New Zealand Data Sheet

1. PRODUCT NAME

Penthrox® 1.5mL volatile liquid for inhalation
Penthrox® 3mL volatile liquid for inhalation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Penthrox® 1.5mL bottle contains 1.5mL of Methoxyflurane 99.9% w/w.
Penthrox® 3mL bottle contains 3mL of Methoxyflurane 99.9% w/w.

Excipient(s) with known effect

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Volatile liquid for inhalation.
Clear, almost colourless mobile liquid, with a characteristic odour (mildly pungent odour).

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- 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).
- 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).

4.2. Dose and 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. 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.

Dose

Adults

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 total maximum dose must not be exceeded.

Patient should be instructed to inhale intermittently to achieve adequate analgesia. Continuous administration will reduce time of analgesia. To maximise safety, the lowest effective dosage of Penthrox® (methoxyflurane) to provide analgesia should be used. Administration of consecutive days or daily use is not recommended because of nephrotoxic potential and the total weekly dose should not exceed 15 mL. Exceeding the recommended dose may cause renal failure (see section 4.4).

Special populations

Children

Limited data is available regarding the administration of Penthrox® using the Penthrox® Inhaler (see section 4.4). The minimum effective dose to produce analgesia should be administered to children.

Elderly population

The minimum effective dose to produce analgesia should be administered (see section 4.4).

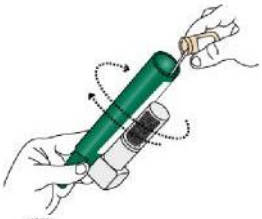
Method of Administration

Instructions on the preparation of the Penthrox® Inhaler and correct administration are provided below.

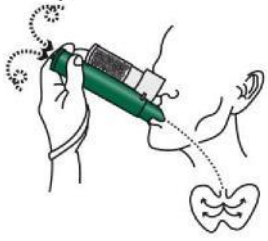
1 Ensure the Activated Carbon (AC) Chamber (where applicable) is inserted into the dilutor hole on the top of the Penthrox® Inhaler.

2 Holding the Penthrox® bottle upright, use the base the Penthrox® Inhaler to loosen the cap with a 1/2 turn. Separate the Inhaler from the bottle and remove the cap by hand.

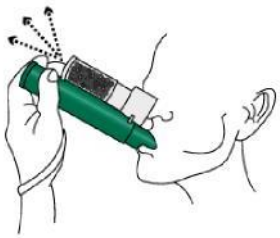
3 Tilt the Penthrox® Inhaler to a 45° angle and pour the contents of one bottle into the base whilst rotating.



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 Penthrox®.



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

Renal disease

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. Methoxyflurane-associated renal failure is generally irreversible. Because of the potential nephrotoxic effects methoxyflurane must not be used as an anaesthetic agent. Furthermore, the lowest effective dose of Penthrox® should be administered, especially in aged or obese patients (see section 5.2).

Liver disease

It is advisable not to administer Penthrox® 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 (see section 4.8).

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.

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.

Cardiovascular effects / Use in elderly

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

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. Interaction with other medicines and other forms of interaction

Enzyme inducing drugs

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.

Adrenaline or noradrenaline

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

Drugs with nephrotoxic effects

The concurrent use of tetracycline and methoxyflurane for anaesthesia has been reported to result in fatal renal toxicity. The possibility exists that Penthrox® 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.

Narcotics

If given concomitantly with Penthrox®, the patient should be observed closely, and the 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.

β-blockers

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

4.6. Fertility, pregnancy and lactation

Pregnancy

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.

Other information

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.

Preeclampsia/ Toxaemia of pregnancy

It is advisable not to administer Penthrox® due to the possibility of existing renal impairment.

Breast-feeding

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

Fertility

No data available.

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. 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; using System Organ Class and Preferred Term; by ≥1% of the safety population of a placebo-controlled study in patients with trauma and associated pain, of which 149 had Penthrox®.

	Methoxyflurane in Inhaler	**Placebo in Inhaler**

		(N=149)		(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	**Placebo in Inhaler**

		(N=49)		(N=48)
	n	N (%)	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%)		
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 experience

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: hepatitis, hepatic failure, 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:

Common: retrograde amnesia, nausea, vomiting, coughing, drowsiness, sleeping, dizziness, dislike of odour, fever, polyuria, headache.
Rare: non-specific hepatitis, malignant hyperthermia
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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions https://nzphvc.otago.ac.nz/reporting/

4.9. Overdose

Symptoms

Patients should be observed for signs of drowsiness, pallor and muscle relaxation following Penthrox® administration. High doses of methoxyflurane cause dose related nephrotoxicity.

Treatment

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Other analgesics, ATC code: N02BG09

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 Plane 1- Light 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

Absorption

Partition coefficients at 37 °C
A water/gas coefficient of 4.5
A Blood/gas coefficient (mean range) of 10.20 to 14.06
An Oil/gas coefficient of 825

The vapour concentration of methoxyflurane is limited by its vapour pressure at room temperature to a maximum of about 3.5% at 23°C.

Distribution

Methoxyflurane has great propensity to diffuse into fatty tissues. Hence methoxyflurane is released slowly from this reservoir and becomes available for biotransformation for many days.

Biotransformation

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.

Elimination

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

Embryo development

Refer to Section 4.6.

Genotoxicity

No data available.

Carcinogenecity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Butylated hydroxytoluene

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months.

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

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.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

The refilling must be conducted in a well-ventilated area to reduce environmental exposure to Penthrox® vapour.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

4 April 2002

10. DATE OF REVISION OF THE TEXT

17 January 2020

Summary table of changes

Section Changed	**Summary of new information**
4.2	Added a further instruction on disposal of Penthrox®
4.4, 4.6, 5.1 and 6.6	Minor editorial changes