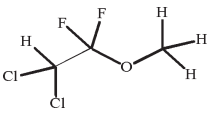
PENTHROX® (METHOXYFLURANE) INHALATION PRODUCT INFORMATION

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. 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.

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 or any ingredients in PENTHROX®
- 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) *Use in the elderly:* Caution should be exercised in the elderly due to possible reduction in blood pressure or heart rate.

(viii) *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.

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 (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 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.

Paediatric Use

Limited data is available regarding the administration of Methoxyflurane using the PENTHROX® Inhaler. The minimum 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 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 ß-blockers, with an increased risk of hypotension.

ADVERSE REACTIONS

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 ≥1% of the safety population of a placebo-controlled study in patients with trauma and associated pain, of which 149 had Penthrox®.

Treatment-Emergent Adverse Events (TEAEs), by System Organ Class and Preferred Term Experienced by ≥1% of the Safety Population

	Methoxyflurane in Inhaler (N=149)		Placebo In Inhaler (N=149)	
	n	N (%)	n	N (%)
Any Adverse Event	**188**	**88 (59.1%)**	**111**	**61 (40.9%)**
Gastrointestinal Disorders	**13**	**12 (8.1%)**	**13**	**10 (6.7%)**
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	**10**	**9 (6.0%)**	**6**	**6 (4.0%)**
Influenza Like Illness	0	0	3	3 (2.0%)
Feeling drunk	2	2 (1.3%)	0	0
Infections And Infestations	**8**	**7 (4.7%)**	**8**	**7 (4.7%)**
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	**9**	**6 (4.0%)**	**2**	**2 (1.3%)**
Fall	2	2 (1.3%)	0	0
Joint sprain	2	2 (1.3%)	0	0

Investigations	**8**	**5 (3.4%)**	**6**	**4 (2.7%)**
Alanine Aminotransferase Increased	1	1 (0.7%)	2	2 (1.3%)
Aspartate Aminotransferase Increased	1	1 (0.7%)	2	2 (1.3%)
Blood lactate dehydrogenase increased	2	2 (1.3%)	0	0
Musculoskeletal And Connective Tissue Disorders	**4**	**3 (2.0%)**	**6**	**6 (4.0%)**
Back Pain	3	3 (2.0%)	2	2 (1.3%)
Nervous System Disorders	**118**	**74 (49.7%)**	**55**	**40 (26.8%)**
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	**2**	**2 (1.3%)**	**0**	**0**
Dysmenorrhoea	2	2 (1.3%)	0	0
Respiratory, Thoracic And Mediastinal Disorders	**5**	**5 (3.4%)**	**6**	**5 (3.4%)**
Cough	2	2 (1.3%)	1	1 (0.7%)
Oropharyngeal Pain	3	3 (2.0%)	3	3 (2.0%)
Skin And Subcutaneous Tissue Disorders	**5**	**5 (3.4%)**	**3**	**2 (1.3%)**
Rash	2	2 (1.3%)	2	1 (0.7%)
Vascular Disorders	**3**	**3 (2.0%)**	**4**	**4 (2.7%)**
Hypotension	2	2 (1.3%)	4	4 (2.7%)

n=number of events, N=number of patients, %=percentage of patients.

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 ≥1/100 to <1/10: uncommon ≥1/1,000 to <1/100; and rare ≥1/10,000 to <1/1,000).

Nervous system disorders: Uncommon: Dysgeusia, Paraesthesia

Gastrointestinal disorders: Uncommon: Oral discomfort

General disorders and administration site conditions: Uncommon: Fatigue, Feeling abnormal, Feeling of relaxation, Hangover, Hunger, Shivering

Eye disorders: Uncommon: Diplopia

Psychiatric disorders: Uncommon: Inappropriate affect

Use of PENTHROX® for pain relief in patients who require it for surgical procedures

The following Table provides drug-associated events (Adverse Reactions) experienced by ≥ 2% of the safety population of a placebo-controlled study in patients in a minor surgical procedure, of which 49 had Penthrox for the relief of pain.

	Methoxyflurane In Inhaler (N=49)	Placebo In Inhaler (N=48)
	N (%)	N (%)
Adverse events 30-45 mins 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%)
Adverse events 48 Hours after Procedure		
Nausea	2 (4.1%)	0 (0%)
Somnolence / depressed level of consciousness	2 (4.1%)	0 (0%)
Confusion	1 (2%)	0 (0%)
Anxiety	0 (0%)	1 (2%)
Vomiting	0 (0%)	1 (2%)
Musculoskeletal / soft tissue	1 (2%)	0 (0%)

Post-marketing

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

- Nervous system disorders: drowsiness, sleepy, agitation, restlessness, dissociation
- Respiratory system: choking
- Hepatic: hepatitis
- Renal: increased serum uric acid, urea nitrogen and creatinine
- Eyes: blurred vision, nystagmus

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

The following adverse effects have been reported in association with historical use 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 hyperthermia
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

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 a PENTHROX® inhaler. On finishing the initial bottle, another bottle 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 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 dressings) must be carefully monitored to ensure that the recommended dose of methoxyflurane is not exceeded.

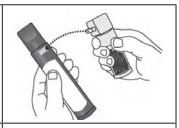
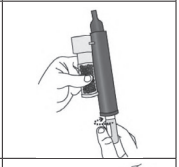
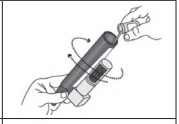
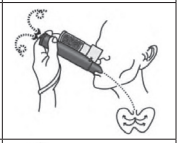
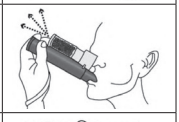
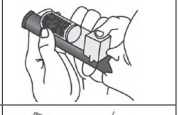
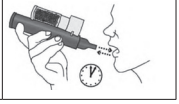
Methoxyflurane may cause renal failure if the recommended dose is exceeded. Methoxyflurane-associated renal failure is generally irreversible.

Administration:

PENTHROX® (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 Activated Carbon (AC) Chamber (where applicable) is inserted into the dilutor hole on the top of the PENTHROX® Inhaler.	
2	Holding the methoxyflurane bottle upright, 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 contents of one bottle into the base whilst rotating.	
4	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.	
5	Patient exhales into Inhaler. The exhaled vapour passes through the AC Chamber to adsorb any exhaled methoxyflurane.	
6	If stronger analgesia is required, patient can cover dilutor hole with finger during inhalation.	
7	Patient should be instructed to inhale intermittently to achieve adequate analgesia. Continuous administration will reduce time of analgesia. Patients should be administered minimum dose.	

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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

PRESENTATION AND STORAGE CONDITIONS

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,
c) Combination pack with two 3 mL sealed bottles and one PENTHROX® Inhaler (pack of 10), and
d) Combination pack with one 1.5 mL sealed bottle and one PENTHROX® Inhaler (pack of 1 or 10) with AC Chamber.

AUST R 43144

Store below 30°C

POISON SCHEDULE OF THE MEDICINE

Schedule 4

NAME AND ADDRESS OF THE AUSTRALIAN SPONSOR

Medical Developments International Ltd.
ABN 14 106 340 667
4 Caribbean Drive,
Scoresby, Victoria, 3179, Australia
Tel: 61-3-9547 1888 Fax: 61-3-9547 0262

NAME AND ADDRESS OF THE NEW ZEALAND SPONSOR

Douglas Pharmaceuticals Ltd
PO Box 45027
Auckland 0651
New Zealand
Phone: 64-9 835 0660 Fax: 64-9-835 0665

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

18 January 1993

DATE OF MOST RECENT AMENDMENT:

2 August 2016

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