To reduce occupational exposure to methoxyflurane, the PENTHROX (e.g. contact dermatitis), or irritation to the eyes and mucous membranes. butylated hydroxytoluene (E321) which may cause local skin reactions episodes for the same patient. PENTHROX contains the excipient, for providing relief of break-through pain/exacerbations in chronic pain ordination and change in mood are known class-effects. The possibility of euphoria, amnesia, ability to concentrate, altered sensorimotor co-ordination and change in mood are known class-effects. The possibility of adverse reactions after being administered with inhaled anaesthetics. Patients who are known to be 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 exposure or halothane use. 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 produces urinary 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. Care should be taken in pregnant women (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 side effects such as 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. The risk of trauma to the head of trauma patients in dams associated with some adverse effects 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 blood uric acid have been observed, in some cases to values not uncommon in clinical practice. Methoxyflurane is metabolised 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 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 been reported. Renal impairment and hyperthermia 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) reducing the apparent metabolism of methoxyflurane. 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. 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 not drive or use 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): Euphoric mood, dry mouth, headache, nausea, tinnitus, weakness, hyperhidrosis, fatigue, feeling abnormal, chills, feeling of relaxation; not known: affect lability, agitation, confusional state, dissociation, restlessness, altered state of consciousness, myasthenia, vision blurred, blood pressure fluctuation, choking, hypoxia, vomiting, 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: POM. NHS Price: £17.89. Marketing Authorisation Holder: Medical Developments UK Limited c/o Price Bailey LLP Causeway House, 1 Dane Street, Bishop’s Stortford, Herts, CM23 3BT, United Kingdom. MA Number: PL 42467/0001. Full prescribing information available from: Galen Limited, Seagoe Industrial Estate, Craigavon, BT63 5UA, United Kingdom. Date of Preparation: January 2019.

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. Medical information enquiries should also be directed to Galen Limited.