VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Penthrox® is used to provide pain relief to conscious adults during emergency situations before being taken to hospital or at Accident and Emergency departments of hospitals.

In 2011-12 and 2012-13, of all the patients that presented in A&E, approximately 24% arrived by ambulance//helicopter[1]. Based on information provided by the Health and Social Care Information Centre, in 2012-13, there were a total of 18,005,435 A&E attendances. Based on the number of attendances by diagnosis, approximately 32.4% of A&E attendances have a high likelihood of requiring pain relief for trauma.

In a large study[2] which evaluated pain management in patients ≥15 years old in 50 emergency departments (EDs) in France, a total of 11 670 patients were included and 7265 patients reported pain on admission. Of those patients communicating pain on admission, 54% of patients (3793 out of 7265 patients) visited the ED for trauma. Therefore, overall, about 33% adult patients reported pain due to trauma. In another study[3], information collected from 1352 adult patients presenting at 11 A&E sites in France over two months in 2010. Forty (40) percent of these (545 out of 1352 patients) reported presenting with trauma. On arrival, 76% of patients reported pain. About 30% of patients therefore reported pain due to trauma.

These numbers in France are similar with the numbers in the UK.

Approximately 75% of patients that went to A&E departments in the UK in 2012-13 were over 18 years of age. These would represent the patients that could use Penthrox®. A range of medicines currently used in managing the levels of pain, as expressed by patients, particularly in pre-hospital and emergency departments, include e.g. Entonox (50% nitrous oxide, 50% oxygen), morphine injection or oral, intranasal fentanyl, ibuprofen, paracetamol and dihydrocodeine.

VI.2.2 Summary of treatment benefits

The main study to demonstrate the treatment benefit of Penthrox® was conducted at several accident and emergency departments at hospitals across the UK. It involved 298 patients of whom 149 received Penthrox® to relieve their pain. The other 149 patients received a placebo, i.e. a treatment that appeared to be Penthrox® but contained no substance that is known to relieve pain.

[1] NHS Accident and Emergency Attendances, 2012-13

[2] Gueant et al. (2011, Feb). Quality of pain management in the emergency department: results of a multicentre prospective study. *European Journal of Anaesthesiology*, 28(2), 97-105.

[3] Boccard et al. (2011). Prise en charge de la douleur chez l'adulte dans des services d'urgences en France en 2010. *Annales francaises de medecine d'urgence*, 1(5), 312-9

The level of pain, as expressed by the patients, was recorded at 5, 10, 15 and 20 minutes after they had received either Penthrox® or placebo.

Overall, the study results demonstrated a significant treatment effect from Penthrox® administration; the greatest treatment effect was seen at 15 minutes. At 5 minutes following Penthrox®, 51.0% of patients experienced clinically important pain reduction compared to 23.5% of patients who received placebo. A total of 84.6% of patients in the Penthrox® group experienced their first pain relief with 1-10 inhalations in comparison to 51% of patients in the placebo group.

VI.2.3 Unknowns relating to treatment benefits

In the main and supporting studies majority of patients were white Caucasian adults. There is no evidence to suggest that results would be any different in non-white patients or the elderly.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Liver toxicity (Hepatotoxicity)	Methoxyflurane had historically been used to put patients to sleep during an operation or procedure or to induce loss of consciousness to prevent pain and discomfort (anaesthetic). Methoxyflurane is a halogenated hydrocarbon anaesthetic and shares the actions of this class. On rare occasions when taken at high doses for anaesthesia and on even rarer occasions when taken at lower doses for pain relief methoxyflurane had been shown to cause liver damage (hepatitis). The liver damage commonly resolved itself without the need for treatment providing no more methoxyflurane was administered. When used at the low doses required to provide pain relief methoxyflurane carries an extremely low risk of causing liver damage. Methoxyflurane must not be used in patients that have been previously known to have developed liver damage after administration of methoxyflurane or other medicines that might damage the liver e.g. halothane.	Patients should talk to their healthcare provider before using methoxyflurane if they have: • problems with the liver Methoxyflurane must not be administered in patients that have problems with the liver as a result of previous methoxyflurane administration or other medicines in this class that might damage the liver e.g. halothane. Patients should tell their doctor immediately if they have any of the following symptoms: • loss of appetite; • feeling sick (nausea); • vomiting; • yellowing of the skin and/or eyes (jaundice); • dark coloured urine; • pale coloured stools; • pain/ache or sensitivity to touch in right stomach area (below ribs). The healthcare provider should consider carefully before

Risk	What is known	Preventability
	Methoxyflurane is broken down by the body by certain liver enzymes.	prescribing methoxyflurane for use on more than one occasion every 3 months or in patients with liver conditions or where there is a risk for causing the liver not to work properly. Penthrox should be avoided together with certain medicines and substances (CYP 2E1 and to some extent CYP 2A6) known to interfere with these liver enzymes at the same time that methoxyflurane is being administered.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Effects on the kidney (Nephrotoxicity)	Effects on the kidney had only been observed when methoxyflurane was historically given in high doses during operations or procedures or when used to induce loss of consciousness to prevent pain and discomfort. No effects on the kidney have been observed when methoxyflurane is administered at lower doses. When the body breaks down methoxyflurane, the resulting products (metabolites) are well below the levels that have shown to be toxic in animal studies and decrease very quickly. There is some evidence to suggest that the metabolite known as inorganic fluoride can cause damage to the kidney. The combined findings from 8 studies with matching results on serum inorganic fluoride levels before and after methoxyflurane pain relief during labour and delivery were compared to the levels of inorganic fluoride in patients that had not received pain relief. The results demonstrated that long-lasting administration of methoxyflurane increased the level of this chemical. However the levels of this chemical in patients given methoxyflurane for pain relief are well below the amount that can cause kidney damage. No evidence of kidney damage was found in the pivotal clinical trial. In another study (Study 06/61), the levels of fluoride were higher in patients that had received treatment with methoxyflurane than in patients that had been given a 'dummy' drug, however there was no evidence to suggest damage to the kidney. In another study that included 247 patients experiencing sudden severe back pain, which may be caused by kidney stones (renal colic) and being transported to hospital by ambulance in Western Australia and administered methoxyflurane, there was no increased risk of kidney damage in patients that received methoxyflurane compared to patients that did not. In addition, the time taken for kidney disease to first appear was similar in patients that had received methoxyflurane and patients that had not. Methoxyflurane must not be used in patients that have problems with the kidney (renal impairment) or in patients whose kidneys do not function (renal failure).

Risk	What is known (Including reason why it is considered a potential risk)
Cardiovascular effects	No significant effects on respiration or blood circulation have been observed following the administration of methoxyflurane for pain relief. One study showed no harmful effects on pulse rate, respiratory rate or effects on blood pressure when the heart contracts (systolic blood pressure). Potential effects on blood pressure and heart rate are known class-effects when methoxyflurane was given in high doses in the past during operations to induce loss of consciousness to prevent pain and discomfort. They do not appear to be significant at the doses used for pain relief. There is no particular pattern to blood pressure levels after methoxyflurane administration for pain relief in different age groups. However, the risk may potentially be increased for older people with low blood pressure and slow heart rate (less than 60 beats per minute). Low blood pressure and slow heart rate may result in falls and other negative health consequences especially in older patients. MEOF-003 study was performed to evaluate changes in electrical conduction in the heart following administration of a single dose of methoxyflurane higher than prescribed by a healthcare professional. No evidence for changes in heart rate, electrical conduction or structures of the heart was observed. Methoxyflurane must not be administered to patients that have significant problems with their blood circulation.
Respiratory effects	No significant effects on respiration have been observed following the administration of methoxyflurane for pain relief. One study showed no harmful effects on pulse rate, respiratory rate or effects on blood pressure when the heart contracts (systolic blood pressure). Methoxyflurane must not be administered to patients that have significant difficulties in breathing.
Central nervous system effects	Methoxyflurane is a halogenated hydrocarbon and shares the actions of this class on part of the nervous system which is composed of the brain and spinal cord (central nervous system) including the following: • drowsiness or sleepiness (sedation); • feeling of extreme happiness (euphoria); • loss of memory (amnesia); • ability to concentrate; • altered muscle coordination; • change in mood. All general anaesthetics can potentially cause a depression of part of the nervous system which is composed of the brain and spinal cord (central nervous system depression) which can result in decreased rate of breathing, decreased heart rate, and loss of consciousness possibly leading to coma or death. Methoxyflurane has been shown to weaken a person's ability to concentrate and affect time perception. When used for pain relief in a controlled environment this risk is limited by

Risk	What is known (Including reason why it is considered a potential risk)
	self-administration and can be managed promptly by a healthcare professional. There have been common reports of methoxyflurane affecting the central nervous system in clinical trial patients. The most common non-serious reactions were for example dizziness, sleepiness/drowsiness (somnolence), loss of memory (amnesia), and are generally easily reversible (patient will stop using the inhaler when experiencing sleepiness/drowsiness). There were only three serious reactions related to central nervous system effects in the safety database since the 1970s. One reported a patient that experienced a problem with their nervous system (dizziness, drowsiness/sleepiness, feeling of confusion and disorientation) which was accompanied by a decrease in the levels of oxygen in the blood and the body deprived of adequate oxygen supply. The patient recovered without consequences. The severity of the condition and whether any other medicines could have caused the reaction was unknown. It is unknown how severe the two other reports (affect ability and loss of memory; altered state of consciousness, feeling sick and vomiting) were. However, in the latter instance, morphine sulphate was also suspected to have caused the reaction. Despite the fact that methoxyflurane has been extensively administered in other countries, data on the severity of central nervous system effects in limited. In the MEOF-001 study (which also included older patients), the majority of the reported side effects of a similar nature were mild or moderate. The risk is limited by self-administration and can be managed promptly by a healthcare professional. The risk may be increased in people with altered level of consciousness. A healthcare professional must not prescribe methoxyflurane in patients with an altered level of consciousness.
Malignant hyperthermia	Malignant hyperthermia is a life-threatening condition that is passed down through families and causes a fast rise in body temperature (fever) and severe muscle contractions when the affected person receives medicines in the same class as methoxyflurane. Due to a report to the Australian medicines regulatory group (Therapeutic Goods Administration) describing a patient that possibly experienced this, methoxyflurane is not to be administered to patients with a known or likely inheritance to malignant hyperthermia. However, due to other possible causes, it is unclear whether methoxyflurane caused malignant hyperthermia. The significance of this rare occurrence when methoxyflurane is administered for pain relief is limited.
Abuse Potential	Methoxyflurane is a halogenated hydrocarbon and shares the actions of this class on part of the nervous system which is composed of the brain and spinal cord (central nervous system) including the following: • drowsiness or sleepiness (sedation);

Risk	What is known (Including reason why it is considered a potential risk)
	• feeling of extreme happiness (euphoria); • loss of memory (amnesia); • ability to concentrate; • altered muscle coordination; • change in mood. Self-administration of methoxyflurane by the patient at doses used for pain relief will be limited by the occurrence of these class effects such as drowsiness or sleepiness (sedation). Penthrox® is self-administered under observation (and assisted if necessary) by a person trained in its administration or emergency care, using the hand held Penthrox® Inhaler. Prescription only medicine. Abuse may pose a siginifcant risk to the abuser and may result in overdose and its consequences.
Interaction with CYP enzyme inducing drugs	Methoxyflurane is broken down by the body by certain liver enzymes. Penthrox should be avoided being given together with certain medicines and substances known to interfere with these liver enzymes (CYP 2E1 and to some extent CYP 2A6) if given at the same time as methoxyflurane (alcohol, isoniazid, phenobarbital or rifampicin).
Environmental exposure to methoxyflurane by administering healthcare professionals	Methoxyflurane evaporates during the preparation of the inhaler and thereafter. When a patient uses it intermittently it continues to evaporate into the atmosphere and may be present in a closed environment (such as an ambulance) in small concentrations. Methoxyflurane may also be released into the atmosphere if a patient does not exhale through the mouthpiece of the Penthrox Inhaler. In Europe, Penthrox will only be administered using Penthrox Inhaler with a special AC chamber which captures exhaled methoxyflurane limiting environmental exposure. In Australia, two studies have been performed in ambulance personnel with Penthrox Inhalers which do not have the special AC chamber. Results from these studies showed that methoxyflurane was present in the atmosphere at levels that did not pose any risks to the healthcare professional. No serious adverse events were reported by healthcare professionals who regularly administer Penthrox to patients.

Missing information

Risk	What is known
Limited information on the use in pregnant or breastfeeding women.	The effects of methoxyflurane on pregnant women during early pregnancy or on the unborn child are unknown. As with all medicines care should be exercised when administered during pregnancy especially the first trimester. It is not known whether methoxyflurane passes into human breast milk. Caution should be exercised when methoxyflurane is administered to a nursing mother.

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.

The Summary of Product Characteristics and the Package leaflet for Penthrox® can be found in the Penthrox's® EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in Penthrox's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures concern all the above mentioned risks and consist of educational and training materials for healthcare professionals. The MAH will organise education on Penthrox® use from the time of product launch activities and will target all important risks (identified and potential) to help healthcare professionals to quickly and reliably identify any contraindications or precautions, minimise any potential for risk and thus optimise benefit-risk for the patient.

VI.2.6 Planned post authorisation development plan

List of studies in post authorisation development plan

Study/activity (including study number)	**Objectives**	**Safety concerns /efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
PASS study	To Evaluate the Risks of Hepatotoxicity and Nephrotoxicity from Administration of methoxyflurane (Penthrox®) for Pain Relief in Hospital Accident & Emergency Departments	Hepatotoxicity and Nephrotoxicity	Planned	Final study report within 3 months after study finish
Survey	To evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures: Healthcare Professional and Patient Survey	Hepatotoxicity Nephrotoxicity Cardiovascular effects Respiratory effects Central nervous system effect Malignant hyperthermia Abuse potential Interaction with CYP enzyme inducing drugs Environmental exposure to methoxyflurane by administering healthcare professionals	Planned	Final study report within 2 months after survey finish

Studies which are a condition of the marketing authorisation

None of the above studies are conditions of the marketing authorisation

VI.2.7 Summary of changes to the Risk Management Plan over time

Version 1.0 – 2.0

As a result of the Summary of product Characteristics (SmPC) and Patient Information Leaflet (PIL) changes, the relevant sections of this RMP linking to potential kidney injury and drug-drug interactions have been updated.

The PASS study to evaluate the Risks of Hepatotoxicity and Nephrotoxicity from Administration of methoxyflurane (Penthrox®) for Pain Relief in Hospital Accident & Emergency Departments has been amended.

The survey to evaluate the effectiveness of Penthrox (methoxyflurane) has been amended.

Version 2.0 – 2.1

Section	**Update**
Version No,	Version 2.0 to Version 2.1
Part I Product Overview	Annex 6 (update approval date and version of PASS Survey Study)
	Update to QPPV Name and Signature; update to contact person and contact details
	Update to Overview of Versions, including last version and procedure number
Annex 6	Update to PASS and PASS Survey study timeframes Include approval date and version number of PASS survey study. No change to Protocol provided in RMP version 2.0, Annex 6.2
Annex 10	Clarify proposed additional risk minimisation measures

Version 2.1 – 2.2

Section	Update
Version No,	Version 2.1 to Version 2.2
Annex 10	Clarify educational materials may vary for each EU Member State - at the request of SE during Day 145 in EU procedure UK/H/6350/001/DC
Annex 11	Clarify educational materials may vary for each EU Member State and the mock-ups provided are as an example only-the request of SE during Day 145 in EU procedure UK/H/6350/001/DC

Version 2.2 – 2.3

Section	**Update**
Version No,	Version 2.2 to Version 2.3
Annex 10	Following wording deleted at the request of RMS (MHRA) Day 180 assessment in EU procedure UK/H/6350/001/DC: - statement ""Requirements for educational material may vary for each EU Member State subject to national situations or treatment behaviours / guidelines. Educational materials were developed in accordance with Marketing Authorisation UK/H/5542/01/DC for the UK, Ireland, France and Belgium." - Header statement "if applicable"
Annex 11	Following wording deleted at the request of RMS (MHRA) Day 180 assessment

	in EU procedure UK/H/6350/001/DC: - statement ""Requirements for educational material may vary for each EU Member State subject to national situations or treatment behaviours / guidelines. Educational materials were developed in accordance with Marketing Authorisation UK/H/5542/01/DC for the UK, Ireland, France and Belgium." - Header statement "if applicable"