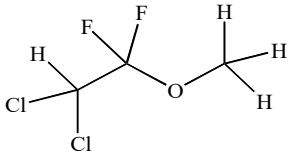
PACKAGE INSERT

PENTHROX®
(methoxyflurane) Inhalation

NAME OF THE MEDICINE

Methoxyflurane is known chemically as 2,2-dichloro-1,1-difluoro-1-methoxyethane. The molecular formula is $C_3H_4Cl_2F_2O$ and the molecular weight is 164.97.
Structural formula:



CAS registry: 76-38-0

DESCRIPTION

A clear, almost colourless mobile liquid, with a characteristic odour. Soluble 1 in 500 of water; miscible with alcohol, acetone, chloroform, ether and fixed oils. It is soluble in rubber. Protect from light. The flash point in oxygen is 32.8°C. The concentration to reach flash point is usually not achieved under normal circumstances.

Methoxyflurane belongs to the fluorinated hydrocarbon group of volatile anaesthetic agents. It is a volatile liquid intended for vaporisation and administration by inhalation using the PENTHROX Inhaler. At low concentrations the inhaled vapour is used to provide analgesia in stable, conscious patients. Methoxyflurane has a mildly pungent odour.

SOME OF THE PHYSICAL CONSTANTS ARE:

Molecular weight	164.97
Boiling Point at 760 mm Hg	104.97°C
Partition coefficients at 37°C	
Water/gas	4.5
Blood/gas (mean range)	10.20 to 14.06
Oil/gas	825
Vapour pressure 17.7°C	20 mm Hg
Flash points	
In air	62.8°C
In oxygen (closed system)	32.8°C
Lower limit of flammability of vapour concentration	
In air	7.0%
In oxygen	5.4%

Methoxyflurane is stable and does not decompose in contact with soda lime. An antioxidant, Butylated Hydroxy Toluene (0.01% w/w) is added to ensure stability on standing. As polyvinyl chloride plastics are extracted by methoxyflurane, contact should be avoided. Methoxyflurane does not extract polyethylene plastics, polypropylene plastics, fluorinated hydrocarbon plastics or nylon.

The vapour concentration of methoxyflurane is limited by its vapour pressure at room temperature to a maximum of about 3.5% at 23°C. In practice, this concentration is not reached due to the cooling effect of vaporisation. Methoxyflurane is not flammable except at vapour concentrations well above those recommended for its use. Recommended concentrations are non-flammable and non-explosive in air and oxygen at ordinary room temperature.

PHARMACOLOGY

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. In light planes of anaesthesia some decrease in blood pressure may occur. This may be accompanied by bradycardia. The hypotension noted is accompanied by reduced cardiac contractile force and reduced cardiac output.

Biotransformation of methoxyflurane occurs in man. As much as 50-70% of the absorbed dose is metabolised to free fluoride, oxalic acid, difluoromethoxyacetic acid, and dichloroacetic acid. Both the free fluoride and the oxalic acid can cause renal damage in large doses, however dose-related nephrotoxicity seen with clinical doses appears related to a combination of free fluoride and dichloroacetic acid. 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.

Approximately 20% of methoxyflurane uptake is recovered in the exhaled air, while urinary excretion of organic fluorine, fluoride and oxalic acid accounts for about 30% of the methoxyflurane uptake. Studies have shown that higher peak blood fluoride levels are obtained earlier in obese than in non-obese and in the elderly.

CLINICAL TRIALS

A randomised, double blind, multi-centre, placebo controlled study has been conducted to evaluate the efficacy and safety of PENTHROX (methoxyflurane) for the treatment of patients aged ≥12 years presenting to Emergency Departments with acute trauma pain. Patients had access to two 3 mL PENTHROX Inhalers or two 5 mL placebo PENTHROX Inhalers to be self-administered as required. Changes of the Visual Analogues Scale (VAS) pain intensity from baseline to 5, 10, 15 and 20 minutes after the commencement of study drug inhalation were analysed.

The type of injuries presented with trauma pain as a result of physical wound or injury included fractures, lacerations, dislocations, injury due to foreign bodies, burns and chemical burns, effusion, sprains, deep vein thrombosis, ulnar collateral ligament tear, muscle strain, ligament injury, soft tissue injury, meniscal injury, soft tissue inflammation, contusion and abrasions, amputations, muscular pain, whiplash association disorder, joint injury, hamstring tear, clinical fracture of radial head, hairline

fracture of greater clavicle, gout, knee injury and crush injury. The results show methoxyflurane administration (n=149) through the PENTHROX Inhaler elicited a higher reduction in VAS pain intensity scores compared to the placebo group (n=149) (-30.2 vs -15.2, respectively; overall treatment effect of -15.1; P<0.001) (Table 1). The median time to first pain relief for the methoxyflurane group was 4 minutes (95% CI: 2.0, 5.0) compared to 10 minutes in the placebo group (95%CI: 5.0, 12.0) (P<0.0001). The greatest treatment effect was seen at 15 minutes (estimated treatment effect of -18.5) (Table 1).

Table 1. Analysis of Visual Analogue Scale (VAS) Pain Intensity Score (ITT Population): Adjusted Change from Baseline

		PENTHROX (N=149)	Placebo (N=149)	Estimated Treatment Effect (95% Confidence Interval)	p-value
Adjusted* change from baseline (mm)	Overall	-30.2	-15.2	-15.1 (-19.2,-11.0)	<0.0001
	5 minutes	-23.1	-11.3	-11.8 (-15.6, -8.0)	
	10 minutes	-28.9	-14.8	-14.1 (-18.4, -9.8)	
	15 minutes	-34.0	-15.5	-18.5 (-23.4,-13.5)	
	20 minutes	-35.0	-19.0	-16 (-21.3,-10.7)	
	Time by treatment interaction				0.0019

N=Number of patients.
* LS Mean has been 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.

Two patients (1.3%) in the PENTHROX group requested the use of rescue medication within 20 minutes of the start of treatment compared with 25 patients (16.8%) in the placebo group (P=0.0002).

A total of 126 patients (84.6%) in the PENTHROX group experienced their first pain relief with 1-10 inhalations in comparison to 76 patients (51%) in the placebo group (Table 2).

Table 2. Inhalations to First Pain Relief (ITT Population)

		PENTHROX (N=149)	Placebo (N=149)
Number of inhalations	1 to 5	74 (49.7%)	31 (20.8%)
	6 to 10	52 (34.9%)	45 (30.2%)
	11 to 20	6 (4.0%)	11 (7.4%)
	More than 20	1 (0.7%)	6 (4.0%)
	No relief without rescue medication	16 (10.7%)	56 (37.6%)

N=Number of patients

Changes in vital signs (heart rate, pulse rate, respiratory rate, blood pressure, level of consciousness, and temperature) were comparable between the methoxyflurane and the placebo group. In the methoxyflurane group, none of the treatment-emergent adverse events relating to biochemistry and haematology investigations were considered related to the study drug.

In another randomised, double-blind, placebo-controlled study, PENTHROX or placebo (a maximum dose of 3 mL of each) was given to adult subjects ≥18 years requiring analgesia associated with a planned bone marrow biopsy (BMB) procedure. Pain intensity was measured using the 11-point numerical rating scale (NRS) rated by subjects during aspiration, during core biopsy and at the end of the BMB. Patients in the methoxyflurane group (n=49) had a lower worst pain score compared to the placebo group (n=48), with an average difference in reduction in pain of 1.64 ($p<0.001$). Total fluoride was significantly greater in the methoxyflurane group compared with the placebo group ($p<0.001$), with maximum fluoride level not exceeding 10 µmol/L (Table 3). No other statistically significant difference was observed for all other vital signs (heart rate, respiratory rate, blood pressure, and temperature), biochemistry and haematology testing.

Table 3: Fluoride levels before and after bone marrow biopsy (BMB)

	Total fluoride levels, µmol/L Mean ± SD (range)	
	Methoxyflurane (n=49)	**Placebo (n=48)**
Before BMB	2.6 ± 1.0 (1.3 – 6.8)	2.5± 0.8 (1.2 – 4.3)
After BMB	4.7 ± 2.2 (1.7 – 10.0)	2.6 ± 1.0 (1.3 – 6.9)
Mean change	2.1 ± 2.3* (-3.0 – 7.0)	0.1 ± 0.6 (-0.9 – 2.7)

*P<0.001, compared with Placebo

Results of the studies and post marketing report show that PENTHROX is well tolerated in patients with pain associated with trauma and surgical procedures.

INDICATIONS

1. For emergency relief of moderate pain by self administration in conscious haemodynamically stable patients with trauma and associated pain, under supervision of personnel trained in its use (see Dosage and Administration)

2. For the relief of moderate pain in monitored conscious patients who require analgesia for surgical procedures (See Dosage and Administration)

Note: the total maximum dose must not be exceeded.

CONTRAINDICATIONS

- Use as an anaesthetic agent
- Clinically significant renal impairment
- Hypersensitivity to fluorinated anaesthetics or any ingredients in PENTHROX
- Clinically evident cardiovascular instability
- Clinically evident respiratory depression
- Altered level of consciousness due to any cause including head injury, drugs or alcohol
- Malignant hyperthermia: patients with known or genetically susceptible to malignant hyperthermia

PRECAUTIONS

(i) Renal disease: methoxyflurane should be used with caution in patients with renal disease. Renal toxicity, which is related to total dose (time and concentration) and frequent exposure, is thought to be associated with inorganic fluoride ions, a metabolic breakdown product, released on the distal tubule that may cause polyuric or oliguric renal failure, oxaluria being the prominent feature. Toxicity in the past when used as an anaesthetic agent has been determined to be associated with serum levels greater than 40 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 methoxyflurane should be administered, especially in aged or obese patients.

Daily use of methoxyflurane is not recommended because of nephrotoxic potential. Nephrotoxicity is greater with methoxyflurane than with other halogenated anaesthetics because of the slower metabolism over several days resulting in prolonged production of fluoride ions and metabolism into other potentially nephrotoxic substances.

Methoxyflurane must not be used as an anaesthetic agent.

(ii) *Liver disease*: it is advisable not to administer methoxyflurane to patients who have shown signs of liver damage.

There have been occasional reports of hepatic dysfunction, jaundice, and fatal hepatic necrosis associated with methoxyflurane use.

(iii) Diabetic patients: may have an increased likelihood of developing nephropathy if they have impaired renal function or polyuria, are obese, or are not optimally controlled.

(iv) In patients under treatment with *enzyme inducing drugs* (e.g. barbiturates) the metabolism of methoxyflurane may be enhanced resulting in increased risk of nephrotoxicity.

(v) Due to possible reduction in blood pressure, methoxyflurane should be used with caution in patients with clinically significant haemodynamic or cardiovascular instability.

(vi) Intravenous adrenaline or nor-adrenaline should be employed cautiously during methoxyflurane administration.

(vii) *Health workers who are regularly exposed to patients using PENTHROX Inhalers should be aware of any relevant occupational health and safety guidelines for the use of inhalational agents.* The use of methods to reduce occupational exposure to methoxyflurane, including the attachment of the PENTHROX Activated Carbon (AC) Chamber, should be considered. Multiple use creates additional risk. Elevation of liver enzymes, blood urea nitrogen and serum uric acid have been reported in exposed maternity ward staff.

Effects on fertility

Study on sperm morphology showed that exposure of mice to 0.01% or 0.1% methoxyflurane for 4h/day on 5 consecutive days did not affect the percentage of abnormal sperm cells.

Use in pregnancy (Category C)

All general anaesthetics cross the placenta and carry the potential to produce central nervous system and respiratory depression in the new born infant. In routine practice, the recommended dose (See Dosage and Administration) appears to have little effect on the foetus. However in a compromised foetus, careful consideration should be given to this potential depression, and to the selection of anaesthetic drugs, doses and techniques. It is advisable not to administer methoxyflurane to patients with *toxaemia of pregnancy* due to the possibility of existing renal impairment.

Neonates delivered of mothers who used methoxyflurane analgesia for childbirth had a briefly raised serum uric acid, not requiring further intervention.

Published animal studies of some anaesthetic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. These studies have demonstrated that anaesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. The clinical significance of these non-clinical findings is yet to be determined.

As with all medicines care should be exercised when administered during pregnancy especially the first trimester.

Use in lactation

Caution should be exercised when methoxyflurane is administered to a nursing mother.

Paediatric use

Safety and efficacy have not been established in children below 12 years of age.

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic/sedative agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/sedation drug administration or other factors such as the surgery or underlying illness.

Use in the elderly

Caution should be exercised in the elderly due to possible reduction in blood pressure.

Genotoxicity

There is no evidence of genotoxicity when methoxyflurane was tested in the Ames test, micronucleus test and sister chromatid exchange test. In vitro studies in several types of mammalian cells (Chinese hamster lung fibroblasts, human lymphoid cell line JC, cactus mouse (*Peromyscus eremicus*) fibroblast cell lines) showed no evidence of chromosome breakage or rearrangements. Chronic exposure to methoxyflurane (0.4% one hour per day for up to 30 weeks) resulted in presence of aneuploidy nuclei in liver, kidney and lungs of mice which was reversible when treatment stopped.

Carcinogenicity

Two studies in mice evaluating the impact of methoxyflurane on tumour incidence did not suggest carcinogenic properties. In one study, 10-week old mice were exposed *in utero* to methoxyflurane in oxygen or in air at 0.125% for 2 h/day with 2- to 3-day intervals. In another study, 4-week old mice were exposed to 0.4% (1h/day) methoxyflurane for up to 30 weeks.

The chemical structure of methoxyflurane does not suggest tumorigenic activity.

Effects on laboratory tests

Methoxyflurane is not known to interfere with any laboratory tests.

Information for patients

The decision as to when patients may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualised. Patients should be warned to take extra care as a pedestrian and not to drive a vehicle or operate a machine until the patient has completely recovered from the effects of the drug, such as drowsiness. The treating doctor should decide when activities such as driving a vehicle or operating a machine may be resumed.

INTERACTIONS WITH OTHER MEDICINES

The concurrent use of tetracycline and methoxyflurane for *anaesthesia* has been reported to result in fatal renal toxicity. The metabolism of methoxyflurane is mediated by the CYP 450 enzymes particularly CYP 2E1, CYP 2B6 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 and CYP 2B6)) which increase the rate of methoxyflurane metabolism might increase its potential toxicity and they should be avoided concomitantly with methoxyflurane.

Concomitant use of PENTHROX with CNS depressants e.g opioids may produce additive depressant effects. If opioids are given concomitantly with PENTHROX, the patient should be observed closely, as is normal clinical practice with opioids.

The possibility exists that methoxyflurane may enhance the adverse renal effects of other drugs including certain antibiotics of known nephrotoxic potential such as gentamicin, kanamycin, colistin, polymyxin B, cephaloridine and amphotericin B.

Dosage for the subsequent administration of narcotics may be reduced.

Interactions may occur with β-blockers, with an increased risk of hypotension.

ADVERSE EFFECTS

The adverse drug reactions related to PENTHROX observed in clinical studies and treatment-emergent events from postmarketing sources are listed in the table below, classified according to frequency (very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and unknown (cannot be estimated from the available data).

MedDRA System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Unknown
Metabolism and nutrition disorders			Increased appetite	
Nervous system disorders	Dizziness	Amnesia Dysarthria Dysgeusia Headache Peripheral sensory neuropathy Somnolence	Paraesthesia	Altered state of consciousness Nystagmus
Psychiatric disorders		Euphoric mood Anxiety Depression	Inappropriate affect	Affect lability Agitation Confusional state Dissociation Restlessness
Vascular disorders		Hypotension	Flushing	Blood pressurefluctuation
Eye disorders			Diplopia	Vision blurred
Respiratory, thoracic and mediastinal disorders		Cough		Choking Hypoxia
Gastrointestinal disorders		Dry mouth Nausea	Oral discomfort	Vomiting
Hepatobiliary disorders				Hepatic failure Hepatitis Jaundice Liver injury
Renal and urinary disorders				Renal failure
General disorders		Feeling drunk	Fatigue Feeling abnormal Chills Feeling of relaxation	
Skin and subcutaneous tissue disorders		Hyperhidrosis		
Investigations				Blood uric acid increased Blood urea increased Blood creatinine increased Hepatic enzyme increased

Hepatic toxicity in association with methoxyflurane is rare but has been observed with analgesic use.

DOSAGE AND ADMINISTRATION

FOR USE ONLY AS AN ANALGESIC AGENT (SEE CONTRAINDICATION)

For Adults and Adolescents aged 12 Years and Above

Dosage: One bottle of PENTHROX (3 ml) to be vaporised in a PENTHROX Inhaler. On finishing the initial bottle (3 ml), another bottle (3 ml) may be used. Up to 6 ml may be administered per day. The refilling must be conducted in a well-ventilated area to reduce environmental exposure to methoxyflurane vapour.

To maximise safety, the lowest effective dosage of PENTHROX (methoxyflurane) to provide analgesia should be used, particularly for adolescents and the elderly. The total weekly dose should not exceed 15 ml. Administration of consecutive days is not recommended.

The cumulative dose received by patients receiving intermittent doses of PENTHROX (methoxyflurane) for painful procedures must be carefully monitored to ensure that the recommended dose of methoxyflurane is not exceeded.

Methoxyflurane may cause renal failure if the recommended dose is exceeded. Methoxyflurane-associated renal failure is generally irreversible.

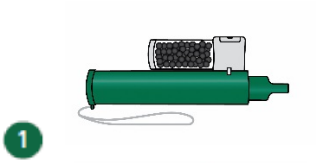
Administration:

PENTHROX (methoxyflurane) is self-administered under observation (and assisted if necessary) by a person trained in its administration using the hand held PENTHROX Inhaler.

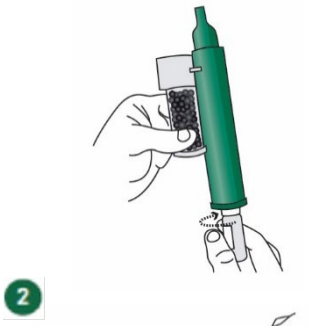
Instructions on the preparation of the PENTHROX Inhaler and correct administration are provided in Figure 1.

Figure 1: How to use the PENTHROX Inhaler

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

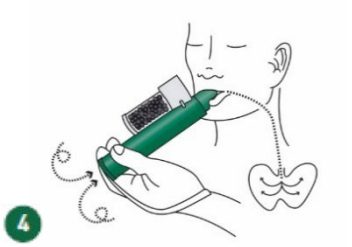


2 Remove the cap of the bottle by hand. Alternatively, use the base of the PENTHROX Inhaler to loosen the cap with a ½ turn. Separate the Inhaler from the bottle and remove the cap by hand.



3 Tilt the PENTHROX Inhaler to a 45° angle and pour the total contents of one PENTHROX bottle into the base of the Inhaler whilst rotating.

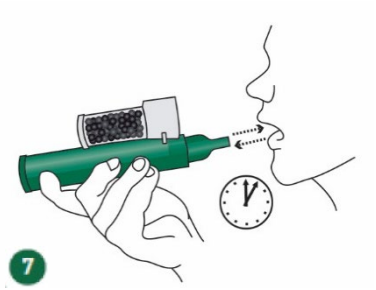
4 Place wrist loop over patient's wrist. Patient inhales through the mouthpiece of the PENTHROX Inhaler to obtain analgesia. First few breaths should be gentle and then breathe normally through Inhaler.



5 Patient exhales into the PENTHROX Inhaler. The exhaled vapour passes through the AC Chamber to absorb any exhaled methoxyflurane.

6 If stronger analgesia is required, patient can cover dilutor hole on the Inhaler or 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 of responsibly.

Pain relief will commence after approximately 6-10 inhalations. PENTHROX can be inhaled continuously or intermittently. For intermittent administration, a top-up of six inhalations may be taken before each of the more painful parts of the procedure.

OVERDOSAGE

Adverse effects will include those for anaesthetic doses, see Adverse Effects.

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

In the event of excessive urinary output following overdosage, fluid and electrolyte losses should be promptly replaced.

PRESENTATION

PENTHROX (methoxyflurane) is supplied in the following presentations:

a) 3 mL sealed bottle with a tear off tamper seal (pack of 10),

b) Combination pack with one 3 mL sealed bottle and one PENTHROX Inhaler (pack of 1 or 10) with or without optional Activated Carbon (AC) Chamber.

Not all presentations are available in Singapore.

STORAGE CONDITIONS

Store below 30°C.

PRODUCT REGISTRANT

Link Healthcare Singapore Pte Ltd
10 Changi South Street 2
#02-01
Singapore 4865964
Under licence from: Medical Developments International Limited

FORENSIC CLASSIFICATION OF THE MEDICINE

Prescription Only Medicine

DATE OF HSA APPROVAL

21 September 2015

DATE OF MOST RECENT AMENDMENT

30 July 2021