PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **PENTHROX®**

Methoxyflurane volatile liquid for inhalation

Volatile liquid, 99.9%, for inhalation

Analgesic

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Importer/Distributor:
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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PENTHROX® (methoxyflurane) is indicated for short-term relief of moderate to severe acute pain, associated with trauma or interventional medical procedures, in conscious adult patients.

Due to dose limitations of a treatment course of PENTHROX and the duration of associated pain relief, PENTHROX is not appropriate for providing relief of break-through pain in chronic pain conditions. PENTHROX is also not appropriate for relief of repetitive pain (see **DOSAGE AND ADMINISTRATION**).

PENTHROX is not indicated for use during pregnancy or the peripartum period, including labour (see **WARNINGS AND PRECAUTIONS**, **Pregnant Women**).

1.1 Pediatrics

Pediatrics (< 18 years of age): Data are not adequate to support use in children. Use is not recommended in children.

1.2 Geriatrics (>65 years of age): PENTHROX has been studied in this population. PENTHROX may be used in the elderly. However, as the risk potentially may be increased for older individuals with hypotension or bradycardia, caution should be exercised in these patients due to possible reduction in blood pressure.

2 CONTRAINDICATIONS

PENTHROX® (methoxyflurane) is contraindicated in patients, with:

- an altered level of consciousness, due to any cause, including head injury, drugs, or alcohol
- clinically significant renal impairment
- a history of liver dysfunction after previous methoxyflurane use or other halogenated anesthetics
- hypersensitivity to methoxyflurane or other halogenated anesthetics or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.
- known or genetically susceptible to malignant hyperthermia or a history of severe adverse reactions in either patient or relatives
- clinically evident hemodynamic instability
- clinically evident respiratory impairment

Use of PENTHROX as an anesthetic agent is contraindicated.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- Supratherapeutic doses of methoxyflurane inhalation, have been shown to lead to serious, irreversible nephrotoxicity in a dose-related manner (see **WARNINGS AND PRECAUTIONS**, **Renal**). Dosing limitations should be followed meticulously to prevent or limit risk of nephrotoxicity (see **DOSAGE AND ADMINISTRATION**).

- Very rare cases of hepatotoxicity have been reported with methoxyflurane inhalation when used for analgesic purposes (see **WARNINGS AND PRECAUTIONS**, **Hepatic**).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

PENTHROX® (methoxyflurane) use should be self-administered under supervision of a healthcare practitioner, trained in its administration, using the hand-held PENTHROX Inhaler.

Avoid use of PENTHROX in patients taking CNS depressants, such as opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines or alcohol (see **DRUG INTERACTIONS**). Also, avoid PENTHROX with potentially nephrotoxic drugs, such as, contrast agents, NSAIDs, some antibiotics (see **DRUG INTERACTIONS**).

PENTHROX should not be used for the treatment of chronic or repetitive pain (see **INDICATIONS**).

4.2 Recommended Dose and Dosage Adjustment

One 3 mL bottle of PENTHROX to be vaporised in a PENTHROX Inhaler. On finishing the 3 mL dose, another 3 mL may be used, if needed. **The dose of PENTHROX should not exceed 6 mL in a single administration, or over the first day of treatment.** The lowest effective

dosage of PENTHROX to provide analgesia should be used.

The frequency at which PENTHROX treatment can be safely used is not established. A maximum daily dose of 6 mL of PENTHROX should not be administered on any two consecutive days. **A treatment course of PENTHROX should be limited to a total dose of 15 mL over one week, with no more than 6 mL to be used in a single 48 hour period.**

Expected onset of pain relief is rapid with a median onset of 5 minutes. Patients should be instructed to inhale intermittently to achieve adequate analgesia. Patients are able to assess their own level of pain and titrate the amount of PENTHROX inhaled for adequate pain control. Continuous inhalation provides analgesic relief for up to 25-30 minutes, or approximately 1 hour when administered intermittently. Patients should be advised to take the lowest possible dose to achieve pain relief.

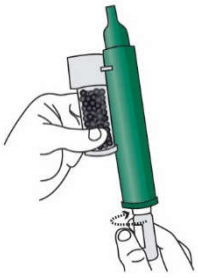
Treatment courses of PENTHROX should not be repeated at an interval of less than 3 months.

4.3 Administration

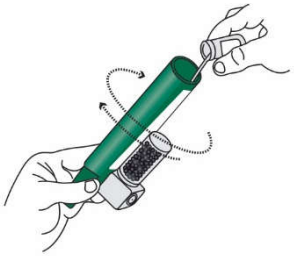
PENTHROX is a portable, lightweight, non-invasive inhaler for self-administration (single patient use). Instructions on the preparation of the PENTHROX Inhaler and correct administration are provided below:

1. Ensure the Activated Carbon (AC) Chamber is inserted into the dilutor hole on the top of the PENTHROX Inhaler.

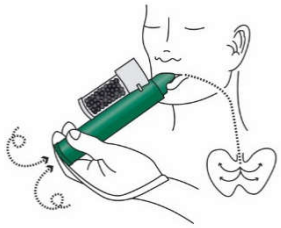
2. Remove the cap of the bottle by hand. Alternatively, use the base of the PENTHROX Inhaler to loosen the cap with a ½ turn. Separate the inhaler from the bottle and remove the cap by hand.



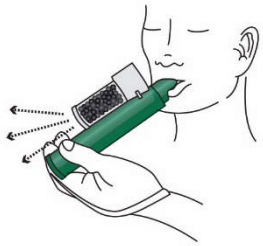
3. Tilt the PENTHROX Inhaler to a 45° angle and pour the total contents of one PENTHROX bottle into the base of the inhaler while rotating to ensure wick is adequately saturated. Note that PENTHROX has a fruity scent.



4. Place wrist loop over patient's wrist. Patient inhales through the mouthpiece of the PENTHROX Inhaler to obtain analgesia. First few breaths should be gentle and then instruct patient to breathe normally through inhaler.

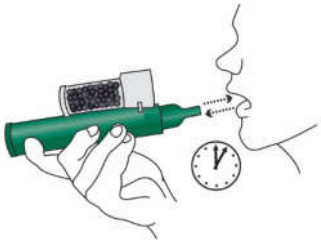


5. Patient should exhale into the PENTHROX Inhaler. The exhaled vapor passes through the AC Chamber to adsorb any exhaled methoxyflurane.



6. If stronger analgesia is required, patient can cover dilutor hole on the AC Chamber with finger during use.

7. Patient should be instructed to inhale intermittently to achieve adequate analgesia. Continuous inhalation will reduce duration of use. Minimum dose to achieve analgesia should be administered.



8. Replace cap onto PENTHROX bottle. Place used PENTHROX Inhaler and used bottle in sealed plastic bag and dispose through normal waste.

5 OVERDOSAGE

Patients should be observed for signs of drowsiness, pallor and muscle relaxation following methoxyflurane administration.

High doses of methoxyflurane cause dose-related nephrotoxicity. High output renal failure has occurred several hours or days after the administration of repeated high analgesic or anesthetic doses of methoxyflurane.

For management of a suspected drug overdose, contact your Regional Poison Control Centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Inhalation	Volatile liquid / 3 mL of 99.9% methoxyflurane	Butylated hydroxytoluene (BHT)

PENTHROX® is packaged into an amber glass screw neck bottle, closed with a white copolymer screw cap.
PENTHROX is supplied in the following presentations:

- Combination pack with a single (3 mL) dose, one PENTHROX Inhaler and one AC Chamber.
- Single dose (3 mL) pack of 10.

7 WARNINGS AND PRECAUTIONS

Cardiovascular
Potential effects on blood pressure and heart rate are known class effects of high dose methoxyflurane when used in anesthesia, as well as other anesthetics. When used at analgesic doses, these effects do not appear to be significant. However, as the risk may be potentially increased for older individuals with hypotension or bradycardia, caution should be exercised in the elderly due to possible reduction in blood pressure.

Drug Dependence
The CNS effects of methoxyflurane can be a risk factor for potential abuse. There have been very rare post-marketing reports of abuse related to anesthetic use.

Driving and Operating Machinery
PENTHROX® may have an adverse influence on the ability to drive and use machines. Dizziness, somnolence and drowsiness may occur following the administration of PENTHROX. Patients should be advised not to drive or operate machinery during PENTHROX administration, or if they are feeling drowsy or dizzy following PENTHROX use.

Hepatic
Methoxyflurane is metabolised in the liver, therefore increased exposures in patients with hepatic impairment can cause toxicity. PENTHROX should be used with care in patients with underlying hepatic conditions or having risk factors for hepatic dysfunction.

PENTHROX must not be used in patients who have a history of showing signs of liver damage after previous methoxyflurane use or halogenated hydrocarbon anesthesia (see **CONTRAINDICATIONS**).

Monitoring and Laboratory Tests
Due to the pharmacologic properties of PENTHROX, standard opioid-associated observation and monitoring post-administration is not required.

Neurologic
Secondary pharmacodynamic effects, including potential CNS effects such as sedation, euphoria, amnesia, ability to concentrate, altered sensorimotor co-ordination and change in mood, are known class effects. Self-administration of PENTHROX in analgesic doses should be limited by occurrence of these CNS effects

Do not administer PENTHROX to patients concomitantly with alcohol ingestion.

Occupational Exposure
Healthcare professionals who are regularly exposed to patients using PENTHROX inhalers should be aware of relevant occupational health and safety guidelines for the use of inhalational agents. To reduce occupational exposure to methoxyflurane, the PENTHROX Inhaler should always be used with the Activated Carbon (AC) Chamber which adsorbs exhaled methoxyflurane. Multiple use of the PENTHROX Inhaler without the AC Chamber creates additional risk. Elevation of liver enzymes, blood urea nitrogen, and serum uric acid, have been reported in healthcare professionals regularly exposed to methoxyflurane inhalational products.

Renal
Consecutive day use of PENTHROX is not recommended because of nephrotoxic potential.

Methoxyflurane causes significant nephrotoxicity at high doses, e.g., extended anesthetic doses (see **CONTRAINDICATIONS**). Serious nephrotoxicity has been reported when methoxyflurane inhalation has been used for analgesia at exposures substantially higher than currently recommended (see **Serious Warnings and Precautions**).The risk of methoxyflurane-induced nephrotoxicity is related to dose, duration of exposure and the rate of metabolism.

Factors that increase the rate of metabolism of methoxyflurane, such as drugs that induce CYP 2E1, e.g., alcohol, isoniazid, and CYP 2A6 isozymes, e.g., phenobarbital, rifampicin, can increase the risk of toxicity with methoxyflurane, since increased levels of fluorinated breakdown products of methoxyflurane are thought to lead to nephrotoxicity (see **DRUG INTERACTIONS**). Patients with genetic variations of these isozymes may result in fast metabolizer status, leading to increased risk of toxicity.

Nephrotoxicity is thought to be associated with inorganic fluoride ions, a metabolic break-down product. Subclinical toxicity in the past when used as an anesthetic agent has been determined to be associated with peak serum levels of 50 – 80 µmol/L. Following a single dose of 3 mL, serum levels did not exceed 10 µmol/L.

Despite this safety margin, the lowest effective dose of PENTHROX should be administered, especially in the elderly or in patients with other known risk factors of renal disease. In addition, PENTHROX should be cautiously used in patients diagnosed with clinical conditions that would predispose to renal injury.

Respiratory
Methoxyflurane causes respiratory depression at anesthetic doses. Clinical history of use in analgesia has provided no indication that methoxyflurane significantly affects respiratory parameters.

Skin
PENTHROX contains butylated hydroxytoluene, a stabilizer. Butylated hydroxytoluene may cause local skin reactions, e.g., contact dermatitis, or irritation to the eyes and mucous membranes.

7.1 Special Populations

7.1.1 Pregnant Women

Methoxyflurane inhalation has not been adequately studied during pregnancy or in labour. Neonates, whose mothers were exposed to methoxyflurane during labour, showed increased levels of serum fluoride after birth. Since safe exposure to methoxyflurane has not been established during pregnancy, its use is not indicated in pregnant women.

7.1.2 Breast-feeding

It is not known if methoxyflurane is distributed into breast milk. Caution should be exercised if methoxyflurane is administered to a nursing mother.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Benefit-risk has not been established in the pediatric population. Use is not recommended in children.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common reactions are related to the CNS system, including dizziness, headache and somnolence.

Serious dose-related nephrotoxicity has only been associated with methoxyflurane when used at high doses over prolonged periods. The recommended maximum dose for PENTHROX® should not be exceeded (see **DOSAGE AND ADMINISTRATION**).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 2 shows adverse events (AE) experienced by ≥ 1% of patients with trauma and associated pain from a placebo-controlled trial, Study MEOF-001. The safety population in this study was defined as those patients who were randomized to treatment and received at least

one dose of PENTHROX (149 patients) or placebo (149 patients). The age range of patients included in the study was 12-84, with 171 (57.4%) male and 127 (42.6%) female.

A total of 243 patients (81.5%) used only one inhaler, with a slightly higher number of patients in the placebo group (125 patients; 83.9%), compared with the PENTHROX group (118 patients; 79.2%).

At least one AE was experienced by 50% of the patients in the study. The proportion of patients reported to have experienced an AE during the study was higher in the PENTHROX group (88 patients; 59.1%), than in the placebo group (61 patients; 40.9%). In this study, PENTHROX had no clinically relevant effects on vital signs, such as blood pressure, heart rate and rhythm or respiratory rate.

Table 2. Adverse Events ≥ 1% of in Adult and Adolescent Patients in Study MEOF-001

	PENTHROX N = 149		**Placebo N = 149**	
	N	**N (%)**	**n**	**N (%)**
Any Adverse Event	**188**	**88 (59.1%)**	**111**	**61 (40.9%)**
Gastrointestinal Disorders				
Dry Mouth	3	3 (2.0%)	0	0
Nausea	2	2 (1.3%)	5	5 (3.4%)
Toothache	2	2 (1.3%)	2	2 (1.3%)
Vomiting	2	2 (1.3%)	5	4 (2.7%)
General Disorders And Administration Site Conditions				
Influenza Like Illness	0	0	3	3 (2.0%)
Feeling drunk	2	2 (1.3%)	0	0
Infections and Infestations				
Influenza	2	2 (1.3%)	1	1 (0.7%)
Nasopharyngitis	2	2 (1.3%)	4	4 (2.7%)
Viral infection	2	2 (1.3%)	0	0
Injury, Poisoning And Procedural Complications				
Fall	2	2 (1.3%)	0	0
Joint sprain	2	2 (1.3%)	0	0
Musculoskeletal And Connective Tissue Disorders				
Back pain	3	3 (2.0%)	2	2 (1.3%)
Nervous System Disorders				
Amnesia	2	2 (1.3%)	0	0
Dizziness	50	44 (29.5%)	15	12 (8.1%)
Dysarthria	2	2 (1.3%)	0	0
Headache	51	32 (21.5%)	34	24 (16.1%)
Migraine	2	2 (1.3%)	1	1 (0.7%)
Somnolence	8	8 (5.4%)	1	1 (0.7%)
Reproductive System and Breast disorders				
Dysmenorrhoea	2	2 (1.3%)	0	0
Respiratory, Thoracic And Mediastinal Disorders				
Cough	2	2 (1.3%)	1	1 (0.7%)
Oropharyngeal Pain	3	3 (2.0%)	3	3 (2.0%)
Skin And Subcutaneous Tissue Disorders				
Rash	2	2 (1.3%)	2	1 (0.7%)

Table 2. Adverse Events ≥ 1% of in Adult and Adolescent Patients in Study MEOF-001

	PENTHROX N = 149		Placebo N = 149	
	N	N (%)	n	N (%)
Vascular Disorders				
Hypotension	2	2 (1.3%)	4	4 (2.7%)

n=number of events, N=number of patients, %=percentage of patients
All adverse events in the table were documented as treatment-emergent adverse events in the clinical study.

Laboratory investigations in Study MEOF-001 revealed that serum AST and ALT were not elevated in patients treated with PENTHROX, compared to placebo. Serum LDH was elevated at 1.3% in PENTHROX-treated patients, compared to 0% of placebo-treated patients.

Table 3 shows all AEs experienced by patients who underwent a bone marrow biopsy (BMB) in a placebo-controlled trial, Study 06/61. The safety population in this study included 49 patients in the PENTHROX group and 48 patients in the placebo group. Safety was assessed by recording adverse events 30-45 minutes, 48 hours and up to 30 days following completion of the procedure. The age range of patients included in the study was 25-82, with 74 (76.3%) male and 23 (23.7%) female.

There were more patients who experienced AEs in the PENTHROX group, compared with the placebo group at 30-45 minutes after the BMB procedure.

The most frequent (>5%) AEs at 48 hours follow-up in the PENTHROX group were pain at BMB site, nausea and somnolence (depressed level of consciousness). The most frequent (>5%) AEs at 30 days follow-up for both arms were fatigue (asthenia, lethargy, malaise), pain, constipation and nausea.

Table 3. Adverse Events ≥ 2% Experienced following BMB – 30-45 Minutes Post-Procedure in Study 06/61

	PENTHROX N = 49	Placebo N = 48
	N (%)	N (%)
Adverse Events 30-45 minutes after procedure		
Dizziness	4 (8.2%)	0 (0%)
Euphoria	2 (4.1%)	0 (0%)
Nausea	1 (2%)	1 (2.1%)
Diaphoresis	1 (2%)	1 (2.1%)
Dysgeusia	1 (2%)	1 (2.1%)
Flushing	1 (2%)	0 (0%)
Hypertension	1 (2%)	0 (0%)
Anxiety	1 (2%)	0 (0%)
Depression	1 (2%)	0 (0%)
Neuropathy: sensory	1 (2%)	0 (0%)
Somnolence / depressed level of consciousness	1 (2%)	0 (0%)
Vomiting	0 (0%)	1 (2.1%)

All adverse events in the table were documented as treatment-emergent adverse events in the clinical study.

8.3 Less Common Clinical Trial Adverse Reactions

The listing below presents AEs which occurred at a rate < 1% in Study MEOF-001.

Eye disorders:	diplopia
Gastrointestinal:	oral discomfort
General disorders and administration site conditions:	fatigue, feeling abnormal, feeling of relaxation, hangover, hunger, shivering
Nervous system disorders:	dysgeusia, paresthesia
Psychiatric disorders:	inappropriate affect

8.4 Post-Market Adverse Reactions

Very rare (≥1/10,000 to <1/1,000) reports of hepatic failure/hepatitis have been observed with analgesic use of methoxyflurane.

Other events linked to methoxyflurane use in analgesia (in addition to the reactions from clinical trials listed above), including reports from the literature include:

- **Nervous system disorders:** drowsiness, agitation, restlessness, dissociation, affect lability, disorientation, altered state of consciousness
- **Respiratory system:** choking, hypoxia, oxygen saturation decreased
- **Cardiovascular system:** blood pressure fluctuation
- **Hepatic:** hepatitis, increased liver enzymes, jaundice, liver injury, hepatic failure
- **Renal:** increased serum uric acid, urea nitrogen and creatinine, renal failure
- **Eyes:** blurred vision, nystagmus

9 DRUG INTERACTIONS

9.1 Overview

The metabolism of methoxyflurane is mediated by the CYP 450 enzymes, particularly CYP 2E1, and to some extent CYP 2A6. It is possible that enzyme inducers, such as alcohol or isoniazid for CYP 2E1, and phenobarbital or rifampicin for CYP 2A6, which increase the rate of methoxyflurane metabolism may increase its potential toxicity (see **WARNINGS AND PRECAUTIONS**, **Renal**). Therefore, concomitant use with methoxyflurane should be avoided.

9.2 Drug-Drug Interactions

Concomitant use of PENTHROX® with CNS depressants, such as opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines and alcohol may produce additive depressant effects (see **DOSAGE AND ADMINISTRATION**). If opioids must be given concomitantly with PENTHROX, the patient should be observed closely.

Concomitant use of PENTHROX with medicines which are known to have a nephrotoxic effect, e.g., contrast agents, NSAIDs, some antibiotics, should be avoided as there may be an additive effect on nephrotoxicity. Antibiotics with known nephrotoxic potential include tetracycline, gentamicin, colistin, polymyxin B and amphotericin B. It is advisable to avoid using sevoflurane anesthesia following PENTHROX analgesia, as sevoflurane increases serum fluoride levels, and nephrotoxicity of PENTHROX is associated with raised serum fluoride.

9.3 Drug-Food Interactions

Interactions with food have not been established.

9.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Methoxyflurane (2,2-dichloro-1,1-difluoro-1-methoxyethane) belongs to the halogenated hydrocarbon group of volatile anesthetic agents. The mechanism of action of methoxyflurane in analgesia has not been elucidated. It is unclear why methoxyflurane is the only member of the halogenated inhalational anesthetic class of compounds to display analgesic properties at sub-anesthetic doses. Potential factors contributing to the analgesic activity of methoxyflurane include effects on substance P and beta-endorphin. Inhaled doses of methoxyflurane are rapidly absorbed into the bloodstream to provide analgesia.

10.2 Pharmacodynamics

Methoxyflurane vapour provides analgesia when inhaled at low concentrations. After methoxyflurane administration, drowsiness may occur. During methoxyflurane administration, the cardiac rhythm is usually regular. The myocardium is only minimally sensitised to adrenaline by methoxyflurane. At analgesic therapeutic doses, pain relief may lead to some decrease in blood pressure, along with heart rate decrease.

10.3 Pharmacokinetics

Absorption: Methoxyflurane has the following partition coefficients (at 37°C):

- a water/gas coefficient of 4.5,
- a blood/gas coefficient of 10.2 - 14.1 and
- an oil/gas coefficient of 825

Methoxyflurane enters the lungs in the form of a vapour and is rapidly transported into the blood, leading to rapid onset of analgesic activity.

Distribution: Methoxyflurane has a high oil/gas coefficient, hence methoxyflurane is highly lipophilic. Methoxyflurane has great propensity to diffuse into fatty tissue, where it forms a reservoir from which it is released slowly over days.

Metabolism: Methoxyflurane is metabolised by dechlorination and o-demethylation in the liver, mediated by CYP 450 enzymes, particularly CYP 2E1 and CYP 2A6. Methoxyflurane is metabolised to free fluoride, oxalic acid, difluoromethoxyacetic acid, and dichloroacetic acid. Both free fluoride and oxalic acid can cause renal damage at concentrations higher than those achievable with single analgesic dose use. Methoxyflurane is more susceptible to metabolism than other halogenated methyl ethyl ethers and has greater propensity to diffuse into fatty tissues. Hence, methoxyflurane is released slowly from this reservoir and becomes available for biotransformation for many days.

Elimination: Approximately 60% of methoxyflurane uptake is excreted in the urine as organic fluorine, fluoride and oxalic acid; the remainder is exhaled unaltered or as carbon dioxide. Higher peak blood fluoride levels may be obtained earlier in obese than in non-obese people, and in the elderly.

Special Populations and Conditions

Pediatrics: Pharmacologic data are not available for this population (see **INDICATIONS**, **Pediatrics**).

Pregnancy and Breast-feeding: See **6.1 Special Populations**.

Hepatic Insufficiency: See **WARNINGS AND PRECAUTIONS**, **Hepatic**.

Renal Insufficiency: See **WARNINGS AND PRECAUTIONS**, **Renal**.

Obesity: Obesity is associated with a two- to three-fold increase in the hepatic content and catalytic activity of CYP 2E1, which has been identified as the predominant enzyme in the human liver catalyzing microsomal defluorination of methoxyflurane. This may result in the elevated plasma fluoride. Caution should be exercised when administering to obese patients.

11 STORAGE, STABILITY AND DISPOSAL

Store between 5-30°C.

After loading the PENTHROX® Inhaler, replace cap onto PENTHROX bottle. After use, place used PENTHROX Inhaler and used bottle in plastic bag provided, seal and dispose through normal waste.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

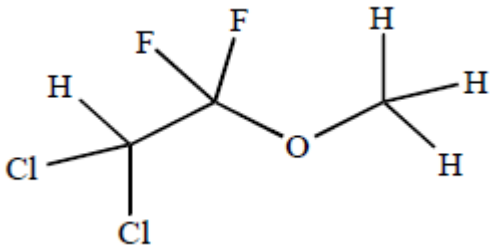
Proper name: Methoxyflurane

Chemical name: 2,2-dichloro-1,1-difluoro-1-methoxyethane

Molecular formula and molecular mass: $C_3H_4Cl_2F_2O$ / 164.97

Structural formula:

Figure 1: Structural Formula - Methoxyflurane



Physicochemical properties: Methoxyflurane has the following partition coefficients (at 37°C):

- a water/gas coefficient of 4.5,
- a blood/gas coefficient of 10.2 – 14.1 and
- an oil/gas coefficient of 825

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 4. Summary of Patient Demographics for the Clinical Trial in Treatment of Acute Pain in Conscious Patients with Trauma Pain

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Sex
MEOF-001	Randomised, double blind, prospective; placebo controlled	One to two PENTHROX Inhalers containing 3 mL methoxyflurane or 5 mL placebo Duration of study: 16 days	n=298 149 PENTHROX 149 placebo 203 adults 95 adolescents	Adult: PENTHROX 36.7 yrs (18 – 74 yrs) Placebo 35.7 yrs (18 – 84 yrs) Adolescents: PENTHROX 14.4 yrs (12 – 17 yrs) Placebo 13.5 yrs (12 – 17 yrs)	PENTHROX (M/F: 53/49) Placebo (M/F: 51/50) PENTHROX (M/F: 32/15) Placebo (M/F: 35/13)

Study MEOF-001
In a randomised, double-blind, multi-centre, placebo-controlled study in the treatment of acute pain in patients with minor trauma presenting to an emergency department, 300 patients were recruited (149 received PENTHROX™ and 149 received placebo). Patients with a pain score of ≥ 4 to ≤ 7 on the Numerical Rating Scale (NRS) were eligible for the study.

Table 5. Summary of Patient Demographics for the Clinical Trial in Treatment of Acute Pain in Conscious Adult Patients Undergoing Bone Marrow Biopsy

Study #	Trial Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (Range)	Sex
06/61	Randomised, double blind, prospective; placebo controlled	One PENTHROX Inhaler containing 3 mL methoxyflurane or 5 mL placebo. Duration of study: 30 days	n=97 49 PENTHROX 48 Placebo	PENTHROX 63 yrs (38 – 82 yrs) Placebo 58.5 yrs (25 – 82 yrs)	PENTHROX (M/F: 39/10) Placebo (M/F:35/13)

Study 06/61
In a randomised, double-blind, multi-centre, placebo-controlled study for procedural pain in patients undergoing bone marrow biopsy, a total of 100 patients were randomised (49 received PENTHROX and 48 received placebo).

13.2 Study Results

Treatment of Acute Pain in Conscious Patients with Trauma Pain (Study MEOF-001)

In Study MEOF-001, to demonstrate the effectiveness of PENTHROX in the treatment of acute pain, the Visual Analogue Score (VAS) of pain intensity, and its change from Baseline after 5, 10, 15 and 20 minutes were measured. The estimated mean change in VAS pain from Baseline to 5, 10, 15 and 20 minutes was significantly greater in the PENTHROX group compared to the placebo group. The greatest treatment effect was seen at 15 minutes, see Table 6, below.

Table 6. Study MEOF-001 – VAS Pain Intensity Score (ITT Population) – Adults

	PENTHROX (N=102)	Placebo (N=101)	Estimated Treatment Effect (95% Confidence Interval)	p-value
Adjusted[a] change from baseline Overall	-29.0	-11.6	-17.4 (-22.3, -12.5)	< 0.0001
5 minutes	-20.7	-8.0	-12.6 (-17.0, -8.3)	
10 minutes	-27.4	-11.1	-16.3 (-21.4, -11.1)	
15 minutes	-33.3	-12.3	-21.0 (-26.8, -15.3)	
20 minutes	-34.8	-15.2	-19.7 (-26.0, -13.3)	
Time by Treatment interaction				0.0004

N=number of patients
a. Adjusted for baseline pain score
Pain scores recorded following the start of the planned ED procedure have been excluded from the analysis.
Pain scores taken after initiation of rescue medication have been included in the analysis.

Table 7, below, documents the mean VAS pain scores from Study MEOF-001, adjusted for baseline pain score (NRS = 4 to NRS = 7) and age group, using repeated measures analysis of variance. The estimated treatment effect was greatest in the subgroups with a baseline NRS pain scores of 5 or 6: -18.6 (p=0.0001; 95% CI -27.8 to -9.4) and -18.3 (p<0.0001; 95% CI -26.3 to -10.3), respectively. The subgroup with a baseline NRS of 7 also had a highly significant estimated treatment effect (-13.2; p=0.0001; 95% CI -19.7 to -6.6). The overall estimated treatment effect for the subgroup with a baseline NRS of 4 did not reach significance (-10.4; p=0.1279; 95% CI -24.2 to 3.4).

Table 7. Analysis of VAS Pain Intensity Score (ITT Population) – Baseline NRS = 4, 5, 6 and 7 – Total Population (Adults and Adolescents)

		Pain Score (NRS)	PENTHROX	Placebo	Estimated Treatment Effect (95% Confidence Interval)	p-value
Adjusted [a] change from baseline	Overall	4	(N=11) -22.6	(N=10) -12.2	-10.4 (-24.2, 3.4)	0.1279
		5	(N=31) -29.6	(N=31) -11.0	-18.6 (-27.8, -9.4)	0.0001
		6	(N=45) -32.5	(N=37) -14.2	-18.3 (-26.3, -10.3)	<0.0001
		7	(N=62) -30.7	(N=71) -17.5	-13.2 (-19.7, -6.6)	0.0001

N=number of patients
a. Adjusted for baseline pain score and age group (adolescent/adult)
Pain scores recorded following the start of the planned ED procedure have been excluded from the analysis.
Pain scores taken after initiation of rescue medication have been included in the analysis.

The use of rescue medication within 20 minutes of the start of treatment, as requested by the patient, is summarised in Table 8, below. There was a significant difference (p=0.0002) between the PENTHROX and placebo group.

Table 8. Use of Rescue Medication (ITT Population) – Total Population (Adults and Adolescents)

		PENTHROX (N=149)	Placebo (N=149)
Rescue med. used [a]	Yes	2 (1.3%)	25 (16.8%)
	No	147 (98.7%)	124 (83.2%)

N=number of patients
a. Rescue medication requested by the patient within 20 minutes of start of treatment.

Treatment of Acute Pain in Conscious Patients Undergoing Procedure (Study 06/61)

Study 06/61 was a randomised, double-blind, single centre, placebo-controlled study to assess the safety and efficacy of PENTHROX for the treatment of incident pain in patients undergoing a bone marrow biopsy (BMB) procedure. In the PENTHROX-treated group, 80% were males, with a mean age of 61 years. The primary endpoint was worst pain during BMB, which was the highest of two pain scores [Numeric Rating Scale (NRS)] recorded, as rated by the patient at two time points: pain during aspiration and pain during core biopsy. Using the NRS, patients were asked to rate the worst pain intensity experienced during aspiration, during core biopsy and at the end of the BMB procedure (overall). The mean worst pain overall, see Table 9 below, was significantly higher in the placebo arm ($p = 0.011$), as was the mean worst pain score during aspiration ($p < 0.001$).

Table 9. Study 06/61 – Mean Pain Score During Procedure

	PENTHROX (N=49)	Placebo (N=48)	Overall (N=97)	p-value [a]
Worst pain during aspiration	3.3	5.0	4.1	<0.001
Worst pain during core biopsy	4.5	5.4	4.9	0.073
Worst pain overall	4.9	6.0	5.4	0.011

N=number of patients
a. Two-sample t-test (or Mann-Whitney test)

14 NON-CLINICAL TOXICOLOGY

Methoxyflurane is highly lipophilic and can diffuse into fatty tissue. Clearance of methoxyflurane by ventilation is relatively low with metabolism the major route of elimination. The metabolites of methoxyflurane are primarily excreted in expired air and in urine.There is no indication of species differences in the biotransformation of methoxyflurane.

Two metabolic pathways have been identified: O-demethylation and dechlorination. The dechlorination pathway leads to the formation of methoxydifluoroacetate, in addition to chloride, fluoride and oxalate. The O-demethylation pathway produces formaldehyde, fluoride and dichloroacetate, the latter being further metabolised to oxalate and other products. The dechlorination pathway is the principal pathway for methoxyflurane, while the O-demethylation pathway appears to be recruited as a second pathway if the methoxyflurane concentration is high.

14.1 Acute Toxicity

Acute toxicity induced by high anesthetic doses of methoxyflurane has been observed in mice and rats. Mortality is dependent on methoxyflurane concentrations and duration of exposure. In mice methoxyflurane inhalation at 1.8% for 4 h or 6.4% for 5 min resulted in death, in rats the LC50 was 0.5% for a 4 h exposure. Death appears to be due to respiratory arrest.

Renal Effects at Anesthetic Doses
In Fisher 344 male rats, anesthetic doses of methoxyflurane induced vasopressin-resistant diuresis and at high doses this was accompanied by increases in serum sodium and urea nitrogen concentrations (at ≥0.5% methoxyflurane for 3 h) and pathological findings of renal tubular necrosis (0.75% methoxyflurane for 6 h) and at 0.75% for 6 h, one rat was euthanized due to oliguric renal failure. For renal toxicity, the margin of safety is roughly 2 times the clinical dose. Importantly, the results are consistent with lack of effects on kidney morphology and function at plasma/serum fluoride concentration of ≤40 μM. The findings in the rat also provide findings consistent with induction of cytochrome P450 resulting in increased renal effects correlating with circulating fluoride concentrations and administration of methoxyflurane with known nephrotoxicants resulting in exacerbation of renal injury. The more recent data conducted in the rat suggest that fluoride alone may not be the penultimate nephrotoxicant, but rather toxicity is related to interactions of fluoride with the metabolite dichloroacetic acid or a yet to be identified metabolite. However, while the mechanism may not be elucidated for methoxyflurane, the results are consistent with dose related predictable renal effects correlating with circulating fluoride concentrations.

14.2 Long-Term Toxicity

No renal effects were reported in male and female Wistar rats, guinea pigs or rabbits exposed to a sub anaesthetic dose of 200 ppm (0.02%) methoxyflurane in air for 7 hours/day, 5 days per week and a total period of 7 weeks. Hepatic changes were observed, consisting of minimal focal fatty metamorphosis in rats, minimal to marked centrilobular fatty metamorphosis in guinea pigs, and minimal centrilobular fatty metamorphosis in rabbits. In the latter species, hepatic findings were occasionally accompanied by elevated serum ALT and AST activities.

Continuous (24 h/day) exposure of Fischer 344 rats to 0.005% methoxyflurane vapor for 14 weeks resulted in depressed growth and hepatic injury (foci of hepatocellular degeneration and necrosis, as well as evidence of liver cell regeneration and varying amounts of fatty change). Hepatic injury had not disappeared one month after cessation of exposure.

14.3 Genotoxicity

Methoxyflurane was not mutagenic in bacterial (Ames) assays conducted with and without metabolic activation. Published in vitro non-GLP studies indicated that methoxyflurane did not cause sister chromatid exchanges in Chinese hamster ovary cells but appeared to interfere with the spindle apparatus of human lymphoid and mouse fibroblast cell, as well as chick embryo cells in vivo, and caused chromosome aberrations in human peripheral blood lymphocytes. However, in vivo, methoxyflurane did not increase the incidence of micronucleated immature erythrocytes in the bone marrow of rats when administered intravenously at doses up to 50 mg/kg.

14.4 Reproduction and Teratology

Methoxyflurane did not affect the percentage of abnormal sperm cells in mice.

Methoxyflurane passes the placenta, but demonstrated no evidence of embryotoxic or teratogenic properties in mice or rats. Methoxyflurane caused delayed fetal development (reduced fetal body weight and decreased ossification). The NOAEL for embryo-fetal development was 0.006% – 4 hours/day in mice (GD6-GD15) and 0.01% - 8 hours/day in rats (throughout gestation). The NOAELs in mouse and rat are 1 to 2 times on a mg/kg basis and 0.1 to 0.3 times on a mg/m2 basis, the proposed maximal human dose.

14.5 Carcinogenicity

The carcinogenicity potential has not been comprehensively evaluated in animals. It is not deemed necessary given the dose and duration of PENTHROX (short term intermittent dose).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrPENTHROX®

Methoxyflurane volatile liquid for inhalation

Read this carefully before you start taking **PENTHROX** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PENTHROX**.

Serious Warnings and Precautions

- **Excessive doses of inhaled methoxyflurane can lead to serious damage to the kidneys. Always follow your healthcare professional's dosing instructions when using PENTHROX. This can help to prevent or limit any kidney problems.**
- **Very rare cases of liver damage have been reported when methoxyflurane was used to treat pain using an inhaler.**

What is PENTHROX used for?
PENTHROX is used for short-term relief of moderate to severe pain following trauma or during medical procedures.

PENTHROX is **NOT** for use:
- in chronic pain conditions or for relief of repetitive pain.
- during pregnancy or labour.
- in children less than 18 years old.

How does PENTHROX work?
PENTHROX contains methoxyflurane. It is used to reduce pain. The way methoxyflurane reduces pain is not exactly known.

What are the ingredients in PENTHROX?
Medicinal ingredients: methoxyflurane
Non-medicinal ingredients: butylated hydroxytoluene (BHT)

PENTHROX comes in the following dosage forms:
Volatile liquid, 3 mL of 99.9% methoxyflurane.

PENTHROX is supplied in 3 mL bottles. **PENTHROX** will be prepared by a healthcare professional, who will load a 3 mL bottle into the inhaler.

Do not use PENTHROX if you:
- are allergic (hypersensitive) to methoxyflurane, BHT or any other inhalational anesthetic.
- Require an anesthetic agent.
- Have a history or family history of malignant hyperthermia.
    - Symptoms include a very high fever, fast, irregular heartbeat, muscle spasms and

breathing problems after you have been given an anesthetic.
- Have had liver damage after previous use of methoxyflurane or any inhalational anesthetics.
- Have kidney disease.
- Have abnormal or unstable blood pressure.
- Have difficulty breathing.
- Have a head injury, are drunk, or under the influence of drugs.
- Are under 18 years of age.
- Are pregnant, intending to become pregnant or if you are breast-feeding.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PENTHROX. Talk about any health conditions or problems you may have, including if you:
- Have kidney or liver problems or are at risk for liver problems.
- Are elderly and have problems with your blood pressure or heart rate.
- Have a medical condition which may cause kidney problems, such as diabetes.
- Have taken PENTHROX before.

Other warnings you should know about:
- This medicine may affect your ability to drive or use machines safely. You may feel dizzy or drowsy after taking **PENTHROX**. Do not drive or use machines while taking **PENTHROX** or if you feel dizzy or drowsy after taking **PENTHROX**.

- Due to the way it works in the body, PENTHROX may cause:
  - euphoria (a state of intense happiness and self-confidence)
  - sedation (a state of calm or sleep)
  - mood changes
  - a change in your ability to concentrate and to be coordinated
  - temporary memory problems

  You will not be given **PENTHROX** if you have been or are drinking alcohol or under the influence of drugs as it could make the symptoms above much worse.

- This medicine contains BHT. BHT may cause skin reactions such as a red, itchy rash. It may also irritate the eyes and mucous membranes (inside the ears, nose, mouth, etc.).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with PENTHROX:
- Phenobarbital to treat epilepsy.
- Rifampicin, isoniazid or other antibiotics to treat infection.
- Medicines, or illegal drugs, that have a dampening effect on the nervous system such as:
  - alcohol
  - narcotics, pain killers, opioids
  - sedatives, sleeping pills, tranquilizers
  - general anesthetics
  - phenothiazines (to treat psychotic disorders)
  - muscle relaxants
  - sedating antihistamines (allergy pills that can make you sleepy).

- Taking **PENTHROX** with certain other drugs may harm your kidneys. These include:
  - antibiotics such as tetracycline, gentamicin, colistin, polymyxin B and amphotericin B.
  - contrast agents, used to help healthcare professionals visualize the different body parts using an x-ray or a type of scan.
  - non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen

How to take PENTHROX:

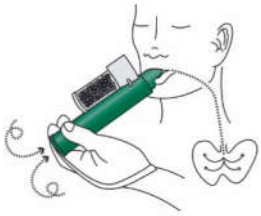
- You will take **PENTHROX** from an inhaler. The inhaler is for single patient use only.
- **PENTHROX** is a liquid that easily evaporates. It is important that you also exhale into the inhaler to help prevent **PENTHROX** from going into the air.
- You will take **PENTHROX** while being supervised by a healthcare professional who will help you with how to use **PENTHROX**.
- Always take this medicine exactly as your healthcare professional has told you.

Usual dose:

- Your healthcare professional will prepare the **PENTHROX** inhaler for you. They will load one bottle of 3 mL of **PENTHROX** into the inhaler. They may add one additional bottle if you need it for pain relief.
- The maximum recommended dosage is 6 mL of **PENTHROX** per day and 15 mL per week.
- You should not be given **PENTHROX** two days in a row or on a regular basis.
- You should not inhale more than the maximum dose.

Steps for using PENTHROX:

1. Your healthcare professional will prepare the **PENTHROX** Inhaler and place the wrist loop over your wrist.

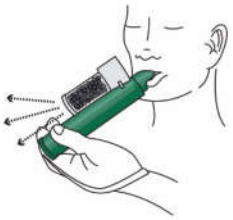


2. **Breathe in through the mouthpiece of the inhaler to obtain pain relief.** Your healthcare professional will show you how if you are unsure.

   Accustom yourself to the fruity smell of the medicine by inhaling gently for the first few breaths. Make sure you also breathe out through the inhaler.

   After the first few breaths, breathe normally through the inhaler.

   Relief will start after approximately 6-10 breaths.



3. **If you need stronger pain relief**, inhale and use your finger to cover the dilutor hole on the see through chamber with pieces of charcoal in it. Your healthcare professional will show you where the hole is.

4. You do not need to breathe in and out of the inhaler all of the time. Your healthcare professional will encourage you to take breaths from the inhaler as needed so that you can have enough pain control.

5. Continue using your inhaler until your healthcare professional tells you to stop, or when you have inhaled the recommended dose.

Overdose:
The healthcare professional giving you **PENTHROX** will be experienced in its use, so it is extremely unlikely that you will be given too much. You should not use more than 2 bottles in one day. If the maximum dose is exceeded, **PENTHROX** may cause irreversible damage to your kidneys. Tell your healthcare professional immediately if you think you may have taken too much **PENTHROX**. The symptoms could include feeling drowsy, having pale skin or having less control over your muscles (they feel very relaxed).

If you think you have taken too much **PENTHROX**, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using PENTHROX?
These are not all the possible side effects you may feel when taking **PENTHROX**. If you experience any side effects not listed here, contact your healthcare professional.

The reported side effects (≥ 3%) that occurred after using **PENTHROX** in the clinical trials were:
- Dizziness
- Drowsiness
- Euphoria
- Headache

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY RARE Serious allergic reaction: symptoms include difficulty breathing and/or swelling of the face.			X
Liver problems, such as loss of appetite, nausea, vomiting, jaundice (yellowing of the skin			X

and/or eyes), dark coloured urine, pale coloured stools, pain/ache or sensitivity to touch in your right stomach area (below your ribs).			
Kidney problems such as reduced of excessive urination or swelling of feet or lower legs.			X

If you have a troublesome symptom or side effect that is not listed here or becomes troublesome enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store between 5-30°C.

After use, a healthcare professional will place the used **PENTHROX** Inhaler in a plastic bag and dispose of it through normal waste.

Keep out of reach and sight of children.

If you want more information about PENTHROX:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the distributor's website www.paladinlabs.com, or by calling 1-888-867-7426.

This leaflet was prepared by Endo Ventures Ltd.

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