AUSTRALIAN PRODUCT INFORMATION
PENTHROX® (METHOXYFLURANE) INHALATION

1 NAME OF THE MEDICINE

Methoxyflurane.

2 AND 3 QUALITATIVE AND QUANTITATIVE COMPOSITION AND PHARMACEUTICAL FORM

Each bottle contains 99.9% methoxyflurane.

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 is a clear, almost colourless mobile liquid, with a characteristic odour that is mildly pungent (see also Section 6.7 Physicochemical Properties).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC 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 Section 4.2 Dose and Method of Administration).
2. For the relief of pain in monitored conscious patients who require analgesia for surgical procedures such as the change of dressings (see Section 4.2 Dose and Method of Administration).

Note: the total maximum dose must not be exceeded.

4.2 DOSE AND METHOD OF ADMINISTRATION

FOR USE ONLY AS AN ANALGESIC AGENT, SEE SECTION 4.3 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.

Method of 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.

8. Replace cap onto PENTHROX® bottle. Place used PENTHROX® Inhaler and used bottle in sealed plastic bag and dispose of responsibly (see Section 6.6 Special Precautions for Disposal)

4.3 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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in hepatic impairment

It is advisable not to administer methoxyflurane to patients who have shown signs of liver damage, especially after previous methoxyflurane or halothane anaesthesia.

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

Renal impairment

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.

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.

Daily use of methoxyflurane is not recommended because of nephrotoxic potential.

Diabetic Patients

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.

Use in the elderly

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

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.

Paediatric Neurotoxicity

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

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. The clinical significance of these nonclinical finding is yet to be determined.

With inhalation or infusion of such drugs, exposure is longer than the period of inhalation or infusion. Depending on the drug and patient characteristics, as well as dosage, the elimination phase may be prolonged relative to the period of administration.

Occupational Exposure

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 laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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.

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.

It is possible that enzyme inducers (such as barbiturates, alcohol, isoniazid, phenobarbital or rifampicin) which increase the rate of methoxyflurane metabolism might increase its potential toxicity and they should be avoided concomitantly with methoxyflurane.

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy (Category C)

Published animal studies of some anaesthetic/analgesic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy.

Published studies in pregnant and juvenile animals demonstrate that the use of anaesthetic/analgesic and sedation drugs that block NMDA receptors and/or potentiate 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. These studies included anaesthetic agents from a variety of drug classes.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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**

	Methoxyflurane in inhaler (N=149)		Placebo in inhaler (N=149)	
	n	N (%)	n	N (%)
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 previous Table. 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: altered state of consciousness, nystagmus
- Respiratory, thoracic and mediastinal disorders: choking, hypoxia
- Hepatobiliary disorders: hepatic failure, hepatitis, jaundice, liver injury
- Renal and urinary disorders: renal failure
- Eye disorders: vision blurred
- Psychiatric disorders: affect lability, agitation, confusional state, dissociation, restlessness
- Vascular disorders: blood pressure fluctuation
- Investigations: blood uric acid increased, blood urea increased, blood creatinine increased, hepatic enzymes increased

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspect adverse reactions at http://www.tga.gov.au/reporting-problems

4.9 OVERDOSE

Adverse effects will include those for anaesthetic doses, see Section 4.8 Adverse Effects (Undesirable 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).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Distribution

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.

Metabolism

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.

Excretion

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Butylated Hydroxytoluene.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

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

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.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

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. Methoxyflurane is 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.

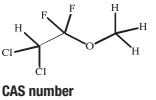
SOME OF THE PHYSICAL CONSTANTS ARE:

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.

Chemical structure



CAS number

76-38-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION

13 December 2019

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