

PENTHROX[®] (methoxyflurane)

Administration Guide

IMPORTANT RISK MINIMISATION INFORMATION FOR HEALTHCARE PROFESSIONALS – PLEASE READ CAREFULLY BEFORE ADMINISTERING METHOXYFLURANE – DO NOT DISCARD.

Dear Healthcare Professional,

The following is important, non-promotional information about the safe and effective use of methoxyflurane.

This information is essential to ensure the appropriate management of important selected risks.

This information does not replace the Summary of Product Characteristics (SmPC) which should be read and understood in full before administering methoxyflurane.

You should also give the patient a copy of the Patient Information Leaflet (PIL) and Patient Alert Card to take away.

Please ensure that the date of administration is filled out on the Patient Alert Card and that you counsel patients regarding the symptoms associated with hepatotoxicity as specified within the alert card.

If you require any further information regarding the use of PENTHROX (methoxyflurane), please refer to the Summary of Product Characteristics at www.hpra.ie or call Galen Pharma Ireland Limited on 048 38334974.

Healthcare professionals are asked to report any suspected adverse reactions via Freepost, HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: 01 6764971; Fax: 01 6762517. Website: <http://www.hpra.ie>; E-mail: medsafety@hpra.ie. Any suspected adverse reactions should also be reported to Galen Pharma Ireland Limited on 048 3833 4974 and select the customer services option, or e-mail customer.services@galen-pharma.com

Learning objectives:

To ensure Healthcare Professionals:

- Are aware of the important selected risks associated with methoxyflurane use.
- Understand why those risks have been identified as important.
- Have a clear understanding of how to minimise the risks associated with methoxyflurane use.

Key points:

- There are risks associated with methoxyflurane use.
- Always administer the lowest effective dose of methoxyflurane and do not exceed the maximum dose of 6 mL methoxyflurane (2 x 3 mL doses) in a single day.

Why is the methoxyflurane indication limited to acute use in adults with trauma-related pain?

Methoxyflurane is indicated for the emergency relief of moderate to severe pain in conscious **adult** patients with trauma and associated pain.

It is **not** indicated for use in children and adolescents, under 18 years, as its safety and efficacy have not been established in this population.

Methoxyflurane is restricted to acute pain relief as the limitations on dose (maximum 2 x 3 mL doses) and duration of analgesia (total dose to a patient in a week should not exceed 15 mL) make it unsuitable for relief of chronic or break-through pain.

It is also **not** appropriate for the relief of trauma-related pain in closely repeated episodes for the same patient due to the potential for nephrotoxicity, which is dose-related.

Important Selected Risks to be Considered when Administering Methoxyflurane:

Hepatotoxicity.....	3
Nephrotoxicity.....	3
Cardiovascular effects	4
Respiratory effects	4
Central Nervous System (CNS) effects	5
Malignant hyperthermia.....	5
Abuse potential.....	6
Interaction with CYP enzyme-inducing drugs.....	6
Occupational exposure.....	7

Risk: Hepatotoxicity

Why?

- Methoxyflurane is metabolised in the liver, therefore increased exposures in patients with hepatic impairment can cause toxicity.
- There is clinical evidence to show that methoxyflurane may cause hepatotoxicity. Isolated post-marketing reports of hepatic failure and hepatitis have been observed with analgesic use of methoxyflurane.
- Repeated exposure at frequent intervals and prior exposure to halogenated hydrocarbon anaesthetics (including methoxyflurane when used in the past as an anaesthetic agent), especially if the interval is less than three months, have been reported to increase the risk of liver toxicity.

How do I minimise this risk?

- Only administer methoxyflurane to patients that do **not** have a history of showing signs of liver damage after previous use of methoxyflurane or halogenated hydrocarbon anaesthesia.
- Exercise care when using methoxyflurane in patients with underlying hepatic conditions or with risks for hepatic dysfunction (such as enzyme inducers – refer to page 6, Interaction with CYP enzyme-inducing drugs).
- Use cautious clinical judgement when administering methoxyflurane more frequently than once every 3 months (it has been reported that previous exposure, especially if the interval is less than three months, may increase the potential for hepatic injury).

Risk: Nephrotoxicity

Why?

- Methoxyflurane causes significant nephrotoxicity at high doses and therefore renal failure may occur if the recommended dose is exceeded.
- There may be an additive effect on nephrotoxicity when methoxyflurane is used concomitantly with medicines (e.g. contrast agents and some antibiotics) which are known to have a nephrotoxic effect. Antibiotics with known nephrotoxic potential include tetracycline, gentamicin, colistin, polymyxin B and amphotericin B.
- Nephrotoxicity is also related to the rate of metabolism.
- The frequency at which methoxyflurane can be safely used is not established.
- Sevoflurane increases serum fluoride levels and methoxyflurane nephrotoxicity is associated with raised serum fluoride.

How do I minimise this risk?

- Only administer methoxyflurane to patients that do **not** have clinically significant renal impairment, such as eGFR <45 mL/min.

- Always use the lowest effective dose of methoxyflurane, especially in the elderly or patients with other known risk factors of renal disease.
- Do not exceed the maximum dose of 6 mL methoxyflurane (2 x 3 mL bottles) in a single day.
- Administration on consecutive days is not recommended and the total dose to a patient in a week should not exceed 15 mL.
- Only administer methoxyflurane to patients who are **not** concomitantly taking drugs known to have a nephrotoxic effect.
- Factors that increase the rate of metabolism such as drugs that induce hepatic enzymes can increase the risk of toxicity as well as sub-groups of people with genetic variations that may result in fast metaboliser status.
- Sevoflurane anaesthesia should be avoided following methoxyflurane analgesia.

Risk: Cardiovascular effects

Why?

- Potential effects on blood pressure and heart rate are known effects of high dose methoxyflurane used in anaesthesia and other anaesthetics. They do not appear to be significant at the analgesic doses.
- The risk may be increased for older patients with hypotension and bradycardia.

How do I minimise this risk?

- Only administer methoxyflurane to patients that do **not** have clinically evident cardiovascular instability.
- Use caution when administering methoxyflurane in elderly patients due to a potential reduction in blood pressure.

Risk: Respiratory effects

Why?

- Methoxyflurane has been reported to cause respiratory depression when used at analgesic doses.

How do I minimise this risk?

- Only administer methoxyflurane to patients that do **not** have clinically evident respiratory depression.
- Respiration should be monitored due to the risk for respiratory depression and hypoxia.

Risk: Central nervous system (CNS) effects

Why?

- Methoxyflurane is a CNS depressant and can produce CNS effects, such as sedation, euphoria, amnesia, ability to concentrate, altered sensorimotor co-ordination and change in mood.
- It is likely to have additive effects when used concomitantly with other CNS depressants, such as opioids, alcohol etc.

How do I minimise this risk?

- Only administer methoxyflurane to patients that do **not** have an altered level of consciousness due to any cause including head injury, drugs or alcohol.
- Methoxyflurane should be administered under supervision.
- If opioids are given concomitantly with methoxyflurane, the patient should be observed closely.

Risk: Malignant hyperthermia

Why?

- Malignant hyperthermia is a rare genetic disorder which manifests clinically as a hypermetabolic crisis.
- It is usually triggered by an anaesthetic, including methoxyflurane.

How do I minimise this risk?

- Only administer methoxyflurane to patients that do **not** have a history of malignant hyperthermia or who are not genetically susceptible to malignant hyperthermia.
- Only administer methoxyflurane to patients who do **not** have a history or family history of severe adverse reactions to inhaled anaesthetics.

Risk: Abuse potential

Why?

- Due to the potential CNS effects of methoxyflurane, such as sedation, euphoria or change in mood, it has some abuse potential.
- As a prescription-only medicine which is administered only in single doses under the supervision of a healthcare professional, the main risk group for abuse is healthcare professionals.

How do I minimise this risk?

- Dispose of used methoxyflurane bottles and inhalers responsibly in the sealed plastic bag provided and place in a designated bin or suitable waste container due to the potential for abuse associated with PENTHROX.

Risk: Interaction with CYP enzyme inducing drugs

Why?

- CYP 450 enzymes mediate methoxyflurane metabolism, particularly CYP 2E1, CYP 2B6 and to some extent CYP 2A6.
- Increasing the rate of methoxyflurane metabolism may increase its potential toxicity.

How do I minimise this risk?

- Only administer methoxyflurane to patients that are **not** concomitantly taking CYP enzyme-inducing agents, particularly CYP 2E1 (e.g. alcohol or isoniazid), CYP 2B6 (e.g. carbamazepine, efavirenz, rifampicin or nevirapine) and CYP 2A6 (e.g. phenobarbital or rifampicin) enzyme inducers.

Risk: Occupational exposure

Why?

- Methoxyflurane is a volatile substance that evaporates during the preparation of the inhaler and thereafter.
- When a patient uses the inhaler intermittently, methoxyflurane continues to evaporate into the atmosphere and may be present in a closed environment (such as an ambulance) in small concentration.
- Additionally, methoxyflurane may be released into the atmosphere if a patient exhales into the atmosphere rather than through the mouthpiece as instructed.
- Multiple use of the inhaler without the activated carbon (AC) chamber creates additional risk.
- Elevation of liver enzymes, blood urea nitrogen and serum uric acid has been reported in exposed maternity ward staff in the past when methoxyflurane was used in patients during labour and delivery.

How do I minimise this risk?

- Always ensure that the AC chamber is attached to the inhaler as this will adsorb any methoxyflurane exhaled through the inhaler.
- Ensure patients self-administer methoxyflurane correctly and always exhale through the mouthpiece of the inhaler.
- Once the contents of the methoxyflurane bottle have been tipped into the inhaler replace the cap on the bottle.
- Place used methoxyflurane bottles and inhalers into the sealed plastic bag provided and dispose of responsibly in a designated bin or suitable waste container.



This medicinal product does not require any special temperature storage conditions.

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