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.

The total weekly dose should not exceed 15 ml.

Administration on consecutive days is not recommended.

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.

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.

The total weekly dose should not exceed 15 ml.

Administration on consecutive days is not recommended.

Method of administration

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

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

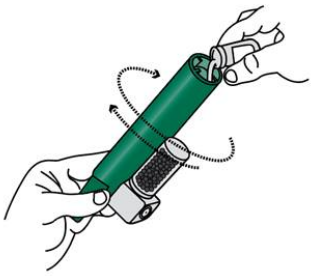
Only PENTHROP is to be used in the PENTHROP Inhaler. No other inhalational anaesthetics or inhalational analgesic may be used.

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. The patient inhales and exhales through the mouthpiece of the PENTHROP Inhaler to obtain analgesia. The first few breaths should be gentle. Thereafter the patient breathes normally through the Inhaler.

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

6. If stronger analgesia is required, the patient can 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. No need to remove the AC Chamber. Put used bottle into the plastic bag provided.

8. The patient should be instructed 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 (see section 6.4).

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 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.

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 other 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.

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).

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.

Caution in hot climates

Do not expose to temperatures above 40 °C, especially when used in conjunction with oxygen.

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. Additionally, the CNS effects can be a risk factor for potential abuse.

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.

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

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).

Special Precautions

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

Malignant hyperthermia.

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

PENTHROP crosses the placenta and carries the potential to produce central nervous system and respiratory depression in the new born infant. In a compromised foetus, careful consideration should be given to this potential depression and to the selection of anaesthetic medicines, doses and techniques.

Neonates delivered of mothers who used methoxyflurane analgesia for childbirth had transient raised serum uric acid.

Breastfeeding

Caution should be exercised when PENTHROP is administered to a mother who is breastfeeding her baby.

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.

4.8 Undesirable effects

The frequent non-serious reactions are central nervous system type reactions such as dizziness, and somnolence, and are generally easily reversible.

Metabolism and nutrition disorders:

Less frequent: Increased appetite

Nervous system disorders:

Frequent: Headache, dizziness, dysgeusia, somnolence

Less frequent: Amnesia, dysarthria, paraesthesia, peripheral sensory neuropathy

Psychiatric disorders:

Frequent: Euphoric mood

Less frequent: Anxiety, depression, disturbance in attention, inappropriate affect, verbigeration

Eye disorders:

Less frequent: Vision impairment

Vascular disorders:

Less frequent: Flushing, hypertension, hypotension

Respiratory, thoracic and mediastinal disorders:

Frequent: Cough

Gastrointestinal disorders:

Frequent: Nausea

Less frequent: Dry mouth, oral discomfort, oral pruritus, salivary hypersecretion, vomiting

Skin and subcutaneous tissue disorders:

Less frequent: Hyperhidrosis

General disorders and administrative site conditions:

Frequent: Feeling drunk

Less frequent: Fatigue, feeling abnormal, chills, feeling of relaxation

Post-marketing experience

Immune system disorders:

Unknown frequency: Hypersensitivity

Psychiatric disorders:

Unknown frequency: Affect lability, agitation, confusional state, dissociation, restlessness

Nervous system disorders:

Unknown frequency: Altered state of consciousness, nystagmus

Respiratory, thoracic and mediastinal disorders:

Unknown frequency: Choking, hypoxia

Hepato-biliary disorders:

Unknown frequency: Hepatitis, jaundice, liver injury, hepatic failure

Renal and urinary disorders:

Unknown frequency: Renal failure

Investigations:

Unknown frequency: Increased hepatic enzymes, increased blood urea, increased blood creatinine, increased blood uric acid

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 reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

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 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

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.

Methoxyflurane diffuses into fatty tissues. Hence methoxyflurane is released slowly from this reservoir and becomes available for biotransformation for many days. Peak serum fluoride levels are seen 2 to 4 days after a dose.

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.

KEEP OUT OF REACH OF CHILDREN.

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

8 REGISTRATION NUMBER(S)

45/2.9/1118

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 5 June 2014

10 DATE OF REVISION OF THE TEXT

5 October 2021

Namibia: 21/2.10/0103 NS3

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Zimbabwe:2021/2.3/6205 P.P.