Future Health Pharma GmbH

Guyer-Zeller-Strasse 10
Postfach
CH-8620 Wetzikon
Switzerland
Tel +41 44 932 20 02
Fax +41 44 932 31 32

www.futurehealth.ch

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

Summary of the Risk Management Plan (RMP)

Version	3.0 (23 July 2021)
Based on	EU Risk Management Plan for Penthrox (Methoxyflurane) Version number: 3.2 Data lock point: 11 November 2020 Date of final sign off: 11 November 2020 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 summary of the RMP 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 summary of the RMP 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 Information for Healthcare Professionals (Arzneimittelinformation / Information sur le médicament) approved by Swissmedic and published on www.swissmedicinfo.ch, 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 Information for Healthcare Professionals (Arzneimittelinformation / Information sur le médicament).

Future Health Pharma GmbH is fully responsible for the accuracy and correctness of the content of the published summary of the RMP of Penthrox®.

Summary of the Risk Management Plan for Penthrox (Methoxyflurane)

This is a summary of the risk management plan (RMP) for Penthrox. The RMP details important risks of Penthrox, how these risks can be minimised, and how more information will be obtained about Penthrox's risks and uncertainties (missing information).

Penthrox's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Penthrox should be used.

I. The medicine and what it is used for

Penthrox is authorised for emergency relief of moderate to severe pain in conscious adult patients with trauma and associated pain.

It contains methoxyflurane as the active substance and it is a liquid for inhalation as a vapor administered using a hand held Penthrox Inhaler.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Penthrox, together with measures to minimise such risks and the proposed studies for learning more about Penthrox's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size – the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status – the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Penthrox, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Penthrox is not yet available, it is listed under ‘missing information’ below.

II.A List of important risks and missing information

Important risks of Penthrox are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Penthrox. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Hepatotoxicity
Important potential risks	Nephrotoxicity Cardiovascular system effects Respiratory system effects Central nervous system effects Malignant hyperthermia Abuse potential Interaction with CYP enzyme inducing drugs Environmental exposure to methoxyflurane by administering healthcare professionals
Missing information	Use in pregnancy and breast-feeding

II.B Summary of important risks and missing information

Important identified risk - Hepatotoxicity	
Evidence for linking the risk to the medicine	There is some clinical evidence to show that hepatic damage (hepatitis) may very rarely occur after high dose exposure to methoxyflurane as an anaesthetic, and quite exceptionally after its limited, low dose use to produce brief analgesia. Based on a small and incompletely recorded series of cases the incidence of liver function impairment is very rare. Liver damage has commonly been self-limiting and recoverable provided further exposure was avoided. It has been shown to involve necrosis of hepatocytes and a reactive inflammatory cell infiltrate, sometimes predominantly composed of eosinophils.
Risk factors and risk groups	Patients previously known to have developed hepatotoxicity after inhalation either of methoxyflurane or halogenated hydrocarbon anaesthetics or who has had exposure to methoxyflurane or halogenated hydrocarbon anaesthesia within the past 3 months.
Risk minimisation measures	- **SmPC:** Section 4.2 Recommendations on administration including observation of patients by trained persons. Section 4.3 Contraindications for patients at risk of hepatotoxicity. Section 4.4 Special warnings and precautions for use in patients at risk of hepatoxicity including dosing limitations to minimise the risk. Section 4.5 Potential interaction with enzyme inducers. Section 4.8 - **PIL:** Section 2 Potential risk factors for hepatotoxicity. Section 4 Possible signs and symptoms of hepatotoxicity. - **Pack size** - **Prescription only medicine** - **Additional risk minimisation measures:** for Healthcare Professionals (Swiss specific) Training of Healthcare Professionals
Additional pharmacovigilance activities	PASS study - To Evaluate the Risks of Hepatotoxicity and Nephrotoxicity from Administration of methoxyflurane (Penthrox®) for Pain Relief in Hospital Accident & Emergency Departments Survey to evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures

Important potential risk - Nephrotoxicity	
Evidence for linking the risk to the medicine	Nephrotoxicity has generally only been associated when methoxyflurane is administered in large doses (40-60 mL) over prolonged periods during general anaesthesia. A meta-analysis of 8 studies (Clark et al. 1976; Clark et al. 1979; Creasser et al. 1974; Cuasay et al. 1977; Dahlgren 1977; Palahniuk and Cumming 1975; Rosen et al. 1972; Young et al. 1976) has been conducted with matching data on serum inorganic fluoride levels before and after methoxyflurane analgesia during labour and delivery, and comparing them with levels in controls. The result confirmed that prolonged administration of methoxyflurane resulted in elevated levels of serum inorganic fluoride. The mean plasma fluoride < 20 µmol/L in patients given methoxyflurane for analgesia was much lower than the minimum level that can result in subclinical nephrotoxicity (Cousins and Mazze 1973).
Risk factors and risk groups	Nephrotoxicity has been associated when methoxyflurane is administered in large doses during general anaesthesia. Older people may be at increased risk due to gradual deterioration of renal function with age and also other predisposing medical conditions. CYP2E1 inducers (such as alcohol or isoniazid) which increase the rate of methoxyflurane metabolism may increase potential toxicity and should be avoided concomitantly with methoxyflurane. Antibiotics which have known nephrotoxic effect and concomitant methoxyflurane may potentially have a summative effect. Reduction of renal blood flow and hence anticipated enhanced effect was described when methoxyflurane was used as anaesthetic agent (higher doses) in combination with drugs (e.g. barbiturates) reducing cardiac output. Exact details of exposure in patients with any of the above risk factors are unknown. However, considering extensive post-marketing exposure (e.g. in older people) and intended indication, the likelihood of the accumulation or risk factors and subsequent occurrence of methoxyflurane renal toxicity is considered very low.

Important potential risk - Nephrotoxicity	
Risk minimisation measures	- **SmPC:** Section 4.2 Recommendations on administration including observation of patients by trained persons and dosage limits to minimise risk. Section 4.3 Contraindications for patients at risk of nephrotoxicity. Section 4.4 Special warnings and precautions for use in subgroups of patients at risk of nephrotoxicity. Section 4.5 Interaction with enzyme inducers, nephrotoxic medicines and sevoflurane anaesthesia. Section 4.8 - **PIL:** Section 2 Potential risk factors for nephrotoxicity. Section 3 Maximum dosage limits. Section 4 Possible signs and symptoms of nephrotoxicity. - **Pack size** - **Prescription only medicine** - **Additional risk minimisation measures:** for Healthcare Professionals (Swiss specific) Training of Healthcare Professionals
Additional pharmacovigilance activities	PASS study - To Evaluate the Risks of Hepatotoxicity and Nephrotoxicity from Administration of methoxyflurane (Penthrox) for Pain Relief in Hospital Accident & Emergency Departments. Survey to evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures

Important potential risk - Cardiovascular system effects	
Evidence for linking the risk to the medicine	Methoxyflurane causes respiratory and cardiac depression at anaesthetic doses in pre-clinical studies. In rats, there is a 2- to 4-fold margin between heart or brain concentrations associated with respiratory arrest or cardiac failure and concentrations in these tissues at anaesthesia. In dogs, the extent of change in respiratory and cardiovascular parameters correlated with methoxyflurane blood levels, but was not affected by exposure duration once steady state was attained. Changes in respiratory and cardiovascular parameters showed recovery when exposure was stopped. In a dog study, aortic pressure and ventricular contractile force were close to control values after 4 h of recovery from anaesthesia, when blood levels had decreased to approximately 7 mg/100 ml (Bagwell et al. 1962). This blood concentration is slightly higher than those reported clinically in analgesia.
Risk factors and risk groups	Older patients with increased risk of hypotension and bradycardia.
Risk minimisation measures	- **SmPC:** Section 4.2 Recommendations on administration including observation of patients by trained persons and dosage limits to minimise risk. Section 4.3 Contraindications for patients at risk of cardiovascular system effects. Section 4.4 Special warnings and precautions for use in the elderly. Section 4.8 - **PIL:** Section 2. Potential risk factors for cardiovascular system effects and caution when used in the elderly. Section 4 - **Pack size** - **Prescription only medicine** - **Additional risk minimisation measures:** for Healthcare Professionals (Swiss specific) Training of Healthcare Professionals
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Survey to evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures

Important potential risk - Respiratory system effects	
Evidence for linking the risk to the medicine	Methoxyflurane causes respiratory and cardiac depression at anaesthetic doses in pre-clinical studies. In rats, there is a 2- to 4-fold margin between heart or brain concentrations associated with respiratory arrest or cardiac failure and concentrations in these tissues at anaesthesia. In dogs, the extent of change in respiratory and cardiovascular parameters correlated with methoxyflurane blood levels, but was not affected by exposure duration once steady state was attained. Changes in respiratory and cardiovascular parameters showed recovery when exposure was stopped.
Risk factors and risk groups	Patients with respiratory depression which may be indicative of severe trauma including head injury.
Risk minimisation measures	- **SmPC:** Section 4.2 Recommendations on administration including observation of patients by trained persons and dosage limits to minimise risk. Section 4.3 Contraindications for patients at risk of respiratory system effects. Section 4.8 - **PIL:** Section 2. Clinical scenarios where Penthrox should not be used. Section 4 - **Prescription only medicine** - **Additional risk minimisation measures:** for Healthcare Professionals (Swiss specific) Training of Healthcare Professionals
Additional pharmacovigilance activities	Survey to evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures

Important potential risk - Central nervous system effects	
Evidence for linking the risk to the medicine	Secondary pharmacodynamic effects including potential CNS effects such as sedation, euphoria, amnesia, ability to concentrate, altered sensorimotor co-ordination and change in mood are also known class-effects. All general anaesthetics carry the potential to produce a central nervous system depression, especially in people with other risk factors. Hosick and colleagues (Hosick et al. 1971) demonstrated methoxyflurane impaired the ability to concentrate and affect time perception.
Risk factors and risk groups	Patients with head injury or altered consciousness or patients taking concomitant medications, which may affect central nervous system.
Risk minimisation measures	- **SmPC:** Section 4.2 Recommendations on administration including observation of patients by trained persons and dosage limits to minimise risk. Section 4.3 Contraindications for patients with altered level of consciousness. Section 4.4 Warning about known class effects of methoxyflurane and CNS effects which can be a risk factor for abuse. Section 4.5 Avoid concomitant use with CNS depressants and need for observation when Penthrox given concomitantly with opioids. Section 4.7 Effect of Penthrox on patient's ability to drive or operate machinery. Section 4.8 - **PIL:** Section 2. Clinical scenarios where Penthrox should not be used. Potential interactions with medicines or illegal drugs. Recommendation not to drink alcohol whilst taking Penthrox. Effect of Penthrox on ability to drive or use machines safely. Section 4 - **Prescription only medicine** - **Additional risk minimisation measures:** for Healthcare Professionals (Swiss specific) Training of Healthcare Professionals
Additional pharmacovigilance activities	Survey to evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures

Important potential risk - Malignant hyperthermia	
Evidence for linking the risk to the medicine	Due to a report to the TGA of a possible case of malignant hyperthermia following methoxyflurane (Penthrane brand) administration, precautions are also listed for patient with known or genetic susceptibility to malignant hyperthermia.
Risk factors and risk groups	Patients with known or genetic susceptibility to malignant hyperthermia.
Risk minimisation measures	- **SmPC:** Section 4.2 Recommendations on administration including observation of patients by trained persons and dosage limits to minimise risk. Section 4.3 Contraindications for patients at risk of malignant hyperthermia. - **PIL:** Section 2. Description of risk factors and possible signs of malignant hyperthermia. Advice on when Penthrox should not be used. - **Prescription only medicine** - **Additional risk minimisation measures:** for Healthcare Professionals (Swiss specific) Training of Healthcare Professionals
Additional pharmacovigilance activities	Survey to evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures

Important potential risk - Abuse potential	
Evidence for linking the risk to the medicine	The abuse of other compounds in this class have been reported, however Penthrox is manufactured, packaged, distributed and disposed of in such a way as to minimise abuse potential. Methoxyflurane will be supplied as 3 mL bottles in an enclosed container system with a tamper proof seal and therefore access to methoxyflurane will be difficult. A bar code system will be included in the carton, bottle and inhaler components of the combination pack.
Risk factors and risk groups	Healthcare professionals are potentially the sole risk group.
Risk minimisation measures	- **SmPC:** Section 4.2 Recommendations on administration including observation of patients by trained persons and dosage limits to minimise risk. Section 4.4 Warning about CNS effects which can be a risk factor for abuse. Section 4.8 - **PIL:** Section 3 and 4 - **Pack size** - **Prescription only medicine** - **Additional risk minimisation measures:** for Healthcare Professionals (Swiss specific) Training of Healthcare Professionals
Additional pharmacovigilance activities	Survey to evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures

Important potential risk - Interaction with CYP enzyme inducing drugs	
Evidence for linking the risk to the medicine	There is no evidence in the published literature and there have been no reports of any drug-drug interactions when methoxyflurane is administered in low (sub-anaesthetic) doses for analgesia. Considering clinical situations where Penthrox is intended to be used, the potential for drug-drug interaction with CYP 450 enzyme inducers is listed as a potential important risk. It is possible that enzyme inducers (such as alcohol or isoniazid for CYP 2E1 and phenobarbital or rifampicin for CYP2A6 and CYP2B6) which increase the rate of methoxyflurane metabolism might increase its potential toxicity and they should be avoided concomitantly with methoxyflurane
Risk factors and risk groups	Patients administrating enzyme inducers (such as alcohol or isoniazid for CYP 2E1 and phenobarbital or rifampicin for CYP 2A6 and CYP2B6) which increase the rate of methoxyflurane metabolism.
Risk minimisation measures	- **SmPC:** Section 4.2 Recommendations on administration including observation of patients by trained persons. Section 4.5 Recommendation to avoid enzyme inducers. - **PIL:** Section 2. Advice regarding medicines that can interact with Penthrox. Patients should not drink alcohol whilst taking Penthrox. - **Prescription only medicine** - **Additional risk minimisation measures** for Healthcare Professionals (Swiss specific) Training of Healthcare Professionals
Additional pharmacovigilance activities	Survey to evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures

Important potential risk - Environmental exposure to methoxyflurane by administering healthcare professionals	
Evidence for linking the risk to the medicine	Requested by the Home Office advisory committee, this has been added as an important potential risk.
Risk factors and risk groups	Healthcare professionals administering Penthrox are the sole potential risk group
Risk minimisation measures	- **SmPC:** Section 4.2 Instructions on usage of AC chamber and method of disposal for used Penthrox inhaler and bottle. Section 4.4 Recommendation that healthcare professionals should be aware of relevant occupational health and safety guidelines for inhalational agents and should use the Penthrox inhaler with the AC chamber. Section 6.6 Method of disposal for used Penthrox inhalers and bottles. - **Additional risk minimisation measures** for Healthcare Professionals (Swiss specific) Training of Healthcare Professionals
Additional pharmacovigilance activities	Survey to evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures

Missing information - Use in pregnancy and breast-feeding	
Risk minimisation measures	- **SmPC:** Section 4.6 - **PIL:** Section 2 - **Additional risk minimisation measure:** for Healthcare Professionals (Swiss specific) Training of Healthcare Professionals
Additional pharmacovigilance activities	Survey to evaluate the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

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

This PASS is a condition of the marketing authorisation of Penthrox by Swissmedic.

II.C.2 Other studies in post-authorisation development plan

There are no studies planned.

Summary of risk minimisation measures

All medicines have an Information for Healthcare Professionals, which provides physicians, pharmacists and other healthcare 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. 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 Marketing Authorisation Holder 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.