**NAME OF THE MEDICINE**

Methoxyflurane is known chemically as 2,2-dichloro-1,1-difluoro-1-methoxyethane.

The molecular formula is \( \text{C}_3\text{H}_4\text{Cl}_2\text{F}_2\text{O} \), and the molecular weight is 164.97.

**Structural formula:**

\[
\text{CH}_3\text{CH}_2\text{Cl} - \text{CF}_2\text{C} = \text{O}
\]

**CAS registry:** 76-38-0

**DESCRIPTION**

A clear, almost colourless, mobile liquid, with a characteristic odour. Soluble 1 in 600 of water; miscible with alcohol, acetone, chloroform, ether and fixed oils. It is soluble in rubber. The flash point in oxygen is 32°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 vapour anaesthesia and administration by inhalation using the PENTHROX® Inhaler. At low concentrations it has the inhalant vapour effect to provide anaesthesia in conscious, stable 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): 0.26 to 1.46
  - Oxygas: 125
- Vapour pressure 17.7°C: 20 mm Hg
- Flash points:
  - In air: 62.8°C
  - In oxygen (closed system): 33.8°C
- Lower and upper flammability of vapour concentration:
  - In air: 1.4% to 4.6%
  - In oxygen: 0.6% to 4.6%

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

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 evaporation. 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.

Bioconversion 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, 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 cephalothin, kanamycin, colistin, polymyxin B, cephaloridine and amphotericin B. Dosage of the subsequent administration of nephrotoxic drugs may be reduced.

**INDICATIONS**

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 cephalothin, kanamycin, colistin, polymyxin B, cephaloridine and amphotericin B. Dosage of the subsequent administration of nephrotoxic drugs may be reduced.

**CONTRAINDICATIONS**

- Use as an anaesthetic agent
- Cardiovascular instability
- Respiratory depression
- Head injury or loss of consciousness

**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, oedema being the prominent feature. Nephrotoxicity is greater in patients methoxyflurane has 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. Therefore the lowest effective dose of methoxyflurane should be administered, especially in aged or obese patients.

**ADVERSE REACTIONS**

- In patients under treatment with enzyme inducing drugs (e.g., barbiturates) the metabolism of methoxyflurane may be enhanced resulting in increased risk of nephrotoxicity.
- Intravenous adrenaline or noradrenaline should be employed cautiously during methoxyflurane administration.
- Use in the elderly: Caution should be exercised in the elderly due to possible reduction in blood pressure or heart rate.
- 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 masks to reduce occupational exposure to methoxyflurane, including the attachment of the PENTHROX® Activated Carbon (AC) Cartridge, 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 after successful anaesthesia should be made to the patient and the responsible carer 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 be informed of any activities such as driving a vehicle or operating a machine may be resumed.

**Use in Pregnancy (Category C)**

All general anaesthetists' 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 fetus, careful consideration should be given to this potential depression, and to the selection of anaesthetic drugs, doses and techniques.

**Use in Elderly Patients**

Older patients may have an increased likelihood of developing hypotension, and to the selection of anaesthetic drugs, doses and techniques.

**Use in Paediatric Patients**

Limited data is available regarding the administration of Methoxyflurane Inhaler. The knowledge of effective dose to produce analgesia should be administered to children.

**INTERACTIONS WITH OTHER MEDICINES**

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 cephalothin, kanamycin, colistin, polymyxin B, cephaloridine and amphotericin B. Dosage of the subsequent administration of nephrotoxic drugs may be reduced.

**ADVERSE EVENTS**

There are no data on the dose-dependency of most of the adverse drug reactions.

Use of PENTHROX® in patients with trauma and associated pain

The following Table provides treatment-emergent adverse events experienced by N of the safety population of a placebo-controlled study in patients with trauma and associated pain, of which 149 had PENTHROX® Placebo In inhaler (N=149) Placebo In Inhaler (N=149)

<table>
<thead>
<tr>
<th>Event</th>
<th>N (%)</th>
<th>Event</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Adverse Events</td>
<td>188</td>
<td>N (%)</td>
<td>111</td>
</tr>
<tr>
<td>Malignant Disorders And</td>
<td>13</td>
<td>8.9%</td>
<td>7</td>
</tr>
<tr>
<td>Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant Disorders And</td>
<td>10</td>
<td>6.9%</td>
<td>6</td>
</tr>
<tr>
<td>Placebo In Inhaler (N=149)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo In Inhaler (N=149)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Any Adverse Event**

<table>
<thead>
<tr>
<th>Any Adverse Event</th>
<th>13</th>
<th>8.9%</th>
<th>7</th>
<th>5.4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Event</td>
<td>111</td>
<td>80 (65.9%)</td>
<td>7</td>
<td>5.4%</td>
</tr>
<tr>
<td>Malignant Disorders And Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant Disorders And Administration Site Conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo In Inhaler (N=149)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo In Inhaler (N=149)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Other reported events: cardiac arrest, respiratory depression, laryngospasm, observed with analgesic use.

Hepatic toxicity in association with methoxyflurane is rare but has been reported in patients in a minor surgical procedure, of which 49 had Penthrox for the treatment which occurred at a rate lower than in the Table above.

In listings below, are Adverse Reactions (adverse effects that are related to the treatment) which occurred at a rate lower than in the Table above. They are listed by system organ class and frequency (common ≥ 1/1,000; and rare ≥ 1/10,000 to <1/100).

Adverse events 48 Hours after Procedure

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=48)</th>
<th>Penthrox (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Confusion</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Hypersalivation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Skin rash</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal / soft tissue</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Adverse events 30-45 mins after Procedure

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (N=48)</th>
<th>Penthrox (N=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Confusion</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Skin rash</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal / soft tissue</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Post-marketing

The following additional adverse effects have also been reported in the literature in association with analgesia:

- Nervous system disorders: drowsiness, sleepiness, agitation, restlessness, dissociation
- Respiratory system: choking
- Hepatic: hepatitis
- Renal: increased serum uric acid, urea nitrogen and creatinine
- Eyes: blurred vision, nystagmus
- Musculoskeletal / soft tissue: muscle relaxation

DOSAGE AND ADMINISTRATION

For use only as an analgesic agent, see "CONTRAINDICATIONS".

Dosage: One bottle of PENTHROX® (1.5 mL or 3 mL) to be vaporised in the PENTHROX® Inhaler. On finishing the initial bottle, another bottle may be used. Up to 6 mL may be administered per day. The nebulising 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 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® (methoxyflurane) for painful procedures (such as wound dressing) 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 assited self-administration 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. 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.

2. Tilting the PENTHROX® Inhaler to a 45° angle and pouring the contents of one bottle into the base whilst rotating.

3. Hold the methoxyflurane bottle upright, use the base of the PENTHROX® Inhaler to loosen the cap with a 1/4 turn. Separate the Inhaler from the bottle and remove the cap by hand.

4. Patient exhales into Inhaler. The exhaled vapour passes through the AC Chamber to adsorb any exhaled methoxyflurane.

5. If stronger analgesia is required, patient can cover dilutor hole with finger during inhalation.

6. Patient should be observed for signs of drowsiness, palor and muscle relaxation following methoxyflurane administration.

Presentation and Storage Conditions

PENTHROX® (methoxyflurane) is supplied in the following presentations:

- 3 mL sealed bottle with a tear off tamper seal (pack of 10),
- Combination pack with two 3 mL sealed bottles and one PENTHROX® Inhaler (pack of 1 or 5 with or without optional Activated Carbon (AC) Chamber).
- Combination pack with two 3 mL sealed bottles and one PENTHROX® Inhaler (pack of 1 or 5 without AC Chamber).

AUST R 43144 Store below 25°C

POISON SCHEDULE OF THE MEDICINE

Schedule 4

NAME AND ADDRESS OF THE AUSTRALIAN SPONSOR

Medical Developments International Ltd.
ABN 14 106 340 667
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Email: admin@mdimeds.com

NAME AND ADDRESS OF THE NEW ZEALAND SPONSOR

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PO Box 45027
Auckland 0651
New Zealand
Phone: 64-9-835 0560
Fax: 64-9-835 0885

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

18 January 1993

DATE OF MOST RECENT AMENDMENT:

2 August 2016

PENTHROX® is a registered trademark of Medical Developments International Limited.

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