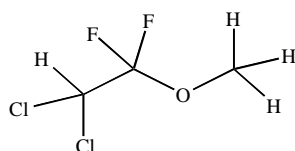


## **PRODUCT INFORMATION**

### **NAME OF THE MEDICINE**

Methoxyflurane is known chemically as 2, 2 – dichloro-1, 1-difluoroethyl methyl ether. The molecular formula is C<sub>3</sub>H<sub>4</sub>Cl<sub>2</sub>F<sub>2</sub>O 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. Store in an airtight containers at a temperature not exceeding 40°C. 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<sup>®</sup> 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

## **PENTHROX<sup>®</sup> (methoxyflurane) Inhalation**

---

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.

### **INDICATIONS**

1. For emergency relief of 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 pain in monitored conscious patients who require analgesia for surgical procedures such as the change of dressings (See Dosage and Administration)

**Note:** the total maximum dose must not be exceeded.

### **CONTRAINDICATIONS**

- Use as an anaesthetic agent
- Renal impairment, including reduced glomerular filtration rate (GFR), urine output and reduced renal blood flow.
- Renal failure
- Hypersensitivity to fluorinated anaesthetics
- Cardiovascular instability
- Respiratory depression
- Head injury or loss of consciousness

- A history of possible adverse reactions in either patient or relatives
- Malignant hyperthermia: patients with known or genetically susceptible to malignant hyperthermia

### PRECAUTIONS

Methoxyflurane impairs renal function in a dose-related manner due to the effect of the released fluoride on the distal tubule and may cause polyuric or oliguric renal failure, oxaluria being the prominent feature. 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 to other potentially nephrotoxic substances.

There have also been occasional reports of hepatic dysfunction, jaundice, and fatal hepatic necrosis.

- (i) **Because of the potential nephrotoxic effects methoxyflurane must not be used as an anaesthetic agent.** The risk is related to the total dose (time and concentration) and frequent exposure. Methoxyflurane impairs renal function in a dose-related manner.

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. Therefore the lowest effective dose of methoxyflurane should be administered, especially in aged or obese patients.

- (ii) *Liver disease*: it is advisable not to administer methoxyflurane to patients who have shown signs of liver damage, especially after previous methoxyflurane or halothane anaesthesia.
- (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) Daily use of methoxyflurane is not recommended because of nephrotoxic potential.
- (v) In patients under treatment with *enzyme inducing drugs* (e.g. barbiturates) the metabolism of methoxyflurane may be enhanced resulting in increased risk of nephrotoxicity.
- (vi) Intravenous adrenaline or nor-adrenaline should be employed cautiously during methoxyflurane administration.
- (vii) *Caution in hot climates*: Do not expose to temperatures above 40°C, especially when used in conjunction with oxygen.

(viii) *Use in the elderly:* Caution should be exercised in the elderly due to possible reduction in blood pressure or heart rate.

(ix) *Health workers who are regularly exposed to patients using PENTHROX<sup>®</sup> 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 Pentrox 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.

### 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.

### USE IN PREGNANCY

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 this dose does not appear to be a problem; however in a compromised foetus, careful consideration should be given to this potential depression, and to the selection of anaesthetic drugs, doses and techniques.

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

**Toxaemia of pregnancy:** It is advisable not to administer methoxyflurane due to the possibility of existing renal impairment.

### USE IN LACTATION

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

### USE IN CHILDREN

Limited data is available regarding the administration of Methoxyflurane using the PENTHROX<sup>®</sup> Inhaler. The minimum effective dose to produce analgesia should be administered to children.

### INTERACTIONS WITH OTHER DRUGS

The concurrent use of tetracycline and methoxyflurane for anaesthesia has been reported to result in fatal renal toxicity. The possibility exists that methoxyflurane may enhance the adverse renal effects of other drugs including certain antibiotics of

## **PENTHROX<sup>®</sup> (methoxyflurane) Inhalation**

---

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  $\beta$ -blockers, with an increased risk of hypotension.

### **ADVERSE REACTIONS**

**Note:** Use in anaesthesia is contraindicated. No systemic data have been collected on the frequency or nature of adverse drug reactions of methoxyflurane when used as an analgesic. There are no data on the dose-dependency of the adverse drug reactions, therefore all documented adverse reactions are possible, however no statement regarding frequency can be made.

When used as an anaesthetic:

- i) Common: retrograde amnesia, nausea, vomiting, coughing, drowsiness, sleeping, dizziness, dislike of odour, fever, polyuria, headache.
- ii) Rare: non-specific hepatitis, malignant hypothermia
- iii) Other reported events: cardiac arrest, respiratory depression, laryngospasm, bronchospasm, hypotension, bradycardia, renal failure, increased serum urea, increased serum creatinine, increased urinary oxalate excretion, increased serum inorganic fluoride, pallor, muscle relaxation

Reported in the literature in association with analgesia:

- Nervous system disorders: euphoria, drowsiness, sleepy, agitation, restlessness, headache, dizziness, dissociation, amnesia
- Respiratory system: cough, choking
- Cardiac hypotension
- Gastrointestinal: nausea, vomiting
- Hepatic: hepatitis, increased liver enzymes
- Renal: increased serum uric acid, urea nitrogen and creatinine
- Eyes: blurred vision, diplopia, nystagmus

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 “CONTRAINDICATIONS”**

**Dosage:** Up to 6 mL (2 x 3mL bottles) of PENTHROX<sup>®</sup> (methoxyflurane) per day, vaporised in a PENTHROX<sup>®</sup> Inhaler. If refilling the Inhaler with a second bottle of

## PENTHROX<sup>®</sup> (methoxyflurane) Inhalation

---

Methoxyflurane, this should occur only once and must be conducted in a well-ventilated area to reduce environmental exposure to Methoxyflurane vapour.

When used with the PENTHROX<sup>®</sup> Inhaler, the inspired concentrations of Methoxyflurane delivered range between 0.2% to 0.4% with the dilution hole open and 0.5% to 0.7% with the dilution hold closed (refer to **Figure 1**). To maximise safety, the lowest effective dosage of PENTHROX<sup>®</sup> (methoxyflurane) to provide analgesia should be used, particularly for children 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<sup>®</sup> (methoxyflurane) for painful procedures (such as wound dressings) 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.

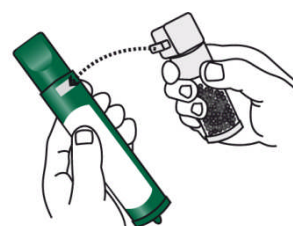
### **Administration:**

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

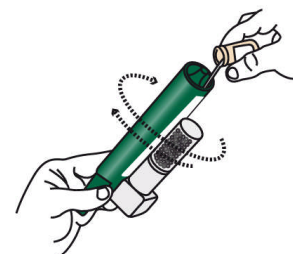
Instructions on the preparation of the PENTHROX<sup>®</sup> Inhaler and correct administration are provided in Figure 1.

### **Figure 1 How to use the PENTHROX<sup>®</sup> Inhaler**

- 1** Ensure the Activated Carbon (AC) Chamber (where applicable) is inserted into the dilution hole on the top of the PENTHROX<sup>®</sup> Inhaler



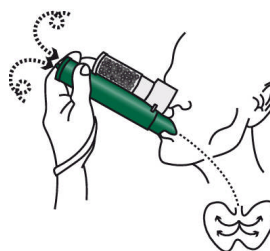
- 2** Tilt the PENTHROX<sup>®</sup> Inhaler and pour the contents of one 3mL bottle into the base whilst rotating



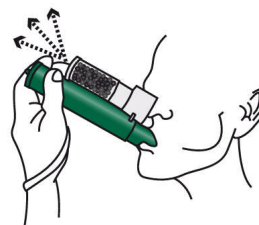
## PENTHROX<sup>®</sup> (methoxyflurane) Inhalation

---

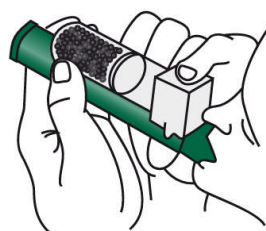
- 3 Place wrist loop over patient's wrist. Patient inhales through the mouthpiece of Inhaler to obtain analgesia. First few breaths should be gentle and then breathe normally through Inhaler.



- 4 Patient exhales into Inhaler. The exhaled vapour passes through the AC Chamber to absorb any exhaled Methoxyflurane



- 5 If stronger analgesia is required, patient can cover dilution hole with finger during inhalation



- Patient should be instructed to inhale intermittently to achieve adequate analgesia.
- 6 Continuous administration will reduce time of analgesia. Patients should be administered minimum dose.



### OVERDOSAGE

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

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

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

### PRESENTATION & STORAGE CONDITIONS

PENTHROX<sup>®</sup> (methoxyflurane) is supplied in the following presentations:

- 3 mL sealed bottle with a tear off tamper seal (pack of 10),
- Combination pack with one 3 mL sealed bottle and one PENTHROX<sup>®</sup> Inhaler (pack of 1 or 10) with or without optional Activated Carbon (AC) chamber and,
- Combination pack with two 3 mL sealed bottles and one PENTHROX<sup>®</sup> Inhaler (pack of 10).

AUST R 43144

## **PENTHROX<sup>®</sup> (methoxyflurane) Inhalation**

---

### **STORAGE**

Store below 30°C

### **POISON SCHEDULE**

Schedule 4

### **NAME AND ADDRESS OF THE AUSTRALIAN SPONSOR**

Medical Developments International Pty. Ltd.

A.C.N. 106 340 667

Factory 7, 56 Smith Road

Springvale, Victoria 3171 Australia

Tel: 61-3-9547 1888 Fax: 61-3-9547 0262

### **NAME AND ADDRESS OF THE NEW ZEALAND SPONSOR**

New Zealand Medical and Scientific Ltd.

P O Box 24-138

Royal Oak

2A Fisher Crescent

Mt Wellington

Auckland

New Zealand

Tel: 64-9 259 4062 Fax 64-9-259 4067

TGA APPROVAL DATE: 6 May 2009