PENTHROX®
(METHOXYFLURANE)

1 NAME OF THE MEDICINAL PRODUCT

PENTHROX® 3 mL inhalation vapour, liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 3 mL of methoxyflurane 99.9%.

3 PHARMACEUTICAL FORM

Inhalation vapour, liquid.

Clear, almost colourless, volatile liquid, with a characteristic fruity odour.

4 CLINICAL PARTICULARS

4.1 Indications

Emergency relief of moderate to severe pain in conscious adult patients with trauma and associated pain.
See sections 4.2 and 5.1.

4.2 Posology and method of administration

PENTHROX should be self-administered under supervision of a person trained in its administration, using the hand held PENTHROX Inhaler.

One bottle of 3 mL PENTHROX to be vaporised in a PENTHROX inhaler. On finishing the 3 mL dose, another 3 mL may be used. Dose of PENTHROX should not exceed 6 mL in a single administration.

Onset of pain relief is rapid and occurs after 6 – 10 inhalations. Patients should be instructed to inhale intermittently to achieve adequate analgesia. Patients are able to assess their own level of pain and titrate the amount of PENTHROX inhaled for adequate pain control. With continuous inhalation, 3 ml PENTHROX provides analgesic relief for up to 25-30 minutes. Intermittent inhalation may provide longer analgesic relief. Patients should be advised to take the lowest possible dose to achieve pain relief.

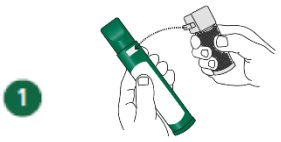
Administration on consecutive days is not recommended and the total dose to a patient in a week should not exceed 15 ml (see section 4.4).

PENTHROX should not be used in children under 18 years.

Method of Administration

Instructions on the preparation of the PENTHROX Inhaler and correct administration are provided in the Figures below.

1 Ensure the optional Activated Carbon (AC) Chamber is inserted into the dilutor hole on the top of the PENTHROX Inhaler.

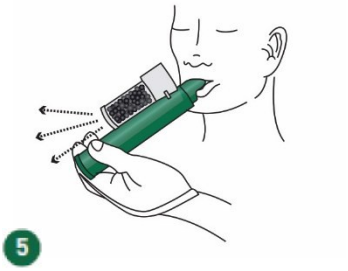


2 Remove the cap of the bottle by hand. Alternatively, use the base of the PENTHROX Inhaler to loosen the cap with a ½ turn. Separate the Inhaler from the bottle and remove the cap by hand.

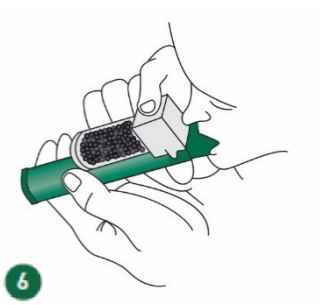
3 Tilt the PENTHROX Inhaler to a 45° angle and pour the total contents of one PENTHROX bottle into the base of the Inhaler whilst rotating.

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

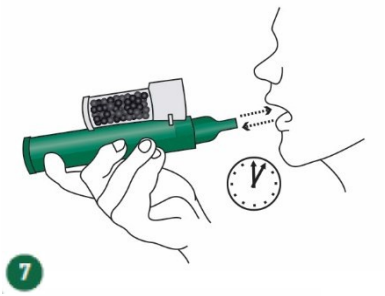
5 Patient exhales into the PENTHROX Inhaler. The exhaled vapour passes through the AC Chamber to adsorb any exhaled methoxyflurane.



6 If stronger analgesia is required, patient can cover dilutor hole on the Inhaler or AC chamber with finger during use.



7 Patient should be instructed to inhale intermittently to achieve adequate analgesia. Continuous inhalation will reduce duration of use. Minimum dose to achieve analgesia should be administered.



8 Replace cap onto PENTHROX bottle. Place used PENTHROX Inhaler and used bottle in sealed plastic bag and dispose of responsibly.

4.3 Contraindications

- Use as an anaesthetic agent.
- Hypersensitivity to PENTHROX or any fluorinated anaesthetic.
- Known genetic susceptibility to malignant hyperthermia or family history of severe drug reactions to inhaled anaesthetics.
- Patients who have a history of showing signs of liver damage after previous methoxyflurane use or halothane anaesthesia.
- Clinically significant renal impairment.
- Clinically evident cardiovascular instability.
- Clinically evident respiratory depression.
- Altered level of consciousness.

4.4 Special warnings and precautions for use

<u>Renal disease</u>

Methoxyflurane causes significant nephrotoxicity at high doses. Nephrotoxicity is also related to the rate of metabolism. Factors that increase the rate of metabolism such as drugs that induce hepatic enzymes can increase the risk of toxicity with methoxyflurane as well as sub-groups of people with genetic variations that may result in fast metaboliser status (see section 4.5).

Nephrotoxicity is thought to be associated with inorganic fluoride ions, a metabolic breakdown product. Methoxyflurane impairs renal function in a dose-related manner. The lowest effective dose of methoxyflurane should be administered, especially in the elderly or patients with other known risk factors of renal disease.

Liver disease

Methoxyflurane is metabolised in the liver, therefore increased exposures in patients with hepatic impairment can cause toxicity. It is advisable not to administer methoxyflurane to patients who have shown signs of liver damage, especially after previous methoxyflurane or halothane anaesthesia.

PENTHROX should be used with care in patients with underlying hepatic conditions or with risks for hepatic dysfunction (such as enzyme inducers - see also section 4.5).

Cardiovascular system depression / Use in elderly

Potential effects on blood pressure and heart rate are known class-effects of high dose methoxyflurane used in anaesthesia and other anaesthetics. They do not appear to be significant at the analgesic doses. There is no particular pattern to the patients' systolic BP levels after methoxyflurane administration as an analgesic across age groups. However, as the risk may potentially be increased for older people with hypotension and bradycardia, caution should be exercised in the elderly due to possible reduction in blood pressure.

Central nervous system effects

Secondary pharmacodynamic effects including potential CNS effects such as sedation, euphoria, amnesia, ability to concentrate, altered sensorimotor co-ordination and change in mood are also known class-effects. Self-administration of methoxyflurane in analgesic doses will be limited by occurrence of CNS effects, such as sedation.

Whilst the possibility of CNS effects may be seen as a risk factor for potential abuse, reports of the latter are very rare in post marketing use.

Occupational exposure

Healthcare professionals 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. To reduce occupational exposure to methoxyflurane, the PENTHROX Inhaler should always be used with the Activated Carbon (AC) Chamber which adsorbs exhaled methoxyflurane. Multiple use of PENTHROX Inhaler without the AC Chamber creates additional risk. Elevation of liver enzymes, blood urea nitrogen and serum uric acid have been reported in exposed maternity ward staff in delivery wards when methoxyflurane was used in the past in obstetric patients at the time of labour and delivery.

Frequent repeated use

Due to the limitations on the dose of PENTHROX (maximum - 6 ml) and the duration

of pain relief, PENTHROX is not appropriate for providing relief of break-through pain/exacerbations in chronic pain conditions. PENTHROX is also not appropriate for relief of trauma related pain in closely repeated episodes for the same patient.

Butylated hydroxytoluene

PENTHROX contains butylated hydroxytoluene (E321). Butylated hydroxytoluene may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes. See section 6.1.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of methoxyflurane is mediated by the CYP 450 enzymes particularly CYP 2E1 and to some extent CYP 2A6. It is possible that enzyme inducers (such as alcohol or isoniazid for CYP 2E1 and phenobarbital or rifampicin for CYP 2A6) which increase the rate of methoxyflurane metabolism might increase its potential toxicity and they should be avoided concomitantly with methoxyflurane.

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.

Concomitant use of methoxyflurane with medicines (e.g. antibiotics) which are known to have a nephrotoxic effect should be avoided as there may be an additive effect on nephrotoxicity. Antibiotics with known nephrotoxic potential include tetracycline, gentamicin, colistin, polymyxin B and amphotericin B. It is advisable to avoid using sevoflurane anaesthesia following methoxyflurane analgesia, as sevoflurane increases serum fluoride levels and nephrotoxicity of methoxyflurane is associated with raised serum fluoride.

4.6 Fertility, pregnancy and lactation

Fertility

No clinical data on effects of methoxyflurane on fertility are available. Limited data from animal studies do not indicate any effects on sperm morphology.

Pregnancy (Category C)

Animal studies do not indicate direct or indirect harmful effects of methoxyflurane with respect to reproductive toxicity (see section 5.3).

Where methoxyflurane has been used for obstetric analgesia in pregnant women, there has been a single report of neonatal respiratory depression associated with a high fetal level of methoxyflurane. However, when low concentrations were administered, or the duration of higher concentrations was kept short, per recommended posology, methoxyflurane was found to have little effect on the fetus. No fetal complications were reported to result from methoxyflurane analgesia in the mother in all the studies completed in obstetric analgesia.

As with all medicines care should be exercised when administered during pregnancy especially the first trimester.

Breast-feeding

There is insufficient information on the excretion of methoxyflurane in human milk. Caution should be exercised when methoxyflurane is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

Methoxyflurane may have a minor influence on the ability to drive and use machines. Dizziness, somnolence and drowsiness may occur following the administration of methoxyflurane (see section 4.8). A 15-minute inhalation of methoxyflurane in healthy volunteers induced an acute but short-lasting impairment of psychomotor and cognitive performance, which returns to normal within 30 minutes after cessation of inhalation.

Patients should be advised not to drive or operate machinery if they are feeling drowsy or dizzy.

4.8 Undesirable effects

Summary of safety profile

The most frequently observed non-serious reactions to PENTHROX are CNS type reactions such as dizziness, and somnolence, and are generally easily reversible.

Serious dose-related nephrotoxicity has only been associated with methoxyflurane when used in large doses over prolonged periods during general anaesthesia. Methoxyflurane is therefore no longer used for anaesthesia. See section 4.4 under renal disease. The recommended maximum dose for PENTHROX should therefore not be exceeded.
Isolated cases of hepatotoxicity have been associated with analgesic use of methoxyflurane. See section 4.4 under liver disease.

Tabulated list of adverse reactions

The adverse drug reactions related to PENTHROX observed in clinical studies and treatment-emergent events from postmarketing sources are listed in the table below, classified according to frequency (very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1,000 to <1/100; rare ≥1/10,000 to <1/1,000; very rare <1/10,000; and not known (cannot be estimated from the available data)).

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MedDRA System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Unknown
Metabolism and nutrition disorders			Increased appetite	
Psychiatric disorders		Euphoric Mood	Anxiety Depression Inappropriate affect	Affect lability^ Agitation^ Confusional state^ Dissociation^ Restlessness^
Nervous system disorders	Dizziness	Amnesia Dysarthria Dysgeusia Headache Somnolence	Paraesthesia Peripheral sensory neuropathy	Altered state of consciousness^ Nystagmus^
Eye disorders			Diplopia	Vision blurred ^
Vascular disorders		Hypotension	Flushing	Blood pressure fluctuation^
Respiratory, thoracic and mediastinal disorders		Cough		Choking^ Hypoxia^
Gastrointestinal disorders		Dry mouth Nausea	Oral discomfort	Vomiting^
Hepatobiliary disorders				Hepatic failure^ Hepatitis^ Jaundice^ Liver injury^
Skin and subcutaneous tissue disorders			Hyperhidrosis	
Renal and urinary disorders				Renal failure^
General disorders		Feeling drunk	Fatigue Feeling abnormal Chills Feeling of relaxation	
Investigations				Blood uric acid increased^ Blood urea increased^ Blood creatinine increased^ Hepatic enzyme increased^

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230 *^Other events linked to methoxyflurane use in analgesia found in post marketing experience*
231 *and in scientific literature*

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4.9 Overdose

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

High doses of methoxyflurane cause dose related nephrotoxicity. High output renal failure has occurred several hours or days after the administration of repeated high analgesic or anaesthetic doses of methoxyflurane.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Class: Analgesic

ATC code: N02BG09

Methoxyflurane vapour provides analgesia when inhaled at low concentrations. The precise mechanism of action whereby methoxyflurane produces analgesia at sub-anaesthetic doses is unknown, although a reduction in substance P and β-endorphine- like immunoreactivity in the brain has been suggested.

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. At analgesic therapeutic doses pain relief may lead to some decrease in blood pressure. This may be accompanied by bradycardia.

Clinical efficacy and safety

The efficacy and safety of PENTHROX was demonstrated in a clinical study in the treatment of acute pain in patients ≥12 years with minor trauma presenting to an Emergency Department. 300 patients were randomised in a 1:1 ratio to receive methoxyflurane or placebo. Patients with a pain score of ≥ 4 to ≤ 7 on the Numerical Rating Scale were eligible for the study. The mean pain scores (Visual Analogue Scale) observed at baseline were similar in the methoxyflurane (64.8) and placebo (64.0) groups.

The primary efficacy variable, the estimated mean change in VAS pain from Baseline to 5 min, 10 min, 15 min and 20 min, was greater for the methoxyflurane group (-23.1, -28.9, -34.0 and -35.0 respectively) when compared to the placebo group (-11.3, -14.8, -15.5 and -19.0 respectively). Overall, there was a highly significant difference between the methoxyflurane and placebo group (estimated treatment effect -15.1; 95% CI -19.2 to -11.0; $p<0.0001$). The greatest treatment effect was seen at 15 minutes (estimated treatment effect of -18.5).

An analysis was undertaken where a responder was defined as a patient who experienced at least a 30% improvement from baseline VAS pain score. Results of this analysis indicated that percentage of responders at 5, 10, 15 and 20 mins was significantly greater for the methoxyflurane group (51.0%, 57.7%, 63.8%, 63.8%) when compared to the placebo group (23.5%, 30.9%, 33.6%, 37.6%), with $p < 0.0001$ at each time-point. A total of 126 patients (84.6%) in the methoxyflurane group experienced their first pain relief after 1-10 inhalations in comparison to 76 patients (51%) in the placebo group.

5.2 Pharmacokinetic properties

Absorption

Methoxyflurane has the following partition coefficients:

- a water/gas coefficient of 4.5,
- a blood/gas coefficient of 13 and
- an oil/gas coefficient of 825

Methoxyflurane enters the lungs in the form of a vapour and is rapidly transported into the blood, therefore there is a rapid onset of analgesic action.

Distribution

Methoxyflurane has a high oil/gas coefficient hence methoxyflurane is highly lipophilic. Methoxyflurane has great propensity to diffuse into fatty tissues where it forms a reservoir from which it is released slowly over days.

Biotransformation

Biotransformation of methoxyflurane occurs in man. Methoxyflurane is metabolised by dechlorination and o-demethylation in the liver, mediated by CYP 450 enzymes particularly CYP 2E1 and CYP 2A6. Methoxyflurane is metabolised to free fluoride, oxalic acid, difluoromethoxyacetic acid, and dichloroacetic acid. Both free fluoride and oxalic acid can cause renal damage at concentrations higher than those achievable with single analgesic dose use. 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.

Elimination

Approximately 60% of methoxyflurane uptake is excreted in the urine as organic fluorine, fluoride and oxalic acid; the remainder is exhaled unaltered or as carbon dioxide. Higher peak blood fluoride levels may be obtained earlier in obese than in non-obese people, and in the elderly.

5.3 Preclinical safety data

Genotoxicity and carcinogenicity

Methoxyflurane is not considered mutagenic as indicated in an *in vitro* Ames study and an *in vivo* micronucleus study in rats.

There is no evidence that methoxyflurane has carcinogenic properties.

Reproductive and developmental toxicity

Methoxyflurane does not affect sperm cells in mice. In studies in mice and rats, methoxyflurane crossed the placenta but demonstrated no evidence of embryotoxic or teratogenic properties. However, delayed fetal development (reduced fetal body weight and decreased ossification) was observed following repeated dosing over 9 days. The no observed adverse effect level (NOAEL) for embryo-fetal development was 0.006% - 4h/day in mice and close to 0.01% - 8 h/day in rats. The NOAELs in

mouse and rat represent a 1- to 2-fold margin on a mg/kg basis and a 0.1- to 0.3-fold margin on a mg/m^2 basis versus the proposed maximum clinical dose. As PENTHROX is not intended for daily use, the risk of delayed fetal development is considered to be very low.

Hepatic effects

Repeated intermittent or continuous administration of subanaesthetic concentrations of methoxyflurane has been associated with limited and commonly reversible hepatic changes (fatty metamorphosis, elevated ALT/AST) in several species. A NOAEL has not been established. These effects were seen at exposures considered sufficiently in excess of those anticipated through normal clinical use of the product.

6 PHARMACEUTICAL PARTICULARS

6.1 Other ingredients

Butylated hydroxytoluene E321.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Please refer to outer box.

6.4 Special precautions for storage

Store below 30˚C.

6.5 Nature and contents of container

PENTHROX may be 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 10) without Activated Carbon (AC) Chamber

c) Combination pack with one 3 mL sealed bottle and one Penthrox® Inhaler with AC Chamber (pack of 1)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product

After loading the PENTHROX Inhaler, replace cap onto PENTHROX bottle. After use, place used PENTHROX Inhaler and used bottle in a plastic bag, seal and dispose of responsibly.

7 MARKETING AUTHORISATION HOLDER

Manufactured by:
Medical Developments International Ltd., Victoria, Australia

Imported by:
DAIICHI SANKYO (THAILAND) LTD.
24th Fl., United Center Bldg.,
323, Silom Rd., Silom, Bangrak, Bangkok, 10500, Thailand
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8 MARKETING AUTHORISATION NUMBER(S)

1C 15075/63 (NC)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 April 2020

10 DATE OF REVISION OF THE TEXT

May 2020