown to increase survival and to improve exercise, sleep and cognitive performance in chronically severe hypoxaemic patients. The guidelines on the management of stable COPD issued by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) advocate the long-term administration of oxygen in chronic hypoxia.

Indication: osteoradionecrosis

Feldmeier and Hampson (2002) reported an overall response rate of 84% based on a review of 14 published studies assessing the efficacy of HBOT in patients with osteoradionecrosis of the jaw. A significant positive effect of the HBOT on the quality of life of osteoradionecrosis patients has been described by Harding (Harding 2012). Moreover, HBOT was suggested to efficiently achieve mucosal coverage with osteoradionecrosis and also appears to reduce the chance of osteoradionecrosis following tooth extraction in an irradiated field (Bennett 2012).

Most European centres adhere fairly closely to the "consensus Marx protocol". A national clinical guideline published by the Scottish Intercollegiate Guidelines Network (SIGN) in 2006 states that there is evidence supporting the use of HBOT as an adjunctive treatment to prevent osteoradionecrosis in irradiated jaws after dental extractions and as an adjunct to surgery and reconstruction for the management of osteoradionecrosis.

Indication: clostridial myonecrosis (gas gangrene)

Hyperbaric oxygen is currently considered to be a useful adjunct to the standard medical and surgical management of clostridial myonecrosis, although no adequately controlled trials of HBOT have been conducted in this context, its use being widely accepted (Smith-Slatas 2006). Several reports have shown a significant decrease in mortality and morbidity when HBOT therapy is associated with surgery and antibiotic treatment.

Indication: gas embolism

No randomized, controlled clinical trial evaluating HBOT in this indication was identified.

Venous gas embolism

HBOT is not a first-line treatment for venous air embolism, but may be a useful adjunct in patients with severe or persistent symptoms, particularly pulmonary oedema. HBOT should certainly be considered in patients manifesting neurological changes, as this may be assumed to reflect paradoxical arterial air embolism (Muth and Shank 2000).

Arterial gas embolism

HBOT is the first-line treatment of choice for arterial embolism (Muth and Shank 2000, and Moon 2014 a) and the definitive treatment for cerebral artery gas embolism, with demonstrated potential to improve neuropsychological outcome (Dexter and Hindman 1997).

Indication: Carbon monoxide poisoning

Standard treatment for CO poisoning includes removal from the site of exposure, administration of oxygen and supportive care (Wolf 2008). The relative merits of normobaric and hyperbaric oxygen therapy are still debated, but HBOT is often recommended for patients with acute CO poisoning, especially if they have lost consciousness or have severe poisoning (Weaver 2002).

The latest Cochrane Review of the efficacy of HBOT compared to normobaric oxygen in preventing neurological sequelae in patients with CO poisoning notes that available clinical data are conflicting and are derived from studies with important limitations, concluding that further research is warranted (Buckley 2011). However, this review also acknowledges that, based on the positive results of the trial reported by Weaver et al. (2002), a considerable proportion of the hyperbaric medicine community consider that HBOT has been established as an effective treatment for CO poisoning and that further placebo-controlled trials would be unethical. Stoller (2007), Weaver et al. (2007), Logue (2008) and Weaver (2009), for example, strongly defend this position (Weaver 2009, Stoller 2007, Weaver 2007, Logue 2008).

Indication: Decompression sickness

As the effectiveness of recompression therapy in treating decompression sickness is widely accepted in clinical practice, randomised clinical trials comparing recompression therapy versus no recompression are essentially precluded for ethical reasons (Bennett 2010). A few published articles were identified establishing the efficacy of HBOT in the treatment of decompression sickness (Bennett 2010, Antonelli 2009, Sayer 2009, Bennett 2003). The HBOT is now considered to be the mainstay of treatment for this condition (Moon 2014 b).

VI.2.3 UNKNOWNS RELATING TO TREATMENT BENEFITS

Not Applicable

VI.2.4 SUMMARY OF SAFETY CONCERNS

Important identified risks

Risk	What is known	Preventability

Risk	What is known	Preventability
Fire due to oxygen	As one of the elements of the fire triangle (heat, fuel and oxygen), the enrichment of normal room air with oxygen increases the energy, heat release and severity of any fire. Apart from smoking, other causes are naked flames (stove oven, candles etc.), the use of greasy substances Deep burns and intoxications by fumes have been reported. Possibly fatal. Other people can be harmed.	To prevent fires: • The risk is mentioned in the product information and patient leaflet. • Specific training of patients (HOT) Specific training of staff using oxygen cylinders
Pulmonary toxicity	Capillary endothelium and alveolar epithelium are the pulmonary tissues with the highest sensitivity to increased oxygen concentration; their alterations may induce swelling of lung and ultimately to fibrosis.	This risk is mentioned in the product information. Care must be taken in patients already exposed to high oxygen concentrations, and drugs known to cause lung damage such as bleomycin, amiodarone, nitrofurantoin and similar antibiotics, should be avoided.
Risk related to HBOT - Central nervous toxicity	Central nervous toxicity can be observed in hyperbaric oxygen therapy settings. Early manifestations include localized muscular spasms (e.g. eyes, mouth, forehead). Continuation of exposure can lead to vertigo and nausea followed by altered behaviour, and finally generalized convulsions.	This risk is mentioned in the product information. Care must be taken in patients breathing 100% oxygen at pressures above 2 ATA, as toxicity to the central nervous system was observed.

Risk	What is known	Preventability
Risk related to HBOT – Barotrauma	Barotrauma is a tissue damage resulting from the mechanical effects of pressure. Barotrauma may affect the external, middle and inner ear, as well as the sinuses, teeth, gastrointestinal tract and pulmonary system.	To prevent barotrauma, the pressure in air-filled organs must be equalized to ambient pressure: equilization techniques or tympanostomy or correction of risk factors. This risk is mentioned in the product information.
Risk related to HBOT – Myopia	Patients with prolonged periods of daily hyperbaric oxygen therapy have been described with myopia. This is explained due to increased refractive index of the lens.	This risk is mentioned in the product information. Care must be taken in case of multiple hyperbaric treatments because of a risk of progressive myopia. Most cases were spontaneously reversible when stopping HBOT. However, risk of irreversibility increased after more than 100 therapies. The threshold of number of HBOT sessions, periods or duration cannot be estimated. It was ranged from 8 to more than 150 sessions.
Risk related to LOX – Frostbite	Liquid oxygen has a boiling point of -183.0°C. Direct contact of liquid oxygen may cause injury.	Following safety measures when manipulating liquid oxygen as mentioned in the product information.
Risks related to damages to VIPRs (Valves with an Integrated Pressure Reducer)	Equipment damages of cylinder may lead to : • Display of wrong information regarding to remaining oxygen inside the cylinder • Obstruction • Wrong flow delivery	Manipulation of cylinders with care. Precautions of use in the product information and labelling Backup oxygen delivery system available

Risk	What is known	Preventability
Respiratory acidosis and worsening hypercapnia in patients with baseline hypercapnia	In patients with baseline elevated carbon dioxide blood level (hypercapnia), medicinal oxygen should be used with caution as administration of oxygen at high concentrations may induce worsening hypercapnia, respiratory acidosis and respiratory arrest.	This risk is mentioned in the product information. Blood gas surveillance
Retinopathy of Prematurity	Retina can be affected in premature neonates exposed to supplemental oxygen therapy resulting in increased risk of retinopathy of prematurity that can permanently lead to blindness. In premature neonates, the immature retina is therefore incompletely vascularised with a peripheral avascular region. Hyperoxia lead to interruptions in vascular growth, partial regression of existing retinal vessels and arrest of the vascularisation process. The consecutive hypoxia lead then to fibrous scar and ultimately to retinal detachment.	All preterm infants should be screened for ROP. This risk is mentioned in the product information.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Vascular effects of hyperoxia	Increased oxygen concentration in the body beyond normal value decreases cardiac circulation flow, on the one hand due to a fall in heart rate caused by increased parasympathetic tone, on the other hand due to a rise in systemic vascular resistance. Vasoconstriction is particularly pronounced in the cerebral and coronary circulations, which

Risk	What is known (Including reason why it is considered a potential risk)
	may redistribute cardiac output in favour of other organs. Supplemental O_2 breathing, mainly in non-hypoxaemic patients, has recently been questioned in various situations such as myocardial ischemia. Results are still controversial but hyperoxia might increase myocardial injury in non-hypoxaemic patients with STEMI.

Missing information

Risk	What is known
None	Not applicable

VI.2.5 SUMMARY OF RISK MINIMISATION MEASURES BY SAFETY CONCERN

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

Full details on these conditions can be found in the Summary of Product Characteristics.

This medicine has no additional risk minimisation measures.

VI.2.6 PLANNED POST AUTHORISATION DEVELOPMENT PLAN

Not Applicable

VI.2.7 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Not Applicable (first version)

Version	Date	Safety Concerns	Comment
Not Applicable	Not Applicable	Not Applicable	Not Applicable