SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

PENTHROP, 99,9 % *m/m*, inhalation

- **To be used under medical supervision only**
- **For use with PENTHROP (methoxyflurane) only**
- **For single patient use**
- **Medical personnel to ensure that the device is safely disposed of into medical waste**

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of Penthrop contains 99,9 % *m/m* methoxyflurane.

Antioxidant: 0,01 % *m/m* butylated hydroxytoluene.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation.

Clear, practically colourless, mobile liquid, having a characteristic 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 healthcare professionals trained in PENTHROP 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).

Note: The total maximum dose must not be exceeded (see section 4.2).

4.2 Posology and method of administration

Posology

For use only as an analgesic medicine, see section 4.3.

Dosage (adults)

Up to 6 mL (2 x 3 mL bottles) of PENTHROP per day, vaporised in a PENTHROP Inhaler. If refilling the inhaler with a second bottle of PENTHROP, this should occur only once and must be conducted in a well-ventilated area to reduce environmental exposure to PENTHROP vapour.

To maximise safety, the lowest effective dosage of PENTHROP to provide analgesia should be used, particularly for children and the elderly.

Administration on consecutive days is not recommended. The total weekly dose should not exceed 15 mL.

The cumulative dose received by patients receiving intermittent doses of PENTHROP for painful procedures (such as wound dressings) must be carefully monitored to ensure that the recommended dose of PENTHROP is not exceeded.

Onset of pain relief is rapid and occurs after 6 – 10 inhalations. Patients should be instructed to inhale intermittently to achieve adequate analgesia. Patients can assess their own level of pain and titrate the amount of PENTHROP inhaled for adequate pain control. With continuous inhalation, 3 mL PENTHROP 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.

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

Paediatric population

1 to 11 years of age: Up to 3 mL (1 x 3 mL) of PENTHROP per day or 15 mL (5 x 3 mL bottles) per week.

12 to 17 years of age: Up to 6 mL (2 x 3 mL) of PENTHROP per day or 15 mL (5 x 3 mL bottles) per week.

Administration on consecutive days is not recommended. The total weekly dose should not exceed 15 mL.

Method of administration

PENTHROP is self-administered, under observation and supervision (and assisted if necessary) by a person trained in its administration, using the handheld PENTHROP Inhaler.

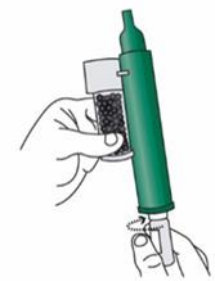
Instructions on the preparation of the PENTHROP Inhaler and correct administration are provided in Figure 1.

Only PENTHROP is to be used in the PENTHROP Inhaler. No other inhalational anaesthetics or inhalational analgesic may be used.

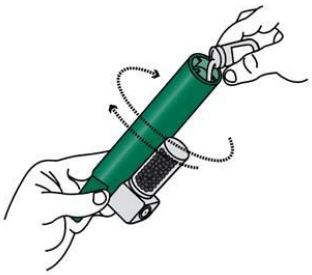
Figure 1. How to use the PENTHROP Inhaler

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

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



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



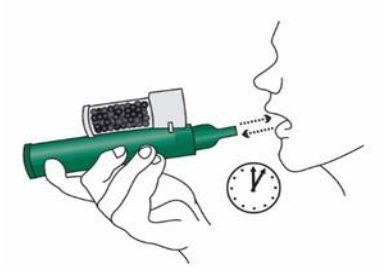
4. Place the wrist loop over the patient's wrist. Instruct the patient to inhale through the mouthpiece of the PENTHROP Inhaler to obtain analgesia. First few breaths should be gentle and then breathe normally through Inhaler.

5. Instruct patient to exhale into the PENTHROP Inhaler so the exhaled vapour passes through the AC Chamber which adsorbs any exhaled methoxyflurane.

6. If stronger analgesia is required, instruct the patient to cover the dilutor hole on the AC Chamber with a finger during use.

7. If further pain relief is required, after the first bottle has been used use a second bottle if available. Alternatively use a second bottle from a new combination pack. Use in the same way as the first bottle in step 2 and 3. There is no need to remove the AC Chamber. Put used bottle into the plastic bag provided.

8. Instruct patient to inhale intermittently to achieve adequate analgesia. Continuous inhalation will reduce duration of use. Patients should be administered the minimum dose to achieve analgesia.



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

4.3 Contraindications

- Hypersensitivity to methoxyflurane, or other inhalation anaesthetics or any of the ingredients of PENTHROP.
- Use as an anaesthetic medicine
- Renal impairment, including reduced glomerular filtration rate (GFR), urine output and reduced renal blood flow
- Renal failure
- Severe hepatic impairment
- Hypersensitivity to fluorinated anaesthetics
- Cardiovascular instability
- Respiratory depression
- Head injury or loss of consciousness
- A history of possible adverse reactions in either patient or relatives to any of the halogenated inhalational anaesthetic medicines
- Malignant hyperthermia: patients with known or genetically susceptible to malignant hyperthermia
- Porphyria

4.4 Special warnings and precautions for use

Nephrotoxicity

Methoxyflurane as contained in PENTHROP impairs renal function in a dose-related manner because of the released fluoride on the distal tubule and may cause polyuric or oliguric renal failure, oxaluria being the

prominent feature.

To ensure the safe use of methoxyflurane as contained in PENTHROP as an analgesic the following precautions should be observed.

- Use the lowest effective dose to control pain.
- Use with caution in the elderly or patients with known risk factors for renal disease.
- Use with caution in patients diagnosed with clinical conditions which may pre-dispose to renal injury.

Nephrotoxicity is greater with methoxyflurane as contained in PENTHROP, 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.

Because of the potential nephrotoxic effects, methoxyflurane as contained in PENTHROP must not be used as an anaesthetic medicine (see section 4.3). The risk is related to the total dose (time and concentration) and frequent exposure.

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

An observational study in 1 236 patients with trauma pain treated with methoxyflurane found that renal events were less frequent than in 1 101 patients treated with other analgesics for trauma associated pain (0,7 % versus 2,6 %, p <0,001).

Liver disease

Methoxyflurane as contained in PENTHROP is metabolised in the liver, therefore increased exposures in patients with hepatic impairment can cause toxicity.

It is advisable not to administer PENTHROP to patients who have shown signs of liver damage, especially after previous methoxyflurane use (as contained in PENTHROP) or halothane anaesthesia (see section 4.3).

There have been reports of hepatic dysfunction, jaundice, and fatal hepatic necrosis.

PENTHROP should be used with care in patients with underlying hepatic conditions or with risks for hepatic dysfunction (such as enzyme inducers, see section 4.1).

Hepatic toxicity in association with methoxyflurane as contained in PENTHROP has been observed with

analgesic use.

An observational study on patients with trauma pain did not find a significant difference in occurrence of hepatic events between 1 236 patients treated with methoxyflurane or and 1 101 patients treated with other analgesics for trauma associated pain (1,6 % versus 2,1 %, p=0.442).

Respiratory depression

Respiratory depression has been reported also from analgesic doses of methoxyflurane (see section 4.8). Respiration should be monitored due to the risk of respiratory depression and hypoxia.

Diabetic patients

Diabetic patients have an increased likelihood of developing nephropathy if they have impaired renal function or polyuria, are obese, or are not optimally controlled.

Interactions

In patients receiving treatment with *enzyme inducing medicines* (e.g., rifampicin**)** the metabolism of methoxyflurane as contained in PENTHROP may be enhanced resulting in increased risk of nephrotoxicity. Intravenous epinephrine (adrenaline) or norepinephrine (nor-adrenaline) should be employed cautiously during methoxyflurane as contained in PENTHROP administration due to the risk of developing a cardiac dysrhythmia.

Use in the elderly

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

Central nervous system effects

Secondary pharmacodynamic effects including potential central nervous system effects such as sedation, euphoria, amnesia, ability to concentrate, altered sensorimotor coordination and change in mood are also known class-effects. Self-administration of methoxyflurane as contained in PENTHROP in analgesic doses

will be limited by occurrence of CNS effects, such as sedation.

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

Health workers

Health workers who are regularly exposed to patients using PENTHROP Inhalers should be aware of any relevant occupational health and safety guidelines for the use of inhalational medicines. The use of methods to reduce occupational exposure to methoxyflurane as contained in PENTHROP, including the attachment of the PENTHROP Activated Carbon (AC) Chamber, should be considered. Multiple use of PENTHROP Inhalation without the AC Chamber creates additional risk. Elevation of liver enzymes, and deterioration in renal function has been reported in exposed maternity ward staff.

There have been reports of non-serious and transient reactions such as dizziness, headache, nausea or malaise, and reports of hypersensitivity reactions to methoxyflurane or other ingredients in healthcare professionals exposed to PENTHROP. Measurements of exposure levels to methoxyflurane in hospital staff showed levels significantly lower than those associated with nephrotoxicity.

The derived maximum exposure limit (MEL) for methoxyflurane is 15 ppm expressed as an 8-hour time weighted average (8-hr TWA). The odour detection threshold for methoxyflurane ranges between 0,13 and 0,19 ppm which is well below the MEL. The exposure levels of medical staff involved in supervising the use of PENTHROP in hospital emergency triage rooms during an 8-hour shift were measured. The measurements showed levels (0,017 ppm, range 0,008 to 0,736 ppm) significantly lower than the MEL of 15 ppm.

Use in children

Limited data is available regarding the use of PENTHROP Inhaler in children. The minimum effective dose to produce analgesia should be administered to children (see section 4.2).

Frequent repeated use

For procedural pain only

Patients receiving PENTHROP on repeated occasions (such as wound dressings) must be carefully monitored to ensure that the recommended dose of PENTHROP is not exceeded (see section 4.2).

Butylated hydroxytoluene

PENTHROP contains the excipient, butylated hydroxytoluene (E321), a stabiliser. 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 medicines and other forms of interaction

The concurrent use of tetracycline and methoxyflurane as contained in PENTHROP for anaesthesia has been reported to result in fatal renal toxicity.

The possibility exists that PENTHROP may enhance the adverse renal effects of other medicines e.g., contrast medicines 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 β-blockers, with an increased risk of hypotension.

The metabolism of methoxyflurane is mediated by the CYP 450 enzymes particularly CYP 2E1, CYP 2B6 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 and carbamazepine, efavirenz, rifampicin or nevirapine for CYP 2B6) which increase the rate of methoxyflurane metabolism might increase its potential toxicity and they should be avoided concomitantly with methoxyflurane as contained in PENTHROP (see section 4.4).

Concomitant use of methoxyflurane as contained in PENTHROP with CNS depressants e.g., opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants,

sedating antihistamines and alcohol may produce additive depressant effects. If opioids are given concomitantly with PENTHROP, the patient should be observed closely, as is normal clinical practice with opioids.

4.6 Fertility, pregnancy and lactation

Safety and efficacy during pregnancy and lactation have not been established.

Pregnancy

Data available from animal studies are insufficient with respect to reproductive toxicity. 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 foetal 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 foetus. No foetal complications were reported to result from methoxyflurane analgesia in the mother in all the studies completed in obstetric analgesia.

A retrospective study examined the prevalence of in utero exposure and perinatal outcomes associated with methoxyflurane exposure during ambulance transport over a 17-year period. It was conducted using linked ambulance, emergency department, hospital, congenital anomaly and mortality data. First-trimester methoxyflurane exposure (n=270) was not associated with an increased risk of congenital anomalies compared to fentanyl (n=75) or no analgesic (n=1 620). Second trimester (n=321) and third trimester (n=403) methoxyflurane exposure was not associated with an increased risk of preterm birth, low birth weight or perinatal mortality compared with fentanyl (n=77 in second-trimester, n=33 in third trimester) and no analgesic (n=2 556 in second-trimester, n=4 687 in third trimester). Methoxyflurane administration on day of delivery (n=657) was also not associated with an increased risk of labour or delivery complications when compared to fentanyl (n=22) and no analgesic (n=2 667).

Breastfeeding

Mothers should not breastfeed their infants when taking PENTHROP. There is insufficient information on the excretion of methoxyflurane in human milk.

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.

4.7 Effects on ability to drive and use machines

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 PENTHROP, such as drowsiness. The treating doctor should decide when activities such as driving a vehicle or operating a machine may be resumed.
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.

4.8 Undesirable effects

The most frequently non-serious reactions are central nervous system 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 nephrotoxicity. The recommended maximum dose for PENTHROP should therefore not be exceeded.

Liver injury may occur rarely (less than 1 case per 1 000 patients) and hepatic enzymes increased may occur uncommonly (less than 1 case per 100 patients) with analgesic use of methoxyflurane. See section 4.4 under liver disease.

Tabulated list of adverse reactions

The adverse drug reactions related to PENTHROP observed in clinical studies and treatment-emergent events from post marketing 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 unknown (cannot be estimated from the available data).

MedDRA System Organ Class	**Very Common ≥1/10**	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1000**	**Unknown**
Immune system disorders					Hypersensitivity ^
Metabolism and nutrition disorders				Increased appetite	
Psychiatric disorders			Disturbance in attention Euphoric mood	Anxiety Depression Inappropriate affect Verbigeration	Affect lability^ Agitation^ Confusional state^ Dissociation^ Restlessness^
Nervous system disorders		Dizziness Somnolence	Amnesia Dysarthria Dysgeusia Headache Paraesthesia	Peripheral sensory neuropathy	Altered state of consciousness^ Nystagmus^
Eye disorders			Vision impairment		
Vascular			Hypotension	Flushing	

disorders				Hypertension	
Respiratory thoracic and mediastinal disorders			Cough		Choking^ Hypoxia^ Respiratory depression^
Gastro-intestinal disorders			Dry mouth Nausea Oral discomfort Vomiting	Oral pruritus Salivary hypersecretion	
Hepato-biliary disorders				Liver injury	Hepatic failure^ Hepatitis^ Jaundice^
Skin and subcutaneous tissue disorders			Hyperhidrosis		
Renal and urinary disorders					Renal failure^
General disorders		Feeling drunk	Fatigue Feeling abnormal Feeling of relaxation	Chills	
Investigations			Increased hepatic enzyme		Increased Blood uric acid ^ Increased Blood urea ^ Increased Blood creatinine^

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

literature

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 providers are asked to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

For reporting of adverse reactions directly to the Holder of Certificate of Registration, email:

pharmacovigilance@equitypharma.co.za

4.9 Overdose

Adverse effects will include those for anaesthetic doses, see section 4.8 and section 4.4.

In the event of overdose, anaesthetic effects may occur with signs of excessive drowsiness (including loss of consciousness), lowering of blood pressure, respiratory depression, pallor and muscle relaxation. After PENTHROP discontinuation such overdose effects usually resolve quickly often with no other intervention required but cardiorespiratory supportive measures can be implemented if necessary.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A. 2.9 Other analgesics

ATC code: N02BG09

Methoxyflurane vapour possesses analgesic properties 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-endorphin-like immunoreactivity in the brain has been suggested. After methoxyflurane administration, drowsiness may occur. The myocardium is minimally sensitised to

epinephrine (adrenaline) by methoxyflurane. The blood pressure decreases in a dose dependant manner. This may be accompanied by bradycardia.

The blood pressure decrease noted is accompanied by reduced cardiac contractile force and reduced cardiac output.

5.2 Pharmacokinetic properties

Absorption

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. In a pharmacokinetic (PK) study in healthy volunteers, the mean plasma concentration-time curves showed an extremely rapid rise in methoxyflurane plasma concentrations. Following a single dose of 3 mL methoxyflurane inhaled intermittently over an hour, the arterial profile is demonstrated by a t_{max} at 0,25 hours (range 0,08 - 0,75 hours), C_{max} of 32.39 ug/mL (SD 13,546 ug/mL, CV 41,8 %) and the AUC of 28,95 h.ug/mL (range 12,3-52,6 h.ug/mL).

Distribution

Methoxyflurane diffuses 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 to 70 % of the absorbed dose is metabolised to free fluoride, oxalic acid, difluoro-methoxyacetic acid and dichloroacetic acid. Both the free fluoride and the oxalic acid can cause renal damage, which is dose related.

Elimination

In a PK study in healthy volunteers who inhaled 3 mL of methoxyflurane over 1 hour, there was an early peak in methoxyflurane plasma concentration-time curves followed by a rapid elimination from the plasma, with methoxyflurane concentrations returning to baseline by 24 hours after administration. Concentrations

of the metabolite, inorganic fluoride, rose less quickly than methoxyflurane (median tmax of 1,5 hours) and were gradually eliminated from the plasma, with significant concentrations measured in plasma 48 hours after methoxyflurane administration. Following a single dose of 3 mL methoxyflurane inhaled intermittently over an hour, the venous median half-life for methoxyflurane is 3,16 hours (range 1,06 - 7,89 hours), and that for inorganic fluoride is 33,30 hours (range 23,50-51,20 hours). The PK profiles for methoxyflurane and inorganic fluoride exhibited high inter-subject variability.

About 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.

Studies have shown that higher peak blood fluoride levels are obtained earlier in obese than in non-obese and in the elderly.

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 at or below 30 °C in its original container.

Do not freeze.

Keep the product in the original container until required for use in order to protect from light. Keep the container tightly closed.

6.5 Nature and contents of container

3 mL of PENTHROP solution is filled into a 5 mL Type I amber glass screw neck bottle and closed with a white cap. PENTHROP is supplied in the following presentations:

- Combination pack containing one sealed bottle filled with 3 mL liquid, one PENTHROP inhaler and one Activated Carbon chamber in an outer carton box (pack of 1 or 10 units).
- Combination pack containing one sealed bottle filled with 3 mL liquid and one PENTHROP inhaler in an outer carton box (pack of 10 units).

6.6 Special precautions for disposal

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Equity Pharmaceuticals (Pty) Ltd.

100 Sovereign Drive

Route 21 Corporate Park

Nellmapius Drive

Irene

Pretoria

Tel: +27 (0) 12 345 1747

8 REGISTRATION NUMBER(S)

45/2.9/1118

Namibia:	21/2.10/0103	NS3
Zambia:	473/006	POM
Zimbabwe:	2021/2.3/6205	P.P.
Botswana:	BOT2103764	S2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 5 June 2014

10 DATE OF REVISION OF THE TEXT

31 March 2026