Penthrox®, Flüssigkeit zur Herstellung eines Dampfes zur Inhalation (Methoxyfluran)

Summary of the Risk Management Plan (RMP)

Version 1.0 (20 July 2018)
Based on Part VI of the EU Risk Management Plan for Penthrox (Methoxyflurane)
RMP version number: 2.4
Data lock point for this RMP: 15 October 2014
Data of final sign off: 4 July 2018
Swiss-specific risk minimisation measures
The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Penthrox® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of “Penthrox® in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedicinfo.ch) approved and authorized by Swissmedic.

Mundipharma Medical Company is fully responsible for the accuracy and correctness of the content of the published summary RMP of Penthrox®.
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 7,265 patients reported pain on admission. Of those patients communicating pain on admission, 54% of patients (3,793 out of 7,265 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.

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.

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

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\(^1\) NHS Accident and Emergency Attendances, 2012-13


Pentrox®, 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 Pentrox® group experienced their first pain relief with 1-10 inhalations in comparison to 51% of patients in the placebo group.

3. Unknowns relating to the 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.

4. Summary of safety concerns
Important identified risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
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<tbody>
<tr>
<td>Liver toxicity (Hepatotoxicity)</td>
<td>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. Methoxyflurane is broken down by the body by certain liver enzymes.</td>
<td>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 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. Pentox 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.</td>
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Important potential risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known (Including reason why it is considered a potential risk)</th>
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<tr>
<td>Effects on the kidney (Nephrotoxicity)</td>
<td>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).</td>
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<td>Cardiovascular effects</td>
<td>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,</td>
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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 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 is limited.

In the MEOF-001 study (which also included older patients), the majority of the
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<th>Table Title</th>
<th>Description</th>
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<tr>
<td><strong>Reported side effects</strong></td>
<td>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.</td>
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<tr>
<td><strong>Malignant hyperthermia</strong></td>
<td>Malignant hyperthermia is a life-threatening condition that is passed down through families and causes a rapid 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.</td>
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<tr>
<td><strong>Abuse Potential</strong></td>
<td>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. 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 significant risk to the abuser and may result in overdose and its consequences.</td>
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<tr>
<td><strong>Interaction with CYP enzyme inducing drugs</strong></td>
<td>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).</td>
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<tr>
<td><strong>Environmental exposure to methoxyflurane by administering healthcare</strong></td>
<td>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.</td>
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professionals  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

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
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<tr>
<td>Limited information on the use in pregnant or breastfeeding women.</td>
<td>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.</td>
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</table>

5. Summary of risk minimisation measures by safety concern

All medicines have an Information for Healthcare Professionals, 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 Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

The Swiss Information for Healthcare Professionals and the Package Information Leaflet for Penthrox® can be found on the Swissmedic Homepage (www.swissmedicinfo.ch).

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures).

These additional risk minimisation measures concern all the above-mentioned risks and consist of educational and training materials for healthcare professionals and patients. 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.
6. Planned post authorisation development plan

List of studies in post authorisation development plan

<table>
<thead>
<tr>
<th>Study/activity (including study number)</th>
<th>Objectives</th>
<th>Safety concerns/ efficacy issue addressed</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post Authorisation Safety Study (PASS)</td>
<td>To Evaluate the Risks of Hepatotoxicity and Nephrotoxicity from Administration of methoxyflurane (Penthrox®) for Pain Relief in Hospital Accident &amp; Emergency Departments</td>
<td>Hepatotoxicity and Nephrotoxicity</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Post Authorisation Safety Study (PASS)</td>
<td>To evaluate Penthrox® (Methoxyflurane) for the relief of moderate to severe trauma associated pain in routine clinical practice in Switzerland</td>
<td>To confirm the safe use of Penthrox® in routine clinical practice in Switzerland</td>
<td>Planned</td>
</tr>
</tbody>
</table>
| 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 | Ongoing |

Studies which are a condition of the marketing authorisation

The Post Authorisation Safety Study (PASS) to evaluate Penthrox® (Methoxyflurane) for the relief of moderate to severe trauma associated pain in routine clinical practice in Switzerland is a condition of the marketing authorisation by Swissmedic.

7. Summary of changes to the Risk Management Plan over time

None since the date of marketing authorisation in Switzerland.