PENTHROX 99.9%, 3 ml inhalation vapour, liquid: Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Abbreviated Prescribing Information.

Presentation: Each bottle of PENTHROX contains 3 ml of methoxyflurane 99.9%, a clear, almost colourless, volatile liquid, with a characteristic fruity odour. Each PENTHROX combination pack consists of one bottle of 3 ml PENTHROX, one PENTHROX Inhaler and one Activated Carbon (AC) chamber.

Indications: Emergency relief of moderate to severe pain in conscious adult patients with trauma and associated pain.

Dosage and administration: PENTHROX should be self-administered under supervision of a person trained in its administration, using the hand held PENTHROX Inhaler. It is inhaled through the custom-built PENTHROX inhaler. **Adults:** One bottle of 3 ml PENTHROX as a single dose, administered using the device provided. A second bottle should only be used where needed. The frequency at which PENTHROX can be safely used is not established. The following administration schedule is recommended: no more than 6 ml in a single day, administration on consecutive days is not recommended and the total dose to a patient in a week should not exceed 15 ml. Onset of pain relief is rapid and occurs after 6-10 inhalations. Patients are able to titrate the amount of PENTHROX inhaled and should be instructed to inhale intermittently to achieve adequate analgesia. Continuous inhalation of a bottle containing 3 ml provides analgesic relief for up to 25-30 minutes; intermittent inhalation may provide longer analgesic relief. Patients should be advised to use the lowest possible dose to achieve pain relief. *Renal impairment:* Methoxyflurane may cause renal failure if the recommended dose is exceeded. Caution should be exercised for patients diagnosed with clinical conditions that would pre-dispose to renal injury. *Hepatic impairment:* Cautious clinical judgement should be exercised when PENTHROX is to be used more frequently than on one occasion every 3 months. **Paediatric population:** PENTHROX should not be used in children and adolescents under 18 years. For detailed information on the method of administration refer to the SmPC.

Contraindications: Use as an anaesthetic agent. Hypersensitivity to methoxyflurane, any fluorinated anaesthetic or to any of the excipients. Patients who are known to be or genetically susceptible to malignant hyperthermia. Patients or patients with a known family history of severe adverse reactions after being administered with inhaled anaesthetics. Patients who have a history of showing signs of liver damage after previous methoxyflurane use or halogenated hydrocarbon anaesthesia. Clinically significant renal impairment. Altered level of consciousness due to any cause including head injury, drugs or alcohol. Clinically evident cardiovascular instability. Clinically evident respiratory depression.

Warnings and Precautions: To ensure the safe use of PENTHROX as an analgesic the lowest effective dose to control pain should be used and it should be used with caution in the elderly or other patients with known risk factors for renal disease, and in patients diagnosed with clinical conditions which may pre-dispose to renal injury. Methoxyflurane causes significant nephrotoxicity at high doses. Nephrotoxicity is thought to be associated with inorganic fluoride ions, a metabolic breakdown product. When administered as instructed for the analgesic indication, a single dose of 3 ml methoxyflurane produces serum levels of inorganic fluoride ions below 10 micromol/l. In the past when used as an anaesthetic agent, methoxyflurane at high doses caused significant nephrotoxicity, which was determined to occur at serum levels of inorganic fluoride ions greater than 40 micromol/l. 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. Methoxyflurane is metabolised in the liver, therefore increased exposures in patients with hepatic impairment can cause toxicity. PENTHROX should be used with care in patients with underlying hepatic conditions or with risks for hepatic dysfunction. Previous exposure to halogenated hydrocarbon anaesthetics (including methoxyflurane when used as an anaesthetic agent), especially if the interval is less than 3 months, may increase the potential for hepatic injury. Potential effects on blood pressure and heart rate are known class-effects of high-dose methoxyflurane used in anaesthesia and other anaesthetics. Caution is required with use in the elderly due to possible reduction in blood pressure. Potential CNS effects such as sedation, euphoria, amnesia, ability to concentrate, altered sensorimotor co-ordination and change in mood are known class-effects. The possibility of CNS effects may be seen as a risk factor for potential abuse, however reports are very rare in post-marketing use. PENTHROX is not appropriate for providing relief of break-through pain/exacerbations in chronic pain conditions or for the relief of trauma related pain in closely repeated episodes for the same patient. PENTHROX contains the excipient, butylated hydroxytoluene (E321) which may cause local skin reactions (e.g. contact dermatitis), or irritation to the eyes and mucous membranes. To reduce occupational exposure to methoxyflurane, the PENTHROX Inhaler should always be used with the 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 when methoxyflurane was used in the past at the time of labour and delivery.

Interactions: There are no reported drug interactions when used at the analgesic dosage (3 – 6 ml). Methoxyflurane is metabolised 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. Concomitant use of methoxyflurane with medicines (e.g. contrast agents and some antibiotics) which are known to have a nephrotoxic effect should be avoided as there may be an additive effect on nephrotoxicity; tetracycline, gentamicin, colistin, polymyxin B and amphotericin B have known nephrotoxic potential. Sevoflurane anaesthesia should be avoided following methoxyflurane analgesia, as sevoflurane increases serum fluoride levels and methoxyflurane nephrotoxicity is associated with raised serum fluoride. Concomitant use of PENTHROX with CNS depressants, such as 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 PENTHROX, the patient should be observed closely. When methoxyflurane was used for anaesthesia at the higher doses of 40–60 ml, there were reports of drug interaction with hepatic enzyme inducers (e.g. barbiturates) increasing metabolism of methoxyflurane and resulting in a few reported cases of nephrotoxicity; reduction of renal blood flow and hence anticipated enhanced renal effect when used in combination with drugs (e.g. barbiturates) reducing cardiac output; and class effect on cardiac depression, which may be enhanced by other cardiac depressant drugs, e.g. intravenous practolol during cardiac surgery.

Fertility, pregnancy and lactation: No clinical data on effects of methoxyflurane on fertility are available. Studies in animals have shown reproduction toxicity. As with all medicines care should be exercised when administered during pregnancy especially the first trimester. There is insufficient information on the excretion of methoxyflurane in human milk. Caution should be exercised when methoxyflurane is administered to a nursing mother.

Effects on ability to drive and use machines: Methoxyflurane may have a minor influence on the ability to drive and use machines. Patients should be advised not to drive or operate machinery if they are feeling drowsy or dizzy.

Undesirable effects: The common non-serious reactions 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. The following adverse drug reactions have either been observed in PENTHROX clinical trials in analgesia, with analgesic use of methoxyflurane following post-marketing experience or are linked to methoxyflurane use in analgesia found in post-marketing experience and in scientific literature (refer to the SmPC for further details): **Very common (≥1/10):** dizziness; **common (≥1/100 to <1/10):** headache, somnolence, dry mouth, nausea; **uncommon (≥1/1,000 to <1/100):** increased appetite, anxiety, depression, disturbance in attention, euphoric mood, inappropriate affect, verbigeration, amnesia, dysarthria, dysgeusia, paraesthesia, peripheral sensory neuropathy, diplopia, flushing, hypertension, hypotension, cough, oral discomfort, oral pruritis, salivary hypersecretion, vomiting, hyperhidrosis, fatigue, feeling abnormal, feeling drunk, chills, feeling of relaxation; **not known:** affect lability, agitation, confusional state, dissociation, restlessness, altered state of consciousness, nystagmus, vision blurred, choking, hypoxia, hepatic failure, hepatitis, jaundice, liver injury, renal failure, hepatic enzyme increased, blood urea increased, blood uric acid increased, blood creatinine increased.

Overdose: Refer to SmPC.

Legal Category: UK: POM; Ireland: This product is subject to medical prescription.

UK NHS Price: £17.89; **Ireland List Price:** €23.05.

Marketing Authorisation Holder: UK: Medical Developments UK Limited c/o Price Bailey LLP, Causeway House, 1 Dane Street, Bishop's Stortford, Herts, CM23 3BT, United Kingdom; Ireland: Medical Developments MD&P Limited, 13A Ballyhoy Avenue, Raheny, D05K068, Ireland.

MA Number: UK: PL 42467/0001; Ireland: PA 22745/001/001.

Full prescribing information available from: Galen Limited, Seagoe Industrial Estate, Craigavon, BT63 5UA, United Kingdom.

Date of Preparation: December 2020.

UK – Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.
Adverse events should also be reported to Galen Limited on 028 3833 4974 and select the customer services option, or e-mail customer.services@galen-pharma.com.

Ireland – Adverse events should be reported. Reporting forms and information can be found at www.hpra.ie.
Adverse events should also be reported to Galen Limited on 048 3833 4974 and select the customer services option, or e-mail customer.services@galen-pharma.com.

Medical information enquiries should also be directed to Galen Limited.