Public Assessment Report

Decentralised Procedure

PENTHROX 3mL inhalation vapour, liquid
(methoxyflurane)

Procedure No: UK/H/5542/001/DC

UK Licence No: PL 42467/0001

Medical Developments UK Ltd
LAY SUMMARY

PENTHROX 3mL inhalation vapour, liquid
(methoxyflurane)

This is a summary of the Public Assessment Report (PAR) for PENTHROX 3mL inhalation vapour, liquid (PL 42467/0001; UK/H/5542/001/DC). It explains how the application for PENTHROX 3mL inhalation vapour, liquid was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use PENTHROX 3mL inhalation vapour, liquid.

For practical information about using PENTHROX 3mL inhalation vapour, liquid, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Penthrox’ in this Lay Summary.

What is Penthrox and what is it used for?
Penthrox is a medicine which is used for the emergency relief of pain, in adults 18 years and older, with trauma and associated pain. It is inhaled through the custom-built Penthrox Inhaler. Penthrox is intended to reduce the severity of pain, rather than stop it completely.

How does Penthrox work?
Penthrox contains the active substance methoxyflurane which reduces pain when inhaled at low concentrations.

How is Penthrox used?
Penthrox is available as an inhalation vapour, liquid. It is a clear almost colourless volatile liquid, with a fruity odour that becomes a vapour when used with the Penthrox Inhaler.

This medicine should be used exactly as instructed by the patient’s healthcare professional. The patient should check with his/her healthcare professional if they are not sure.

This medicine is to be self-administered by the patient using the Penthrox Inhaler, under the supervision of a healthcare professional. The patient’s healthcare professional will prepare the Penthrox Inhaler and give it to the patient.

Adults
One or two 3 mL bottles of Penthrox can be used per administration. The patient should not inhale more than the maximum dose of two 3mL bottles per administration.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Penthrox should not be used in children under 18 years.

This medicine can only be obtained with a prescription.
What benefits of Penthrox have been shown in studies?
The company, Medical Developments UK Limited, provided some data on efficacy and safety of methoxyflurane from its own prospective studies. In addition, data has been provided from the published literature on methoxyflurane. These studies have shown that Penthrox is effective in the proposed indication to reduce pain in adults 18 years and older.

What are the possible side effects of Penthrox?
Like all medicines, Penthrox can cause side effects although not everybody gets them.

Serious side effects
The patient should inform his/her healthcare professional immediately if any of the following side effects are experienced as they could be life-threatening:
• Serious allergic reaction, symptoms include difficulty breathing and/or swelling of the face
• Liver problems, such as loss of appetite, nausea, vomiting, jaundice (yellowing of the skin and/or eyes), dark coloured urine, pale coloured stools, pain/ache or sensitivity to touch in the right stomach area (below the ribs)
• Kidney problems such as reduced or excessive urination or swelling of feet or lower legs.

Common side effects (affects between 1 and 10 people in 100 patients)
• Dizziness
• Drowsiness
• Euphoria
• Difficulty in speaking
• Memory loss
• Anxiety or depression
• Taste disturbance, loss of taste or dry mouth
• Headache or nausea
• Numbness
• Low blood pressure
• Coughing
• Feeling drunk
• Sweating

For the full list of all side effects reported with Penthrox see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Penthrox.

Why is Penthrox approved?
It was concluded that, in accordance with EU requirements that, for Penthrox, its benefits are greater than the risks and it was recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Penthrox?
A Risk Management Plan (RMP) has been developed to ensure that Penthrox is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Penthrox, including the appropriate precautions to be followed by healthcare professionals and patients. In addition to the safety information provided in the Penthrox product information, the RMP includes educational activities/training and materials for healthcare professionals to ensure the safe and effective use of Penthrox. Materials for healthcare professionals are available on-line.
Known side effects will be continuously monitored in the post-marketing setting. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

The Applicant has committed to conduct a Post Authorisation Safety Study (PASS) to further monitor and evaluate the risks of unwanted effects on the liver, kidney and potential for abuse following methoxyflurane administration.

**Other information about Penthrox**
Belgium, France, Ireland and the UK agreed to grant a Marketing Authorisation for Penthrox on 15 April 2015. A Marketing Authorisation for Penthrox (PL 42467/0001) was granted in the UK to Medical Developments UK Limited on 27 October 2015.

The full PAR for Penthrox follows this summary.

For more information about treatment with Penthrox, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in February 2017.
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Scientific discussion

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for PENTHROX 3mL inhalation vapour, liquid (PL 42467/0001; UK/H/5542/001/DC) could be approved. The product will be referred to as ‘Penthrox’ in this report.

Penthrox is a prescription-only medicine (POM), which is indicated for the emergency relief of moderate to severe pain in conscious adult patients (aged 18 years and older) with trauma and associated pain. Penthrox is self-administered under the supervision (with assistance if necessary) of a healthcare professional using the hand-held Penthrox Inhaler. The healthcare professional must prepare the inhaler for use and give it to the patient. The proposed dosage regimen is one 3mL dose. A second 3mL bottle of methoxyflurane can be given to extend the period of pain relief. The maximum dose to be used is two bottles of 3mL, and this should not be exceeded.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Belgium, France and Ireland as Concerned Member States (CMS). The application was submitted under Article 8(3) of Directive 2001/83/EC, as amended, as a new active substance. Although methoxyflurane has previously been used in clinical practice, this is the first time that a Marketing Authorisation application has been submitted in the European Union.

Methoxyflurane was used in the 1960s as an anaesthetic, either as a sole agent or in combination with nitrous oxide. It was subsequently determined that methoxyflurane when administered in large doses (40-60 mL, at 0.16% minimum alveolar concentration) was associated with high output renal failure. As such methoxyflurane in anaesthesia is now medically contraindicated. However, in the late 1960’s significant analgesia was demonstrated with methoxyflurane at sub-anaesthetic doses (<15 mL) and was clinically used for this purpose. Penthrox is currently approved in Australia, New Zealand and a number of other countries. Penthrox has been used as an analgesic in Australia for more than 40 years.

The active substance, methoxyflurane, is a fluorinated hydrocarbon. The mode of action of methoxyflurane as an analgesic has not been defined in the literature, although a role for substance P and endogenous opioid peptides is hypothesised.

The non-clinical dossier is largely based on available data in the published literature, with three safety pharmacology studies and four genotoxicity studies being conducted in compliance with GLP by the Applicant. The GLP status of the literature studies cannot be verified.

The clinical dossier supporting this application consisted of three clinical studies (two studies on efficacy and one thorough QTc study), evidence from published literature and evidence of continued clinical use of this product in Australia. The Applicant sought scientific advice from the MHRA, Agence francaise de sécurité sanitaire des produits de santé (Afssaps), Agence fédérale des médicaments et des produits de santé (FAMHP) and the Paediatric Committee (PDCO) in the planning of the clinical studies.

The three clinical studies are stated to have been conducted in accordance with the current ICH – GCP guidelines and have complied with local guidelines, as appropriate. It is presumed that the literature-based studies, which cover a long period of time, were generally conducted in line with the prevailing standards at that time.
A modified Paediatric Investigation Plan (PIP) was agreed with the Paediatric Committee (PDCO) in November 2012. Development was waived in children less than 6 years of age on the grounds that Penthrox does not represent a significant therapeutic benefit over existing treatments. For children above 6 years of age, the applicant has committed to conducting two studies; one of which has been completed and submitted in support of this application. On assessment, it was concluded that this clinical study was not in accordance with the agreed PIP which precluded the MAH from claiming any benefits under the Paediatric regulation. The Applicant has committed to conduct the second study in a post-marketing setting in accordance with the agreed PIP.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates issued by the inspection services of the competent authorities of those countries with which the EEA has a Mutual Recognition Agreement for their own territories, as certification that acceptable standards of GMP are in place at those non-Community sites.

During assessment of the application the application was considered by the Committee on Human Medicines (CHM) at their meetings in November 2013 and December 2014. In response to the CHM advice, the applicant provided additional data and detailed clarification of the points that had been raised. The information provided was adequate and the outstanding points were resolved. The RMS and CMS considered that the application could be approved at the end of procedure on 15 April 2015.

Following the positive conclusion of the DCP, but prior to the grant of a Marketing Authorisation in the UK, the MHRA received communication from some stake-holders expressing concerns regarding the methodology used to calculate the safety margins for the exposure of methoxyflurane. Concerns were raised that the margin of safety was less than initially proposed based on the Applicant’s estimate of exposure using calculations of MAC-hours. In addition, there were concerns that certain sub-groups at risk of renal injury could have a lower threshold of exposure for nephrotoxicity. There were also concerns on risks of occupational exposure in confined areas.

The applicant responded to the above concerns prior to the grant of the Marketing Authorisation by submitting revised calculations which showed that a dose of 6 mL of Penthrox results in exposure of 0.59 MAC hours, as proposed during the initial application.

Following discussion and utilising several different methods of calculating the exposure, it was agreed that the initial safety margin for Penthrox (6 mL of Penthrox can produce a maximum of 0.59 MAC hours) was an appropriate estimate and that there is an adequate safety margin for nephrotoxicity based on the maximum dose of 6 mL (two bottles of 3mL each) per administration.
The Applicant addressed the stakeholders’ concerns to the satisfaction of the stakeholders as well as the RMS, and committed to submit a variation to add additional cautionary wording to the SmPC, PIL and training materials regarding the sub-groups with higher risk of nephrotoxicity. They also committed to include these sub-groups for specific monitoring and reporting in the Post-Approval Safety Study.

The assessment of the Applicant’s response to the above concerns was considered by the CHM at their meeting in October 2015. The committee concluded that the information provided was adequate and advised the grant of a Marketing Authorisation.

A Marketing Authorisation was granted in the UK on 27 October 2015.

II QUALITY ASPECTS

II.1 Introduction
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product, Penthrox, is a clear, almost colourless, volatile liquid (for oral inhalation), with a characteristic fruity odour.

Each bottle of Penthrox contains 3 mL of methoxyflurane 99.9%. Penthrox also contains butylated hydroxytoluene E321 (stabiliser). An appropriate justification for the inclusion of butylated hydroxytoluene E321 (stabiliser) has been provided.

The finished product is supplied in the following presentations:
1. 3 mL bottles with a tear off tamper-evident seal, in a pack size of ten bottles
2. combination packs with one 3 mL bottle, one Penthrox Inhaler and one Activated Carbon (AC) chamber, in pack sizes of 1 or 10 combination packs.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

Suppliers’ statements of compliance with current European regulations for plastic materials have also been provided for the Penthox Inhaler and the activated charcoal chamber.

II.2 DRUG SUBSTANCE

Methoxyflurane

INN: Methoxyflurane
Chemical Name: 2,2-dichloro-1,1-difluoroethyl methyl ether;
2,2-dichloro-1,1-difluoro-1-methoxyethane
Molecular Formula: C₉H₄Cl₂F₂O
Structure

\[ \text{\begin{tikzpicture}
  \node (o) at (0,0) [shape=circle,draw] {O};
  \node (h1) at (-0.3,0.3) [shape=circle,draw] {H};
  \node (cl1) at (-0.3,-0.3) [shape=circle,draw] {Cl};
  \node (h2) at (0.3,0.3) [shape=circle,draw] {H};
  \node (cl2) at (0.3,-0.3) [shape=circle,draw] {Cl};
  \node (f1) at (-0.6,0) [shape=circle,draw] {F};
  \node (f2) at (0.6,0) [shape=circle,draw] {F};
  \draw (o) -- (h1);
  \draw (o) -- (cl1);
  \draw (o) -- (h2);
  \draw (o) -- (cl2);
  \draw (o) -- (f1);
  \draw (o) -- (f2);
\end{tikzpicture}} \]

M: 164.97
Appearance: Clear, almost colourless mobile liquid, with a characteristic odour.
Solubility: Solubility of 1 in 500 of water and miscible with alcohol, acetone, chloroform and ether.

Methoxyflurane is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential and known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging. The primary packaging has been shown to comply with current guidelines concerning contact with food.

The stability of the active substance is satisfactory.

II.3 MEDICINAL PRODUCT

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable inhalation vapour liquid containing the active substance, methoxyflurane, that could be dispensed “as is” in small volumes (3mL) in amber Type I glass bottle with screw caps.

The sole excipient, butylated hydroxytoluene, complies with its European Pharmacopoeia monograph. A Satisfactory Certificate of Analysis has been provided for butylated hydroxytoluene, showing compliance with the proposed specification.
Neither the drug substance nor butylated hydroxytoluene contain any materials of animal or human origin and no genetically modified organisms (GMO) have been used in its preparation.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with production-scale batches and has shown satisfactory results.

**Control of Finished Product**
The finished product specification is acceptable. Test methods have been described and have been validated adequately. Batch data that comply with the release specification have been provided. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. Based on the results, a shelf-life of 36 months, with no special temperature storage conditions, has been accepted.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that a Marketing Authorisation is granted for Penthrox.

**III NON-CLINICAL ASPECTS**

**III.1 Introduction**
The non-clinical dossier is largely based on available data in the published literature with only three safety pharmacology studies and four genotoxicity studies being conducted by the Applicant. Given the extensive clinical experience with methoxyflurane as both an analgesic and anaesthetic, some omissions in non-clinical data can be accepted in line with the Guideline on the non-clinical documentation for mixed marketing authorisation applications (CPMP/ SWP/799/95). Areas that generally cannot be addressed by human data such as data on reproduction and developmental toxicity and genotoxicity data have been provided. The Non-clinical Overview covers all expected Module 4 headings and justifies the absence of any specific type of data.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

**III.2 Pharmacology**
Methoxyflurane has been used clinically for a number of years as both an analgesic and anaesthetic agent, with established efficacy. No new primary or secondary pharmacology studies have been submitted in support of this application and there is a paucity of relevant data in the literature to characterise the mechanism of action of methoxyflurane. The Applicant has postulated that the analgesic effect of methoxyflurane is related to a reduction in substance P. While methoxyflurane is considered as a new active
substance in Europe, the extensive clinical experience with this active substance in other countries in the acute management of pain is considered supportive. It is considered that conducting studies in anti-nociceptive animal models or mechanistic studies is not warranted.

Data from both newly conducted and literature safety pharmacology studies do not indicate that methoxyflurane will have an effect on vital organs at the proposed clinical dose. Results of a thorough QT study in man (See Section IV.5, Clinical Safety) provide further reassurance in this respect.

### III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies have been conducted in support of this application. Based on available literature data, methoxyflurane is highly lipid soluble, rapidly absorbed on inhalation administration and widely distributed. Methoxyflurane crosses the placenta and blood brain barrier.

Two routes of metabolism have been identified for methoxyflurane, O-demethylation and dechlorination. Metabolism is primarily mediated by CYP 2E1. Clinical literature data estimate the extent of elimination by metabolism to be approximately 75% of the dose. In rats, the major routes of elimination were found to be urine and expired air. No information on excretion in milk has been provided. The Applicant states that based on the solubility characteristics of methoxyflurane, transfer into milk cannot be excluded.

Age-dependent differences in the pharmacokinetic profile of methoxyflurane have been reported in rats, with a slower clearance observed in older rats.

Limited pharmacokinetic interaction data from the literature have been presented which highlight the risk of increased toxicity on enhanced metabolism of methoxyflurane.

While it is acknowledged that there is a paucity of non-clinical pharmacokinetic (PK) data, the PK profile of methoxyflurane has been reasonably characterised in man following years of clinical use. These data supersede non-clinical data and negate the need for further non-clinical studies as laid out in the Guideline on the non-clinical documentation for mixed marketing authorisation applications (CPMP/SWP/799/95).

### III.4 Toxicology

With the exception of four genotoxicity studies, no new toxicity studies were conducted in support of this application.

In published acute toxicity studies in mice and rats using high anaesthetic doses the target organ was found to be the kidney. This effect is well known with this active substance and is in line with effects seen in man resulting in the discontinuation of the use of methoxyflurane as an anaesthetic. Sensitivity to renal toxicity of methoxyflurane was found to be strain- and species-dependent, with Fischer 344 rats being the most sensitive. The induction of renal toxicity does not appear to be a common property of halogenated anaesthetics as no effect on renal functional parameters and no histopathological changes in kidney were seen in literature studies with halothane and isoflurane.

Mechanistic toxicity studies in Fischer 344 rats have attributed the renal toxicity to the fluoride metabolite with potential contribution from the dichloroacetic acid metabolite. The identified effects of methoxyflurane on renal blood flow are likely to affect the clearance of these metabolites, thus accounting for the difference between this active substance and other halogenated anesthetics.
In 7-week repeat-dose toxicity studies in rats, guinea pigs and rabbits using subanaesthetic doses (200 ppm) of methoxyflurane for 7h/day for 5 days/week no renal effects were seen. On repeated administration of lower doses the liver appears to be the target organ in all species tested with effects including fatty metamorphosis, foci of hepatocellular degeneration and necrosis, elevation of serum ALT and AST and reduced levels of hepatic CYP450 levels. In rats all of these effects, except the presence of fat in the liver, were still apparent following a 4-week recovery period. A No Observed Adverse Effect level (NOAEL) for the hepatic effects has not been established which is of concern, especially given that hepatic effects have been seen in man.

Given the lack of a NOAEL for hepatic effects in all species in repeated-dose toxicity studies and very small safety margins based on dose, the Applicant provided additional discussion of the potential mechanism behind the liver toxicity in order to decipher the clinical relevance of this finding, inform the risk:benefit analysis and aid risk minimisation. This highlighted that the exposures and dosing duration in the cited toxicity studies in which hepatotoxicity was seen were considerably more extreme than can be expected through normal clinical use of the proposed product. As these data were used to calculate safety margins, it is agreed that the use of these to form any conclusions on clinical relevance may not be appropriate. The SmPC has been revised to include the hepatotoxicity findings.

No toxicological information was provided for the excipient butylated hydroxytoluene (BHT), and the Applicant was asked to provide this and to confirm whether BHT is commonly used in inhaled products and comment on the potential for local toxicity. In response, the Applicant has provided an appropriate risk assessment for inhalational exposure to BHT. Using a worst-case scenario, the amount of BHT that will be inhaled through clinical use of the Penthrox product is well below published safe limits. No further toxicological qualification is required.

Three in vitro (Ames) and one in vivo genotoxicity (micronucleus) study have been conducted by the Applicant to supplement the available literature data published in 1970s and 80s. Based on a weight of evidence approach, methoxyflurane is not considered to be genotoxic.

No carcinogenicity data has been generated in support of this application or found in the literature. Data from short-term studies conducted in the 1970s have been presented although important details are lacking and consequently it is difficult to garner any useful information on the carcinogenic risk of methoxyflurane. However, based on the proposed indication, this product is not likely to be used for more than 6 months continuously and in line with ICH S1A it is considered that long term carcinogenicity studies are not warranted and the lack of reliable carcinogenicity data in the literature is acceptable in this instance.

There is a paucity of data on the effect of methoxyflurane on fertility, however no further studies are considered necessary in line with the Guideline on the non-clinical documentation for mixed Marketing Authorisation applications (CPMP/SWP/799/95) which states that investigations regarding fertility and general reproductive performance are generally not necessary for active substances with substantial clinical experience unless there is cause for concern.

In literature 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. The NOAEL for embryo-fetal development was 60 ppm - 4h/day in mice (GD6-GD15) and close to 0.01% - 8 h/day in rats (throughout gestation). 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/m² basis versus the proposed maximum clinical dose. The effects on embryo-fetal development were seen following
repeated dosing over 9 days, and considering that Penthrox is not intended for daily use, the risk of delayed fetal development is considered very low. These findings have, however, been included in section 5.3 of the SmPC, and section 4.6 of the SmPC reflects the available clinical and non-clinical data as outlined in the SmPC guideline and the Guideline on risk assessment of medicinal products on human reproduction and lactation: From data to labelling (EMEA/CHMP/203927/2005).

No pre or post-natal development data with methoxyflurane has been presented. No effects were seen on a number of relevant endpoints in a short-term carcinogenicity study where methoxyflurane was dosed to pregnant mice and eventually their offspring for up to 10 weeks. Given that there is clinical information following use of this drug as an anaesthetic in obstetrics, it is unlikely that the generation of further non-clinical pre or post-natal data will help inform the benefit:risk analysis and as such no further studies are requested. As excretion of methoxyflurane into milk cannot be excluded, section 4.6 of the SmPC has been adequately revised.

No new juvenile toxicity studies have been conducted in support of this application. In the UK, the product is only indicated for use in adults aged 18 years and over. Two studies published in the 1970s in which anaesthetic doses of methoxyflurane were used have been described. No effect was seen on pup bodyweight or survival in mice aged 5 days to 10 weeks following inhalation of methoxyflurane 0.125% for 2 h/day. In a second study in rats aged between 6-weeks and 12-months, expected renal effects were seen in rats >3 months of age following a single dose of methoxyflurane at 0.5% over 2 h. An increase in sensitivity to renal changes correlated with an increase in age. This trend was attributed to age-related differences in clearance. The NOAEL for renal toxicity in 6-week old rats was the only dose tested, 0.5% for 2 hours.

Data on structurally similar compounds has identified genotoxic potential possibly through formation of a reactive epoxide. However, a thorough toxicological evaluation of process impurities concluded that none of the impurities were considered to be genotoxic or mutagenic. This conclusion has been based on a comprehensive risk assessment of structurally similar compounds and lack of apparent direct alkylating potential based on the chemical structure.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP/4447/00 Corr 2], the Applicant submitted an Environmental Risk Assessment (ERA) for methoxyflurane.

The published log n-octanol/water partition coefficient (logK_{ow}) value for methoxyflurane is below the guidance lower limit value of 4.5 and therefore methoxyflurane is unlikely to be a persistent, bioaccumulative, toxic (PBT) substance. In the Phase I assessment, the Predicted Environmental Concentration_{surfacewater} (PEC_{sw}) value (0.117 μg/l) for methoxyflurane, calculated using a maximum daily dose of methoxyflurane consumed per inhabitant (DOSE_{ai}) of 23.5 mg and the default values for fraction of market penetration (F_{pen}), amount of wastewater per inhabitant per day (WASTEW_{inhab}) and dilution factor (DILUTION) results, was above the the threshold (0.01 μg/L) triggering a Phase II ERA.

Considering metabolism and route of administration for this product, an overestimation of PEC_{surfacewater} is not likely. The main metabolites of methoxyflurane have been classified and characterised under REACH (EU Regulation 1907/2006). In addition, based on physicochemical information it is unlikely that unchanged methoxyflurane would remain in the aqueous environment.
It is concluded that Penthrox is of negligible risk to the environment when used in accordance with the product information.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Penthrox.

IV. CLINICAL ASPECTS
IV.1 Introduction
The application for Penthrox was submitted under Article 8.3 of Directive 2001/83/EC, as amended, as a new active substance application.

To support this mixed dossier application, the Applicant provided the following:
   a) Three clinical studies submitted by the Applicant – two studies on efficacy/safety and one safety study evaluating effects of methoxyflurane on thorough QTc.
   b) Substantial evidence from published literature to support efficacy and safety of methoxyflurane in the proposed dose and method of use.
   c) Evidence of its clinical use in Australia for a number of years.

The Applicant’s clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics
No new clinical pharmacokinetic studies have been provided by the Applicant and none are required. The pharmacokinetics of methoxyflurane is based on published literature. The available pharmacokinetic data from published literature is considered adequate to support the proposed use of methoxyflurane. A brief summary of the pharmacokinetic characteristics of methoxyflurane as presented by the Applicant is given below:

Methoxyflurane is a clear, colourless, fruity-smelling liquid. Methoxyflurane has a low saturation vapour pressure at ambient temperatures (25 mm Hg at 20°C); therefore the maximum concentration attainable is approximately 3%. Methoxyflurane enters the lungs in the form of a vapour and is rapidly transported into the blood/systemic circulation; therefore there is a rapid onset of analgesic action. With continued inhalation of methoxyflurane for short periods of time (around 1 hour) of a given concentration by a conscious patient, there is no accumulation in blood over time as reported from studies. This is largely because the ventilation rate and depth is altered with the analgesic dose resulting in correction of the hyperventilation stage associated with pain. However when methoxyflurane is administered in the anaesthetic setting, there is an increase in systemic exposure with continued administration.

The blood/gas coefficient shows that methoxyflurane is highly lipophilic. Methoxyflurane has a great propensity to diffuse into fatty tissues where it forms a reservoir from which it is released slowly over many days.

Biotransformation of methoxyflurane occurs in man. Methoxyflurane is metabolised via two main pathways, O-demethylation and dechlorination (Figure 2.5.3-1). The dechlorination pathway leads to the formation of methoxydifluoroacetate, in addition to chloride, fluoride and oxalate. The O-demethylation pathway produces formaldehyde, fluoride and dichloroacetate. Dichloroacetate is further metabolised to oxalate and other products.
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 achieved with analgesic dose use. The nephrotoxicity associated with inorganic fluoride has been demonstrated to be dose related. MAC is the minimum alveolar concentration to produce surgical anaesthesia in 50% of healthy patients. A more useful term is the MAC hours, which takes into account a duration of anaesthesia of one hour. For reference, the MAC for methoxyflurane is 0.16%, which led to peak serum inorganic fluoride levels of <40 μmol/L which was not associated with nephrotoxicity. The mean threshold of subclinical toxicity was approximately 2.5-3.0 MAC hours, corresponding to a peak serum inorganic fluoride level of 50-80 μmol/L. Clinical toxicity was present in all patients at dosages >5.0 MAC hours, corresponding to a peak serum inorganic fluoride level of >90 μmol/L. The proposed maximum dose/day for the analgesic use is 6 ml of methoxyflurane which corresponds to an estimated 0.59 MAC hours, which is below the threshold of concern for nephrotoxicity.

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. 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.

The literature provides data on the pharmacokinetic profile of methoxyflurane in children and the obese. Specific detailed pharmacokinetic data in the elderly, patients with hepatic or renal failure are not available. From a published study which compared the systemic serum fluoride concentrations in adults and children after treatment with methoxyflurane, it was noted that the levels were lower in children as compared to adults at all time points. This could be due to lower levels entering the systemic circulation or lower metabolism rate. It has been reported that the systemic levels of the harmful metabolite, serum fluoride is higher in the obese individuals as compared to individuals of normal weight.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted in support of this application and none were required as the pharmacodynamic properties of methoxyflurane are well-known. The Applicant has submitted pharmacodynamic data from the literature in support of the application. A brief summary of the pharmacodynamic characteristics of methoxyflurane as presented by the Applicant is given below.

The mode of action of methoxyflurane as an analgesic has not been defined in the literature, although a role for substance P and endogenous opioid peptides is hypothesised.

Analgesia with methoxyflurane occurs at low (sub-anaesthetic) doses. The average blood level of methoxyflurane producing analgesia is lower than the blood levels required for anaesthesia. Methoxyflurane related nephrotoxicity is dose-dependent. For many years it was postulated that methoxyflurane was linked to nephrotoxicity due to increased plasma fluoride concentrations resulting from its metabolism. However, recent evidence has suggested that the co-formation of fluoride and dichloroacetate was more toxic than fluoride alone.

Methoxyflurane administered at doses below 2 MAC hours results in peak serum inorganic fluoride levels of <40 μmol/L, a level that is not associated with subclinical or clinical nephrotoxicity. It has been reported that when methoxyflurane was used as an anaesthetic agent, subclinical but reversible renal toxicity was occasionally detected by changes in biochemical parameters at 2.5-3.0 MAC hours, corresponding to a peak
serum inorganic fluoride ion concentration of 50-80 μmol/L. In administrations lasting longer than 5.0 MAC hours, evidence of clinical toxicity progressing through to irreversible clinical situations was noted, corresponding to a peak serum inorganic fluoride level of >90 μmol/L. By way of comparison, the maximum achievable concentration of methoxyflurane used for analgesia is 0.59 MAC hours, well below the level of 2 MAC hours which may cause subclinical toxicity.

The literature evidence confirms the low levels of inorganic fluoride (in most cases less than half the 50 μmol/L level associated with subclinical toxicity) associated with the lower doses of methoxyflurane used for analgesia. Where methoxyflurane administration was reported in two patients to be associated with higher inorganic fluoride levels (>50 μmol/L), there was no clinical or laboratory evidence of renal dysfunction. The Applicant notes that analgesic doses of methoxyflurane have been reported with fluoride levels of 20-40 μmol/L.

Evidence from studies in humans suggests that the mechanism of action may involve drowsiness and an altered perception of pain to reduce suffering. “Mood-modifying” effects have also been reported in conjunction with analgesia, including sedation, tranquillity, dissociation from the surroundings and/or amnesia. Methoxyflurane is also reported to impair the ability to concentrate and affect time perception and has demonstrated effects on sensorimotor co-ordination in healthy volunteers lasting up to 2 hours after inhalation.

At analgesic concentrations of methoxyflurane there is no clinical depression of respiration or circulation. In a retrospective observational study (Penthrox Vital Signs Report) nearly all patients (>95%) both before and after Penthrox administration had levels of systolic blood pressure within normal limits. The proportion of patients that had abnormal values (both above and below normal levels) decreased after Penthrox administration, and there was no indication that Penthrox inhalation increased the probability of exhibiting abnormal systolic blood pressure.

There are no reported drug interactions of clinical significance when methoxyflurane has been used at analgesic doses. However when used at the higher anaesthetic doses, there are some reports of drug interaction with:

a) Hepatic inducers increasing nephrotoxicity of methoxyflurane
b) Reduction of renal blood flow and hence anticipated enhanced effect when used in combination with drugs reducing cardiac output
c) Class effect on cardiac depression which may be enhanced by other cardiac depressant drugs.

In addition, there are other effects on respiratory depression and general central nervous system effects which can be additive.

The known effects of methoxyflurane are important information for the prescriber and the user and though it is acknowledged that these effects are unlikely to occur at the analgesic doses, the potential for such interactions occurring and for such reactions being significant at higher doses have been included in the SmPC.

**IV.4 Clinical Efficacy**

To support the application, the following were submitted:

a) Three clinical studies—two studies on efficacy.
b) Substantial evidence from published literature to support efficacy and safety of methoxyflurane in the proposed dose and method of use.

c) Evidence of its clinical use in Australia for a number of years.

The evidence from the clinical studies was submitted to establish methoxyflurane’s analgesic activity. The Applicant’s studies do not per-se establish the appropriate setting in which methoxyflurane is to be used. To substantiate the relevance of methoxyflurane both in a hospital and pre-hospital setting, the Applicant has provided evidence of clinical use (in the form of publications, hospital guidelines, ambulance guidelines and treatment protocols) of methoxyflurane.

**Efficacy Study 1**

**Methods**
A randomised, double blind, multi-centre, placebo controlled study of methoxyflurane (Penthrox) for the treatment of acute pain in patients presenting to an Emergency Department with minor trauma. Treatment with methoxyflurane was only administered prior to treating the injury. Patients were followed up two weeks after receiving study treatment for safety. The study is summarised below.

**Study Participants**
Patients aged 12 years and older with a pain score between 4 and 7 on a numerical rating scale due to minor trauma were randomised in a 1:1 ratio to methoxyflurane or placebo. Randomisation was stratified by centre and age group (adolescent or adult). 300 patients were randomised: 151 to methoxyflurane and 149 to placebo, of whom two in the active arm did not receive study treatment.

**Treatments**
Methoxyflurane was delivered in a Penthrox inhaler in a 3mL dose. Placebo (5mL normal saline) was also delivered in a Penthrox inhaler. As methoxyflurane has a distinctive smell, a drop of methoxyflurane was added to the outside of the placebo packets to maintain the blinding for patients and treating doctors and nurses. As the treatment was self-administered, patients could request a second inhaler if the first had run out.

**Rescue medication**
Rescue medication was available to all patients upon request at any time during and after treatment with the study medication. Rescue medications available for administration included:

- Intravenous, intranasal or oral opioids or paracetamol, which would be allowed while the patient was in the Emergency Department (ED). These medications could be initiated by the investigator prophylactically if, for example, the patient was about to have a painful experience;

- Following discharge from the ED, patients were supplied with 16 x 500 mg paracetamol tablets to treat their pain. Patients were instructed to return to their healthcare provider if their pain persisted after discharge, or if unexpected pain occurred.

**Outcomes/endpoints**

**Primary endpoint**
The primary endpoint was defined as the change in pain intensity VAS (Visual Analogue Scale) score from baseline to 5, 10, 15 and 20 minutes after the commencement of study drug inhalation and was analysed using repeated measures analysis.
Secondary endpoints
The secondary endpoints included amongst others:

- Use of rescue medication (requested by the patient) within 20 minutes of start of treatment (yes/no)
- Time from start of treatment to first request for rescue medication
- Time from the start of treatment to first pain relief (without rescue medication before the pain relief)
- The number of inhalations taken before first pain relief
- The number and percentage of responders at each assessment

Results
Primary endpoint
The primary efficacy variable was the VAS pain intensity. All efficacy analyses are presented using the Intent-to-Treat (ITT) population. The Intention-to-Treat (ITT) Population was defined as those patients in the Safety Population who had at least one post-baseline efficacy assessment. Patients who received the wrong treatment in error were analysed as randomised. The results for the primary endpoint are summarised in the table below:

<table>
<thead>
<tr>
<th>Adjusted* change from baseline</th>
<th>Methoxyflurane (N=149)</th>
<th>Placebo (N=149)</th>
<th>Estimated Treatment Effect (95% Confidence Interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>-30.2</td>
<td>-15.2</td>
<td>-15.1 (-19.2, -11.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5 mins</td>
<td>-23.1</td>
<td>-11.3</td>
<td>-11.8 (-15.6, -8.0)</td>
<td></td>
</tr>
<tr>
<td>10 mins</td>
<td>-28.9</td>
<td>-14.8</td>
<td>-14.1 (-18.4, -9.8)</td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>-34.0</td>
<td>-15.5</td>
<td>-18.5 (-23.4, -13.5)</td>
<td></td>
</tr>
<tr>
<td>20 mins</td>
<td>-35.0</td>
<td>-19.0</td>
<td>-16 (-21.3, -10.7)</td>
<td></td>
</tr>
</tbody>
</table>

N=Number of patients.
* Adjusted for baseline pain score and age group (adolescent/adult).
Pain scores recorded following the start of the planned ED procedure have been excluded from the analysis.
Pain scores taken after initiation of rescue medication have been included in the analysis.

The results in this study showed that overall change from baseline in the methoxyflurane arm was -30.2 as compared to -15.2 in the placebo arm. The estimated treatment difference of -15.1 (95% CI -19.2 -11.0) was statistically significant. The difference between treatments, even at the first time-point of assessment (5min), suggests a quick onset of treatment effect.

The proportion of patients with a 30% improvement from baseline was also significantly more in the methoxyflurane group (52.8 – 76.1%) as compared to placebo (24.5 – 43%) at all evaluated time-points (See Table 11.46 below).
The results on the primary endpoint indicate there is a significant and clinically relevant (beneficial) effect on pain reduction by methoxyflurane as compared to the placebo.

Some trial participants gave pain scores at time points beyond 20 minutes and these contribute to the difference between the overall estimate and the estimate at 20 minutes.

By 20 minutes, approximately 21% of the methoxyflurane group and 24% of the placebo group had missing values for the primary endpoint (see the denominator column in Table 11-46 below). It is understood from the data listings that many of these patients underwent their ED procedure before they had been on study treatment for 20 minutes and it is then correct that pain measurements after the start of the ED procedure are not included in the primary analysis. There were a small number of patients who did not have pain scores to 20 minutes because the study staff at the site failed to record the pain scores. These are unlikely to impact significantly on the conclusions drawn from this study.

Dropout rates were similar between the groups at 10, 15 and 20 minutes. On request, the Applicant provided tabulated data that showed that the numbers and reasons for missing data were balanced between the treatment groups.

A number of sensitivity analyses were conducted that were supportive. In particular, when pain scores following rescue medication were imputed with the value 100, representing “worst pain possible”, the difference between methoxyflurane was maintained. These results are shown in the table below (Table 11-21).

Table 11-21: Analysis of Visual Analogue Scale (VAS): Scores following Rescue Medication imputed as 100: Adjusted Change from Baseline (ITT Population)

<table>
<thead>
<tr>
<th>Adjusted* change from baseline</th>
<th>Methoxyflurane (N=149)</th>
<th>Placebo (N=149)</th>
<th>Estimated Treatment Effect (95% Confidence Interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>-30.2</td>
<td>11.9</td>
<td>-18.3 (12.9, 13.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5 mins</td>
<td>-23.2</td>
<td>-11.1</td>
<td>12 (15.9, -8.2)</td>
<td></td>
</tr>
<tr>
<td>10 mins</td>
<td>-29</td>
<td>13</td>
<td>16 (20.6, -11.3)</td>
<td></td>
</tr>
<tr>
<td>15 mins</td>
<td>-33.8</td>
<td>-11.5</td>
<td>22.3 (28.9, 16.5)</td>
<td></td>
</tr>
<tr>
<td>20 mins</td>
<td>-34.8</td>
<td>11.8</td>
<td>23 (29.5, -16.6)</td>
<td></td>
</tr>
<tr>
<td>Time by treatment interaction</td>
<td></td>
<td></td>
<td>0.0003</td>
<td></td>
</tr>
</tbody>
</table>

N=Number of patients.

* Adjusted for baseline pain score and age group (adolescent/adult).

Pain scores recorded following the start of the planned ED procedure have been excluded from the analysis.

Pain scores taken after initiation of rescue medication have been imputed as 100 in the analysis.
Secondary endpoints
Rescue medication
The results for the use of rescue medication (requested by the patient within 20 minutes of the start of study treatment) in the intent-to treat population are shown in the table below:

<table>
<thead>
<tr>
<th>Table 11-25: Use of Rescue Medication (ITT Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxyflurane (N=149)</td>
</tr>
<tr>
<td>Adjusted¹ logistic regression analysis</td>
</tr>
<tr>
<td>95% confidence interval</td>
</tr>
<tr>
<td>p-value (Wald)</td>
</tr>
<tr>
<td>Rescue medication used²</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

N=Number of patients.
¹: Adjusted for baseline pain score and age group (adolescent/adult).
²: Rescue medication requested by the patient within 20 mins of start of treatment.

The use of rescue medication is a good marker of efficacy and the results demonstrate that, statistically, significantly fewer patients in the methoxyflurane group requested rescue medication within 20 minutes of the start of treatment than in the placebo arm.

Time to request for rescue medication
The adjusted Cox regression analysis (in which scores were adjusted for baseline pain score and age group) showed that the difference between the methoxyflurane and placebo group in the probability of requesting rescue medication, resulted in a hazard ratio of 0.24. There was a significant difference (p<0.0001; 95% CI 0.13 to 0.44) between the methoxyflurane and placebo group. In the Kaplan-Meier estimate, times were censored at the soonest of: 2 hours from start of treatment, investigator initiated rescue medication, start of treatment for the injury or early withdrawal. The number of patients who requested rescue medication prior to censoring in the methoxyflurane group (14 patients; 9.4%) was lower than that of the placebo group (42 patients; 28.2%).

Time to first pain relief
The adjusted Cox regression analysis (in which scores were adjusted for baseline pain score and age group) showed that the difference between the methoxyflurane and placebo group in the probability of having pain relief, resulted in a hazard ratio of 2.35. There was a significant difference (p<0.0001; 95% CI 1.77 to 3.10) between the methoxyflurane and placebo group.

In the Kaplan-Meier estimate, times were censored at the soonest of: 2 hours from start of treatment, investigator initiated rescue medication, start of treatment for the injury or early withdrawal. The number of patients who experienced pain relief prior to censoring was higher in the methoxyflurane group (130 patients; 87.2%) compared to the placebo group (92 patients; 61.7%). The number of patients who did not experience any pain relief prior to censoring was lower in the methoxyflurane group (19 patients; 12.8%) in comparison to the placebo group (57 patients; 38.3%). Half of the patients in methoxyflurane group experienced pain relief by 4 minutes in comparison to 10 minutes in the placebo group. The majority of
patients in the methoxyflurane group experienced pain relief prior to the censored time point and the time to first pain relief was shorter than that of the placebo group. The median time for the methoxyflurane group of 4 minutes (95% CI: 2.0, 5.0) was lower in comparison to the placebo group of 10 minutes (95% CI: 5.0, 12.0).

**Inhalations to first pain relief**
The number of inhalations prior to the first pain relief is presented in the table below (Table 11-41):

<table>
<thead>
<tr>
<th>Number of inhalations</th>
<th>Methoxyflurane (N=149)</th>
<th>Placebo (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 to 10</td>
<td>126 (84.6%)</td>
<td>76 (51.0%)</td>
</tr>
<tr>
<td>11 to 20</td>
<td>6 (4.0%)</td>
<td>11 (7.4%)</td>
</tr>
<tr>
<td>21 to 30</td>
<td>1 (0.7%)</td>
<td>3 (2.0%)</td>
</tr>
<tr>
<td>More than 30</td>
<td>0</td>
<td>3 (2.0%)</td>
</tr>
<tr>
<td>No relief without rescue medication</td>
<td>16 (10.7%)</td>
<td>56 (37.6%)</td>
</tr>
</tbody>
</table>

N=Number of patients.

For the majority of patients receiving pain relief in the methoxyflurane group, pain relief was achieved in fewer than 10 inhalations. This suggests a very quick onset of action.

To use this data from a safety perspective, one would need the duration for which the efficacy was maintained after cessation of treatment. The Applicant was asked to discuss if the duration of maintenance of efficacy after discontinuation could be inferred from the study as it is noted that VAS (Visual Analogue Scale) assessments were planned till discharge or other treatment intervention. However, no relevant data was collected and hence any meaningful conclusions on the maintenance of efficacy after cessation of administration of methoxyflurane are not possible based on the results of this study.

**Response rates**
The number and percentage of responders (achieving the listed percentage reduction in their VAS pain score compared to baseline) in the ITT Population at each assessment is presented in the table below (Table 11.46). Any VAS pain scores recorded following the start of a planned ED procedure were excluded from this analysis.
Responders were considered to be patients who experienced at least a 30% improvement from baseline VAS pain score. The results in the table indicated that response rates were higher in the methoxyflurane arm than the placebo arm, even with missing responses counted as failures. Counting missing responses as failures in this case penalises patients who had missing values (for this analysis) because of the start of the ED procedure too harshly. Therefore, it would be reasonable to use a Last Observation Carried Forward (LOCF) approach for those patients and a “missing equals failure” approach for patients who have missing data for other reasons.

The Applicant provided adjusted odds ratios and 95% confidence intervals for response rates at 5, 10, 15 and 20 minutes, where a responder was defined as a patient who experienced at least a 30% improvement from baseline VAS pain score. Patients with missing values because of the start of their ED procedure were to be treated as responders if they were a responder at the last available timepoint before the start of the ED procedure. Patients with missing values for other reasons were to be treated as failures. The results of these analyses showed that there is a statistically significant benefit of Penthrox over placebo in response rate at each timepoint.

Table 11-46: Response Rates (ITT Population)

<table>
<thead>
<tr>
<th>Improvement in VAS Score</th>
<th>Denominator</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxyflurane (N=149)</td>
<td>N</td>
<td>109</td>
<td>89</td>
<td>76</td>
<td>57</td>
<td>41</td>
<td>26</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>144</td>
<td>75.7</td>
<td>61.8</td>
<td>52.8</td>
<td>39.6</td>
<td>28.5</td>
<td>18.1</td>
<td>10.4</td>
<td>7.6</td>
<td>6.3</td>
</tr>
<tr>
<td>5 mins</td>
<td>N</td>
<td>111</td>
<td>99</td>
<td>85</td>
<td>72</td>
<td>56</td>
<td>39</td>
<td>24</td>
<td>15</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>133</td>
<td>83.5</td>
<td>74.4</td>
<td>63.9</td>
<td>54.1</td>
<td>42.1</td>
<td>29.3</td>
<td>18.1</td>
<td>11.3</td>
<td>7.5</td>
</tr>
<tr>
<td>10 mins</td>
<td>N</td>
<td>108</td>
<td>97</td>
<td>89</td>
<td>76</td>
<td>63</td>
<td>50</td>
<td>32</td>
<td>25</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>124</td>
<td>87.1</td>
<td>78.2</td>
<td>71.8</td>
<td>61.3</td>
<td>50.8</td>
<td>40.3</td>
<td>25.8</td>
<td>20.2</td>
<td>13.7</td>
</tr>
<tr>
<td>15 mins</td>
<td>N</td>
<td>102</td>
<td>97</td>
<td>89</td>
<td>83</td>
<td>69</td>
<td>53</td>
<td>36</td>
<td>24</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>117</td>
<td>87.2</td>
<td>82.9</td>
<td>76.1</td>
<td>70.9</td>
<td>59</td>
<td>45.3</td>
<td>30.8</td>
<td>20.5</td>
<td>13.7</td>
</tr>
<tr>
<td>20 mins</td>
<td>N</td>
<td>72</td>
<td>51</td>
<td>35</td>
<td>19</td>
<td>12</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>143</td>
<td>50.3</td>
<td>35.7</td>
<td>24.5</td>
<td>13.3</td>
<td>8.4</td>
<td>5.6</td>
<td>2.1</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Placebo (N=149)</td>
<td>N</td>
<td>75</td>
<td>58</td>
<td>46</td>
<td>33</td>
<td>25</td>
<td>13</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>133</td>
<td>56.4</td>
<td>43.6</td>
<td>34.6</td>
<td>24.8</td>
<td>18.8</td>
<td>9.8</td>
<td>5.3</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>10 mins</td>
<td>N</td>
<td>72</td>
<td>55</td>
<td>47</td>
<td>38</td>
<td>27</td>
<td>17</td>
<td>9</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>122</td>
<td>59</td>
<td>45.1</td>
<td>38.5</td>
<td>31.1</td>
<td>22.1</td>
<td>13.9</td>
<td>7.4</td>
<td>4.9</td>
<td>4.1</td>
</tr>
<tr>
<td>15 mins</td>
<td>N</td>
<td>74</td>
<td>62</td>
<td>49</td>
<td>42</td>
<td>33</td>
<td>19</td>
<td>12</td>
<td>10</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>114</td>
<td>64.9</td>
<td>54.4</td>
<td>43.0</td>
<td>36.8</td>
<td>28.9</td>
<td>21.7</td>
<td>10.5</td>
<td>8.8</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Any VAS scores recorded following the start of the planned ED procedure are excluded from this summary.
Overall conclusion of Efficacy Study 1
The results presented show that methoxyflurane is effective when compared to placebo at providing short-term pain relief in patients with injuries who are in moderate pain. The overall mean difference in change from baseline in VAS pain score according to the primary analysis was -15.1 mm (95% CI -19.2 – -11.0) in favour of methoxyflurane. Rescue medication was only requested by 2 patients in the methoxyflurane arm compared to 25 in the placebo arm. Response rates were also greater in the methoxyflurane arm.

All the secondary endpoints and ancillary analyses were supportive of the inferences drawn from the primary endpoint regarding the analgesic efficacy of methoxyflurane. The responder analysis showed a clear clinically relevant analgesic effect for methoxyflurane as compared to placebo. Generally a 30% improvement on VAS is considered an appropriate measure to compare and for this comparison the response rates for methoxyflurane ranges from 52.8-76.1% as compared to the placebo 24.5-43% dependent on the time point of assessment.

The results showed that there is a difference between treatments even at the first time-point of assessment (5 min), suggesting that the onset of treatment effect is rapid.

This study conclusively showed that methoxyflurane has analgesic efficacy and is appropriate for providing quick emergency relief from pain. It was anticipated that the duration of pain relief with Penthrox will be short and, in any case, the study evaluated effect on pain for up to 20 minutes only. Therefore, it can only be inferred that the pain relief is provided for a short duration while methoxyflurane is being inhaled. As there are limitations with the total dose that can be administered per day (6mL/day), this means that at the maximum dose methoxyflurane inhalation can provide up to 1 hour of pain relief if inhaled continuously.

This study provides evidence that methoxyflurane, used as proposed, has an analgesic effect.

Efficacy Study 2
A randomised, double-blind and placebo-controlled study, conducted in a single centre with the aim of assessing the efficacy and safety of Penthrox as an analgesic for incident pain in subjects requiring analgesia while undergoing a planned bone marrow biopsy (BMB) procedure.

Aim
To investigate the administration of methoxyflurane in adults, at analgesic doses, with the Penthrox Inhaler.

Study treatments
The Penthrox Inhalers were loaded in the pharmacy with either a one dose (3mL) vial of methoxyflurane or placebo (sterile normal saline), and the weight recorded no more than 4 hours prior to commencement of BMB. The loaded inhaler was then sealed into a plastic bag, labelled with the appropriate randomisation code from the randomisation chart, and taken to the treatment area for use by the subject. Due to the distinctive smell of methoxyflurane, a drop of methoxyflurane was added to each bag prior to it being sealed, in order to maintain the blind. As treatment was self-administered the amount of methoxyflurane or placebo inhaled was subject controlled and therefore no standard dose was administered. Following its use, the inhaler was returned to the pharmacy and re-weighed within 4 hours to determine the dose by weight of methoxyflurane inhaled by the subject.
Patients
100 adult patients from a single centre were assigned to receive either methoxyflurane or placebo using the adaptive biased coin method.

Data sets analysed
Three subjects withdrew before undergoing the BMB procedure and were consequently excluded from the final analysis. Therefore, 49 patients in the methoxyflurane arm and 48 patients in the placebo arm were included in the analysis.

Results
Primary endpoint
Worst pain overall was 4.9 in the methoxyflurane group and 6.0 in the placebo group, giving a difference of 1.1 on the 11-point numerical rating scale. (p=0.011).

Secondary endpoints
Use of rescue medication
Only one patient in the placebo arm used rescue medication and no patients in the methoxyflurane arm used rescue medication during the procedure.

Subject global medication performance assessment
There was a significant statistical difference in subjects’ rating between the different arms of the study (p = 0.005); medication was globally better rated by subjects in the methoxyflurane arm (see Table 12-4 below).

<table>
<thead>
<tr>
<th></th>
<th>Methoxyflurane</th>
<th>Placebo</th>
<th>Overall</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient rating</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>8 (16.3%)</td>
<td>15 (31.3%)</td>
<td>23 (23.7%)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Fair</td>
<td>10 (20.4%)</td>
<td>9 (18.8%)</td>
<td>19 (19.6%)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>7 (14.3%)</td>
<td>16 (33.3%)</td>
<td>23 (23.7%)</td>
<td></td>
</tr>
<tr>
<td>Very Good</td>
<td>16 (32.7%)</td>
<td>7 (14.6%)</td>
<td>23 (23.7%)</td>
<td></td>
</tr>
<tr>
<td>Excellent</td>
<td>8 (16.3%)</td>
<td>1 (2.1%)</td>
<td>9 (9.3%)</td>
<td></td>
</tr>
</tbody>
</table>

* Exact Wilcoxon rank sum test

Operator medication performance Assessment
There was no statistically significant difference in operator’s rating between arms for the global medication assessment. Cohen’s kappa statistical analysis of the data found a fair agreement between the operator and the subject ratings.

Nurse medication performance assessment
There was a statistically significant difference between arms (p < 0.001) when the research nurse rated global medication performance (Table 12-6 below). Medication was globally better rated for subjects who received Methoxyflurane. Cohen’s kappa statistical analysis of the data found a moderate agreement between the research nurse and the subject ratings.
Current pain intensity
Immediately following both aspiration and core biopsy, subjects were asked to rate their current pain using the NRS. There was no strong evidence of a statistical difference in pain intensity at the completion of aspiration and core biopsy.

Conclusion on efficacy – Study 2
This study shows moderate efficacy of methoxyflurane over placebo for pain relief in patients undergoing bone marrow biopsy with a statistically significant difference of 1.1 on the numerical rating scale. On the primary endpoint of worst pain the results in the methoxyflurane treatment arm was more favourable (worst score of 4.9) as compared to the placebo group (worst score of 6.0). This difference of 1.1 between treatments on the 11 point scale is around a 10% better efficacy than placebo which is not conclusive of a clinically relevant effect on pain. The results on the secondary endpoint also reflect the results from the primary endpoint

The need for rescue medication in either treatment group is expected to be low for a short procedure; overall there was only one patient in the placebo group who received rescue treatment.

The results on the subject and nurse assessment of the performance of the medication were in favour of the methoxyflurane treatment arm. However these are subjective measures and an indirect measure on the performance of the medicine rather than a direct assessment on the pain. Therefore the evidence on efficacy from this study is not as convincing as that from Efficacy Study 1. However it is acknowledged that the difference in pain model, assessments and the sample size may have affected the results.

Nevertheless this study can be considered to provide supportive evidence for the fact that methoxyflurane at the proposed dose has an analgesic effect.

Supportive evidence from literature
The application is substantially supported by published literature. The Applicant has systematically reviewed and presented the evidence from published literature. The databases searched include PubMed (1966 to date), the Cochrane Database of Systematic Reviews, Embase (1974 to date) and the Australian Medical Index (AMI). Searches were conducted in March 2007, February 2010, and January 2012. The search strategies employed were kept very broad.

The below table presents an overview of the published studies on the clinical efficacy of methoxyflurane as an analgesic:
The literature reports cover methoxyflurane inhalation for analgesia in approximately 21,902 patients (18,282 pre-hospital patients, 2,600 obstetrics patients, 520 dental patients, 170 burns patients, 280 patients

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of publications</th>
<th>Number of patients allocated methoxyflurane</th>
<th>Inhaler product used</th>
<th>Study population age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency Analgesia</td>
<td>5</td>
<td>138 (Includes 1 unpublished)</td>
<td>Penthrox®: 4, Analgizer®: 0, Other: 1</td>
<td>&gt;3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-hospital Analgesia</td>
<td>8</td>
<td>29396</td>
<td>Penthrox®: 6, Analgizer®: 1, Other: 1</td>
<td>1.25-100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Exclusion: age range not documented for 2 studies)</td>
</tr>
<tr>
<td>Burns Analgesia</td>
<td>7</td>
<td>216 (842 occasions)</td>
<td>Penthrox®: 0, Analgizer®: 2, Other: 6</td>
<td>0.33-83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(1 study compared 2 devices)</td>
</tr>
<tr>
<td>Dental Analgesia</td>
<td>4</td>
<td>553 (575 occasions)</td>
<td>Penthrox®: 1, Analgizer®: 0, Other: 3</td>
<td>1-69</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Exclusion: age range not documented for 1 study)</td>
</tr>
<tr>
<td>Analgesia</td>
<td>2</td>
<td>26</td>
<td>Penthrox®: 0, Analgizer®: 0, Other: 2</td>
<td>29-51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Exclusion: age range not documented for 1 study)</td>
</tr>
<tr>
<td>Post-operative Analgesia</td>
<td>2</td>
<td>60</td>
<td>Penthrox®: 0, Analgizer®: 2, Other: 0</td>
<td>19-78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operative Analgesia</td>
<td>2</td>
<td>73</td>
<td>Penthrox®: 1, Analgizer®: 1, Other: 0</td>
<td>15-84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Exclusion: age range not documented for 16 of the 19 studies)</td>
</tr>
<tr>
<td>Obstetric Analgesia</td>
<td>19</td>
<td>2004</td>
<td>Penthrox®: 0, Analgizer®: 6, Other: 17</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(4 studies used 2 devices)</td>
</tr>
</tbody>
</table>
presenting for emergency analgesia or for dressing changes, as well as addicts and 110 healthy subjects), and covers a range of short term exposures of methoxyflurane inhalation for analgesic use. In this application, the Applicant has applied for the indication “emergency relief of moderate to severe pain in conscious adult patients (age 18 years and older) with trauma and associated pain”. The data provided from burns, dental, post-operative and obstetric use is not relevant to the proposed indication under consideration for this application and is not discussed in much detail. However, it is noted that the results of these studies further provide supportive evidence on the efficacy of methoxyflurane as an analgesic.

Most studies were retrospective observational studies and so could not be considered to provide conclusive evidence. Two randomized double-blind placebo controlled studies suggested similar efficacy as that inferred in Study 1. However, as the full reports were not available, the results of these studies were considered as providing supportive evidence only.

The studies evaluated methoxyflurane administration through different formulations/devices including the Penthrox, Analgizer or other products. Of these, the studies that included the largest number of subjects were in pre-hospital emergency treatment and the formulation/device used most commonly in this indication was Penthrox. These studies include both placebo and active controlled studies. These studies evaluated the efficacy in children and adults and some of the studies included children as young as 1 year old.

The studies (individually and collectively), predominantly indicated that methoxyflurane was an effective analgesic, which provided rapid pain relief of short duration. However it is noted that there are literature reports that suggest that the analgesic efficacy of methoxyflurane may not be comparable to fentanyl or morphine. Also, data from one study did not support the analgesic efficacy of methoxyflurane in children aged 5 years and under.

**Supportive evidence from clinical use, especially in in Australia**

The major evidence to support clinical utility is the clinical use of this product in Australia. The Applicant has described in detail the extent of use in Australia and justified how this experience can be extrapolated to UK/Europe.

Since 1975, more than five million 3 mL bottle units have been sold in Australia. It is evident that Penthrox is used both in the hospital and pre-hospital setting for use as an analgesic for emergency treatment of pain for short durations. The approved SmPC in Australia is also clear that Penthrox is approved for use both in a pre-hospital setting and in the hospital (for surgical procedures such as change of dressings). There are clinical guidelines for use of Penthrox both in a hospital setting and in a pre-hospital setting. The use in Australia is not confined to peripheral areas, but is used in hospitals and ambulance services in major cities. The trauma patients that are treated are similar to the patients seen in the accident and emergency units in Europe and similar to the patient population studied in Efficacy Study 1.

Further it is noted that the extensive use in Australia is performed by people who are appropriately trained in the usage of the product and who are fully aware of its limitations, benefits, advantages and adverse effects (as evidenced by the clinical guidelines submitted by the Applicant).
Overall conclusion on efficacy
Taken together, the evidence from clinical studies, published literature and clinical use in Australia is considered adequate to support an inference of efficacy for methoxyflurane in the restricted indication of emergency pain relief for a short duration (on continuous inhalation for up to 60 minutes) using 2 bottles of Penthrox which is the maximum recommended dose.

Overall, the evidence from the two prospective clinical studies, literature and evidence of its continued clinical use in Australia taken together is considered sufficient to support the efficacy of Penthrox as an analgesic for emergency pain relief in patients with trauma and associated pain.

IV.5 Clinical Safety
The evidence of the safety for Penthrox is supported by three prospective clinical studies (the two efficacy studies discussed above and one thorough QTc study discussed below) conducted by the Applicant and a number of other clinical studies from published literature.

The Safety Population was defined as those patients who were randomised to treatment and received at least one dose of methoxyflurane or placebo. Patients who received the wrong treatment in error were analysed as treated.

Study 3 (QT/QTc study)
This was a Phase I thorough QT/QTc study to evaluate the effect of a supratherapeutic single dose of methoxyflurane (Penthrox) on cardiac repolarisation in healthy male and female subjects aged 18 to 45 years inclusive. The study was designed as a double-blind, double-dummy, randomised, placebo- and positive-controlled, 3-way crossover study. The primary endpoint variable of the study was the change from pre-dose baseline in the QTcF interval.

A total of 42 subjects were recruited and 39 subjects received an oral dose of a moxifloxacin tablet (400 mg) or placebo tablet and also an inhaled dose of methoxyflurane or placebo (12 mL self-administered via inhalation using the Penthrox Inhaler) in each study period (3 treatments groups) as a randomised crossover design (refer to Table 2.5.5-1 below). The oral dose was administered first. The start of inhalation for the inhaled dose was required to be within 5 minutes after the oral dose.

Table 2.5.5-1: Study treatments in the Phase I thorough QT/QTc

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Study medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Single oral dose of moxifloxacin placebo + single inhaled dose of methoxyflurane (supratherapeutic dose)</td>
</tr>
<tr>
<td>B</td>
<td>Single oral dose of moxifloxacin (400 mg) + single inhaled dose of methoxyflurane placebo</td>
</tr>
<tr>
<td>C</td>
<td>Single oral dose of moxifloxacin placebo + single inhaled dose of methoxyflurane placebo</td>
</tr>
</tbody>
</table>

Results
Thirty-nine subjects (93%) completed all three treatment periods, with the remaining three attending the first treatment period only; these subjects were therefore excluded from the ECG set. Of the 39 subjects in the electrocardiogram (ECG) analysis set, 22 (56.4%) were male and 17 (43.6%) were female. The full database consisted of 4317 ECGs, of which 4312 had valid respiration rate data and 4310 had valid QT data. After the calculation of mean values for each triplicate ECG, the database contains 1439 records. In the ECG analysis set, the triplicate mean database contains 1403 ECGs.
For the primary endpoint for methoxyflurane (QTcF; Table 11 and Figure 9), the analysis of covariance showed a statistically significant increase in mean QTcF at the 15min time point (QTcF point estimate 3.54, upper 95% CI 5.94, P value 0.017). Apart from this, there are no significant differences between methoxyflurane and placebo at any time point.

The primary endpoint, QTcF, showed statistically significant increases with moxifloxacin at all assessment time points from 30min onwards, with a maximal effect of 10.12 msec at the 4hr time point. The lower 98.33% one-sided confidence limit exceeds 5 msec at this time point, and also at the 2hr time point. These were two of the time points nominated for the confirmation of assay sensitivity; these results therefore demonstrate the presence of assay sensitivity in this study.
There were no QTcF values exceeding 480 msec, and (for methoxyflurane and placebo) only a few exceeding 450 msec only one subject had more than one instance of a triplicate mean QTcF value exceeding 450 msec during the methoxyflurane period; of the 5 time points where this was recorded, one was one of the pre-dose time points.

No subjects (in the ECG analysis set) showed a change from baseline QTcF triplicate mean value exceeding 30 msec on any of the three treatments.

The analyses of heart rate and the respiration rate interval at each time point confirmed that methoxyflurane has no effect on heart rate of sufficient magnitude to be of clinical concern.

The uncorrected QT interval showed a statistically significant increase, compared with placebo, in the methoxyflurane group at only the 15 minutes time point. Since no heart rate changes were observed at this time, or in general, this observation indicates a potential effect of methoxyflurane on the QT interval at this time point.

**Conclusion of the QT/QT<sub>c</sub> study**
The thorough QTc study demonstrated that methoxyflurane can cause some prolongation of QTc at 15 minutes, however the extent of prolongation at four times (12ml) the proposed therapeutic dose (3ml) and two times the maximum recommended daily dose (6ml) is below the threshold (a mean change of 5 msec and one-sided upper 95% CI of 10 msec) of regulatory concern. Hence it is agreed that at the proposed dose, there is negligible risk of clinically significant QTc prolongation with methoxyflurane.

**ADVERSE EVENTS**

**Efficacy Study 1**
Overall, the most common Treatment-Emergent Adverse Events (TEAEs; ≥4 events) that were considered related to the study treatment were TEAEs related to dizziness (58 events), TEAEs related to somnolence (eight events), headache (seven events), hypotension (four events) and nausea (four events).

For the drug-related TEAEs relating to dizziness (including light-headedness, woozy, head rush, giddy), the incidence was higher in the methoxyflurane group (48 events) than in the placebo group (10 events).

All of the drug-related TEAEs related to somnolence (including sleepy, drowsiness and sleepiness) occurred in the methoxyflurane group. Sleepiness was always easily rousable, and never affected the patient’s ability to maintain an airway.

For the drug-related TEAEs of headache and hypotension, the incidence was comparable between the methoxyflurane group (4 events of headache; two events of hypotension) and placebo group (three events of headache; two events of hypotension).

For the drug-related TEAEs of nausea, the incidence was higher in the placebo group (three events) in comparison to the methoxyflurane group (one event).

In the methoxyflurane group, none of the TEAEs relating to laboratory investigations (eight events) were considered related to the study drug, whilst in the placebo group, five of the six events were considered related to the study drug.
In the methoxyflurane group, other TEAEs that were considered as drug-related were three events of dry mouth and two events each of amnesia and dysarthria. There were single cases of dysgeusia, paraesthesia, oral discomfort and fatigue that were drug-related TEAEs in the methoxyflurane group.

The number of patients experiencing TEAEs leading to withdrawal of study treatment was lower in the methoxyflurane group (1.3%) compared to that of the placebo group (2%) with 4 TEAEs recorded in both the methoxyflurane and placebo group.

**Efficacy Study 2**

The most frequent (>5% events) treatment emergent adverse events at 30 days follow-up for both arms were fatigue (asthenia, lethargy, malaise), pain, constipation and nausea. All events were considered mild in accordance with National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) criteria and there were no adverse event (AEs), considered by the Investigator as related to study treatment.

<table>
<thead>
<tr>
<th>Table 2.5.5-6:</th>
<th>Adverse events 30-45 min after bone marrow biopsy (BMB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methoxyflurane</td>
</tr>
<tr>
<td>Mood alteration-euphoria</td>
<td>2 (15.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Taste alteration</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Confusion</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Sweating</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Neurology other-respiratory depression</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (53.3%)</td>
</tr>
</tbody>
</table>

**Study 3 (QT/QTc study)**

Common adverse events were headache (five subjects [12%], six AEs), dizziness including postural dizziness (five subjects [12%], six AEs), back pain (four subjects [10%], four AEs), upper respiratory tract infection (four subjects [10%], four AEs), and nausea or vomiting (three subjects [7%], four AEs).

There were 11 AEs in eight subjects (19%) that were deemed on blinded evaluation to be related to methoxyflurane. Of these, only two AEs (mild dizziness; mild headache) occurred in a study period where it was found, on unblinding, that methoxyflurane was the treatment actually administered. There were no clinically significant abnormalities reported for clinical laboratory tests, vital signs, and electrocardiogram (ECG) assessments.

**Overall conclusion of the prospective studies (two efficacy studies and the QT/QTc study)**

In the prospective studies, the incidence of adverse events was higher in the methoxyflurane treatment arms as compared to the placebo arm. Most of the events were mild and the common events included dizziness, euphoria, hallucinations, headache, nausea, vomiting, back pain, upper respiratory tract infection, fatigue,
pain, constipation, somnolence and dry mouth. None of these common adverse events are considered a major safety concern as the events are not significant in terms of outcomes or severity.

**Supportive data**

**Penthrox Vital signs Report**

The Applicant makes reference to a retrospective, observational study that investigated in a real life setting whether Penthrox, when used as an analgesic, had any impact on cardiovascular and respiratory functions (Penthrox Vital Signs Report).

The cohort comprised a total of 590 patients that had received at least one dose of methoxyflurane and had at least three sets of observations for systolic blood pressure (BP), pulse rate, and respiratory rate (in the period between 15 August 2011 and the 04 April 2012). The observations indicated that, in this otherwise unselected, large group of cases who had received Penthrox for pain, there were no deleterious effects on pulse rate, systolic BP, or respiratory rate.

**Records Linkage Study**

The Applicant makes reference to a long-term post-hoc safety assessment of methoxyflurane for patients receiving the product during ambulance transport. This study was performed through a health record linkage analysis. The aim of the study was to determine any difference in the event rates of various states between the two groups.

The cohort comprised a total of 135,770 patients of which 17,629 (13%) received at least one dose of methoxyflurane. Of the 17,629 patients [13%] who received methoxyflurane on at least one occasion, 14,410 (81.7%) patients received it only once 1,575 (8.9%) received it on two separate occasions with a further 341 (2.0%) receiving it on three separate occasions. There was one patient who received methoxyflurane on 27 separate occasions.

Aspects of the findings of this study is provided below in the ‘Significant Safety Events’ sub-section.

**Literature**

The literature covered a range of short term exposures for analgesic use in approximately 22,000 patients. The inhaled concentration covered the range 0.2% to 0.7% as recommended by MDI, and included durations of inhalation longer than the 50-55 minute approximate duration of the 6 mL methoxyflurane used with the Penthrox Inhaler.

In addition, there were eight studies which specifically reported safety of Penthrox inhaler. They included a total of 939 patients that inhaled methoxyflurane from a Penthrox Inhaler, which included children from 15 months to adults. The Inhaler was used in the prehospital situation (ambulances), for minor surgeries, dental procedures, and in Emergency Departments. Of the studies that recorded AEs (five), 28% of patients reported a mild AE, the most common being dizziness, euphoria, and hallucinations. There were no serious adverse events (SAEs).

**DEATHS AND SERIOUS ADVERSE EVENTS**

**Studies**

No deaths were reported in any of three prospective studies (Studies 1-3). Also, there were no related serious adverse events reported with methoxyflurane in the three prospective studies.
Literature
There were five deaths reported to be associated with methoxyflurane (reported between 1970 and 1987). It is important to note that, where details of the dose of methoxyflurane are available, the deaths resulted from inhaled doses significantly larger than those proposed for use by the Applicant (up to 3ml twice a day for 16 out of 21 days, and 5ml twice a day for 6 out of 14 days respectively, resulting in 60ml methoxyflurane over 16 and 14 days respectively). Two deaths were caused by renal failure, one from fulminant hepatitis associated with methoxyflurane abuse, one from necrotising kidney tubules, and one from cholestatic jaundice. Unfortunately there is very little information recorded in relation to the two latter deaths.

Post-marketing safety data
There were 15 serious adverse events reported with sub-anaesthetic doses of methoxyflurane between 1970 and 2010. Five of these cases were hepatitis.

Two of the post-marketing adverse effects reported were fatalities, six were resolved without sequela, one was resolved with sequela and the outcome of six remains unknown.

Four of the adverse reactions were reported to the Food and Drug Administration (FDA) between 1970 and 1972, while methoxyflurane was still in use in the United State of America. The reports included one case of hepatitis (from which the patient recovered), one case of acute kidney failure, of which the outcome was not recorded, and two deaths, one from necrosis of kidney tubules and one from cholestatic jaundice. Unfortunately, there is very little information recorded as part of these reports.

The remaining 11 adverse events were reported to the regulatory agency of Australia, Therapeutic Goods Administration (TGA), between 1985 and 2010. These reports included one case of cholestatic hepatitis in which the patient had received 6 ml methoxyflurane in one day (no other details of dosing are available). The patient was also receiving halothane, pethidine, fentanyl, and thiopentone, amongst other drugs. The condition was resolved after 3-4 weeks.

Other cases included malignant hyperthermia (methoxyflurane dose and outcome unknown; patient was also receiving propofol, suxamethonium and sevoflurane), hepatic failure (3 ml of methoxyflurane per week, for two weeks; recovered with sequela), acute hepatitis, hepatomegaly (3 ml methoxyflurane per week for 3 weeks; resolved without sequela), vomiting and jaundice (3 ml methoxyflurane in one day; resolved without sequela), dizziness, confusion and hypoxia, among other symptoms (3 ml methoxyflurane in one day; resolved without sequela), medication error (6 ml methoxyflurane, duration of exposure not known that was resolved without sequel), blood pressure fluctuation (Penthrox; outcome unknown), amnesia and lability affected (dose and outcome unknown), increased lipase and pancreatitis (dose and outcome unknown), and altered state of consciousness, nausea and vomiting (dose and outcome unknown).

After the first round of assessment, there were some safety concerns which the applicant was required to address. A summary of the Applicant’s response to issues raised concerning nephrotoxicity and hepatotoxicity is included in the sub-section ‘Significant Safety Events’ below.
Significant Safety events

Nephrotoxicity

Extensive clinical experience of the use of methoxyflurane as an anaesthetic has shown an association with a notable incidence of high output renal dysfunction and even dose-related, frank renal failure due to proximal tubular damage. This use has involved inhalation of a high dose of methoxyflurane, as the MAC required to produce surgical anaesthesia has been reported in the literature to be ranging from about 0.16% to 0.35% and the period of administration has mainly been > 60 minutes. The renal damage has been shown to be produced by the catabolism of methoxyflurane and the release of inorganic fluoride ions and perhaps other metabolites. Whether the more important site of the toxic metabolism is the liver and kidney or the kidney alone is not certain.

One published controlled study in humans showed that renal damage after exposure to high doses of methoxyflurane did not occur if the exposure was ≤ 2 MAC-hours and the serum fluoride was ≤40μmol/L. These values have been confirmed in many other clinical reports and analogous results have been obtained in animal experiments.

The analgesic use of methoxyflurane in the Penthrox Inhaler limits the maximum possible dose of methoxyflurane to around an estimated 0.59 MAC-hours, i.e. well below the upper limit of renal safety demonstrated by one group of investigators. Blood fluoride levels in patients using the Penthrox Inhaler to obtain analgesia have been reported as averaging 4.7μmol/L and peaking at 10μmol/L in Efficacy Study 2 - well below that required to produce a toxic level of catabolites.

The duration of exposure to methoxyflurane associated with complete continuous use of one Penthrox inhaler would be, at the most, no more 55 minutes (using 2 single doses of 3 mL consecutively), and the usual pattern of self-administration is for intermittent periods whenever the patient feels the need for pain relief. As a device for self administration, it is very likely that a patient would cease to inhale from the Penthox Inhaler once pain relief had been achieved or distraction by other events or drowsiness might lead the subject to abandon it.

The safe limit of serum fluoride ≤40μmol/L corresponds to inhalation of methoxyflurane ≤ 2MAC-hour. Nephrotoxicity would not be expected to occur after methoxyflurane exposure ≥2.5-3 MAC-hours based on a published controlled clinical investigation and generally supported by less intensive clinical experience and study. Such an intensity of exposure corresponds to inhalation of >0.3% methoxyflurane and usually continuous administration for several hours, an intensity and duration of treatment far exceeding the recommendations for use of the Penthrox Inhaler.

Based on the limited quantity of methoxyflurane available from a Penthrox Inhaler (3 mL) and the maximum daily dose of 6 mL, the serum fluoride will not exceed about 15-20 μmol/L and it will often be lower depending on the pattern of inhalation from the patient-controlled device. The serum fluoride should be compared with the safe limit of 40 μmol/L and exposure ≥2.5-3 MAC-hours which will require exposure to methoxyflurane ≥16 mL. The notional safety margin then would be about 8 (calculated as MAC-hours), 2-2.3 (calculated as serum fluoride) or 2.7 (as total dose of methoxyflurane). Considering the pattern of use of methoxyflurane as intermittent, short term inhalation over about 1h per device and not more than 2 devices per day the true safety margin would be even greater in clinical practice but by an uncertain amount depending on the individual subject’s actual rate of use of the device.

There were no cases of nephrotoxicity reported in the efficacy studies (Studies 1 and 2). However, in efficacy Study 2 fluoride levels did increase significantly more in methoxyflurane- treated patients after
treatment than in patients given placebo but the maximum observed concentration (10µmol/l) was much lower than levels associated with nephrotoxicity.

Hence the Applicant concluded that experimental and clinical evidence showed that use of methoxyflurane in the Penthrox Inhaler does not carry any particular risk of causing renal dysfunction or damage; this was accepted.

**Hepatotoxicity**

The Applicant has conducted an extensive literature search and discussed in detail the hepatotoxicity potential of methoxyflurane/Penthrox. A formal data linkage study (2010) of 17,629 patients receiving analgesic doses of methoxyflurane did not reveal any instances of liver damage. An expert report on the available literature has also been submitted.

There seems to be reports of 25-50 cases of hepatotoxicity with the anaesthetic use of methoxyflurane. However with the analgesic use of methoxyflurane (6 mL with Penthrox, 15 mL with Analgizer), there are 10 cases of hepatotoxicity.

Out of a total of 10 cases of liver damage reported after analgesic use of methoxyflurane, 4 of them occurred in Australia where Penthrox was the sole product used (more than 5 million units sold) and where the dose is limited to a maximum of 6ml/day. Three of the four cases of hepatitis recovered while one case required transplantation. The patient who required transplantation had received 3 mL/week of Penthrox over two times.

Of the remaining six cases (four from USA, one from Israel and one from Japan), one cases recovered, one was fatal and the outcome in one case is unknown. There are no details on the fatal case that was reported in 1970 other than that the reported event was cholestatic jaundice and exposure to methoxyflurane was only one day (however the dose is not known – though at the time the analgesic doses marketed in US was around 15 mL).

The detailed review of the cases and probable mechanisms and risk factors by the Applicant’s expert concluded that the events are likely to be idiosyncratic Drug-Induced Liver Injury (IDILI) and repeated exposures at short intervals are likely to increase the risk of IDILI. The risk of IDILI after limited brief exposure to methoxyflurane as an analgesic is very low.

Of the 10 cases of hepatotoxicity, two cases had unacceptable consequences (one with Penthrox and one with another product marketed at a higher dose) and in one case the consequence was unknown. For use of Penthrox in Australia, where around 5 million products have been supplied a total of four cases of hepatotoxicity where one case required liver transplant and in three cases the liver function recovered without adverse consequences. This suggests that risk of hepatotoxicity with Penthrox is small and acceptable.

**Potential for Abuse/Misuse**

The Applicant has presented an independent evaluation report on the potential for abuse/misuse of methoxyflurane. The salient features of the report were:

- Penthrox is a volatile substance which is highly lipid soluble. Relative to the other volatile substances with similar properties (both drugs and consumer products), its attractiveness for abuse is
limited as the central nervous system effects are characterised by slow induction times (onset of action) and due to the packaging
- Penthrox does not trigger key neurotransmitters in key regions of the brain associated with abuse and dependency;
- Penthrox is not listed by any regulatory authority as a drug of abuse or dependence.

Whilst no studies specifically investigating the abuse potential of methoxyflurane were identified, five papers have reported cases of methoxyflurane abuse. Of the five published cases, two described hepatitis and three described renal toxicity associated with increases in plasma fluoride or oxalic acid (two metabolites of methoxyflurane).

The Applicant has reported an additional 6 cases of drug abuse (by health professionals/health professional contacts) from the use of methoxyflurane as an analgesic, in Australia and New Zealand. The Applicant has confirmed that methoxyflurane is not listed as a controlled drug in any country where it is marketed nor is it listed as a drug of abuse and dependence by any regulatory authority. Further in these countries, Penthrox can be legally used by certain identified and trained personnel (e.g. para-medical personnel, ambulance crew, rescue teams, personnel with first-aid certificate, personnel responsible for emergency management in mines, sports fields and ski fields). Taking in to account the duration for which Penthrox has been available and the level of control and access described above, the risk of abuse is considered small as evidenced by the low numbers of abuse that have been reported.

**Malignant hyperthermia**

One clinical case of malignant hyperthermia has been reported (to the TGA) to date with the clinical use of methoxyflurane. It should be noted that the patient with the report of malignant hyperthermia was also on propofol, suxamethonium and sevoflurane. Therefore the cause of the malignant hyperthermia cannot be directly attributed to methoxyflurane. Nevertheless, malignant hyperthermia cannot be ruled out as a risk with methoxyflurane. Proposed precautions are listed in the SmPC for patients with known or genetic susceptibility to malignant hyperthermia; this is considered acceptable.

**Cardio-respiratory depression**

The Applicant provides the following information on respiratory and cardiovascular depression in the overview.

In line with other anaesthetics, methoxyflurane also has cardiorespiratory depressant effects. These effects are anticipated at the anaesthetic doses. Clinical history of use in analgesia has provided no indications that methoxyflurane significantly affects respiratory or haemodynamic parameters.

In efficacy Study 2, there were no clinically significant/relevant changes observed for vital signs (heart rate, respiratory rate, blood pressure and temperature). Likewise, in efficacy Study 1, there was little change in the systolic blood pressure, diastolic blood pressure, respiration rate, heart rate, heart rate rhythm (regular and irregular rhythm specified) between the evaluations in patients in the methoxyflurane group. The results were comparable to that of the placebo group.

The Applicant has presented a retrospective observational study (Penthrox Vital signs report) to inform on the effects of methoxyflurane on cardio-respiratory depression. In the Penthrox Vital Signs report on 590 pre-hospital patients, the administration of low dose methoxyflurane used for analgesia did not produce any deleterious effect on cardiovascular or respiratory parameters. The proportion of patients that had abnormal systolic blood pressure values (both above and below normal levels) decreased after Penthrox
administration, and there was no indication that Penthrox inhalation increased the probability of exhibiting abnormal systolic blood pressure. There was no indication that Penthrox inhalation increased the probability of exhibiting abnormal pulse rates.

From the available data, clinically significant cardiorespiratory depressant effects appear unlikely, especially at the proposed analgesic doses. The proposed SmPC has sufficient warnings and information on these aspects.

**Safety in special populations**
The use of methoxyflurane in children appears to be well reported and it appears that there are no special safety concerns with its use in children as compared to adults.

The use in elderly is not extensively reported. There is a potential for increased risk in elderly patients with concomitant cardiovascular disease due to the possibility of a depressant effects on heart rate and blood pressure by methoxyflurane. Accordingly, appropriate warnings have been proposed and accepted in the SmPC.

From the available safety data it can be accepted there are no particular concerns with the safety of the proposed use and dose in adults 18 years and older.

**Post-marketing safety**
As methoxyflurane has been available since the mid 1960s, the published literature presented above represents post-marketing experience.

Methoxyflurane has been marketed for analgesia in Australia since 1975, with over five million units sold. During this time, only eleven (11) adverse events have been reported (seven of which listed methoxyflurane as the sole suspected cause), despite Australia having one of the highest spontaneous adverse event reporting rates in the world (10,000 reports per year for a population of approximately 20 million people). No new significant safety concerns have been identified from these reports.

**Overall conclusions on clinical safety**
The identified/potential risks with methoxyflurane are malignant hyperthermia, cardio-respiratory depression, nephrotoxicity, hepatotoxicity and potential of abuse. The incidence of these safety events have been higher with anaesthetic use of methoxyflurane, however for the present application, the incidence with analgesic use of methoxyflurane is more relevant.

With the analgesic use of Penthrox, there has been one case of malignant hyperthermia (in a patient who also received propofol, suxamethonium and sevoflurane) and one case of nephrotoxicity (associated with hepatic failure and so could possibly be due to hepato-renal failure). The published literature supports the observation that nephrotoxicity occurs only with higher doses of methoxyflurane. Furthermore, the Applicant has provided suitable argument to support the claim that the risk of nephrotoxicity with Penthrox, at analgesic doses is low. Considering that Penthrox has been in used in Australia since the 1970s, the risk of malignant hyperthermia and nephrotoxicity are considered negligible.

A retrospective observational study report (Penthrox Vital signs report), of 590 patients who used Penthrox for analgesia, showed no significant cardiac or respiratory depressant effects. Furthermore, in the three
controlled studies conducted by the Applicant, there were no significant cardiac or respiratory depressant effects. Therefore it is accepted that cardio-respiratory depression is not a significant risk with Penthrox.

At the analgesic dose, 10 cases of hepatotoxicity have been reported with the use of methoxyflurane. Of the 10 cases of hepatotoxicity, two cases had unacceptable consequences (one with Penthrox and one with another product marketed at a higher dose) and in one case the consequence was unknown. Of the 10 cases, four of them (one case required liver transplant and, in three cases, the liver function recovered without adverse consequences) occurred in Australia where Penthrox was the sole product used (more than five million product sold) and where the dose is limited to a maximum of 6 mL/day. A detailed review of the cases and probable mechanisms and risk factors by the Applicant’s expert concluded that the events are likely to be idiosyncratic Drug-Induced Liver Injury (IDILI) and repeated exposures at short intervals are likely to increase the risk of IDILI. The risk of IDILI after limited brief exposure to methoxyflurane as an analgesic is very low. This conclusion of a small risk of hepatotoxicity with Penthrox is accepted. However, as patients can have unacceptable outcomes, the risk of hepatotoxicity should be actively monitored in the post-marketing setting.

With regards to the risk of abuse, there are no clinical studies which have evaluated the abuse potential of methoxyflurane. With the analgesic use of methoxyflurane, there have been three health professionals/health professional contacts each in New Zealand and Australia who have reportedly abused methoxyflurane since it was introduced in the 1970s. The Applicant has confirmed that in all the countries where Penthrox is available its legal status is similar to prescription only medicines in Europe and it is not a controlled drug. In addition, Penthrox can also be legally used by certain identified and trained personnel (like para-medical personnel, ambulance crew, rescue teams, personnel with first-aid certificate, personnel responsible for emergency management in mines, sports fields and ski fields). Taking in to account the duration for which Penthrox has been available and the level of control and access described above, the risk of abuse is considered small as evidenced by the low numbers of abuse that have been reported.

Overall, of all the safety concerns reported with methoxyflurane, there appears to be a small but significant risk of hepatotoxicity and risk of abuse with the proposed use of Penthrox. However based on the incidence rates of these events observed in Australia where the duration of use (since 1975) and extent of use (five million 3 mL units sold) is approximately known, the level of risk is considered acceptable.

**IV.6 Risk Management Plan**

The MAH has submitted a Risk Management Plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to PENTHROX inhalation vapour, liquid.

The Applicant proposes the following Summary of Safety Concerns which is considered to adequately reflect the data available:

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
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<tr>
<td><strong>Important identified risks</strong></td>
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<td><strong>Important potential risks</strong></td>
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**Pharmacovigilance Plan**

The Applicant has proposed routine pharmacovigilance activities for the majority of safety concerns identified in the table. In addition, at the close of the DCP procedure, the Applicant agreed to:

- conduct a Post Authorisation Safety Study (PASS) to further monitor and evaluate the risks of hepatotoxicity, nephrotoxicity and abuse potential from methoxyflurane administration. A protocol synopsis has been provided by the Applicant. A full protocol will be submitted and approved prior to market launch of the product.
- conduct and analyse surveys assessing the effectiveness of risk minimisation educational materials. A full protocol for distribution and analysis of the survey, together with the proposed Healthcare Professional and Patient Questionnaires will be submitted and approved prior to market launch of the product.

At Day 210, the primary and secondary objectives of the PASS were:

- The primary objective of the PASS is to evaluate whether there is an increased risk of hepatotoxicity from administration of methoxyflurane during routine clinical practice in pre-hospital, and hospital A&E departments in the UK.

- Secondary objectives of the PASS are to:
  - assess whether there is an increased risk of nephrotoxicity
  - estimate use in patients with a history of drug and alcohol abuse, or who are morbidly obese;
  - assess any off-label use;
  - assess whether there is overdosage of Penthrox.

Post Day 210, concerns were expressed, by some stakeholders, regarding some sub-groups at risk of renal injury. The Applicant has agreed to update the PASS study to include objectives on providing data from follow-up of specific sub-group of patients having:

a) Crush injury  
b) Heavy bleeding  
c) Low Blood pressure  
d) Contrast injection following treatment with methoxyflurane  
e) Anaesthesia with sevoflurane following treatment with methoxyflurane  
f) Diabetes

In addition, changes to the wording of the SmPC, PIL and training materials regarding the use of Penthrox in patients at risk of renal injury related to contrast media and sevoflurane will be submitted as a post-marketing variation.

**Risk Minimisation Measures**

In addition to routine risk minimisation activities, the Applicant has agreed to provide the following:

- Educational activities/training and materials for healthcare professionals to address each of the risk(s)
PENTHROX 3mL inhalation vapour, liquid

included in the Summary of Safety concerns. In addition, materials will be made available on-line.

The objectives of the additional risk minimisation measures for Penthrox are to:

i) ensure that healthcare professionals are aware of and understand the limitations of the product in terms of the authorised indication (acute moderate to severe traumatic pain, adults) and posology.

ii) ensure that the correct patients are treated with Penthrox i.e. that healthcare professionals are aware of the contra-indications and the importance of adhering to these in clinical practice.

iii) ensure that healthcare professionals know how to administer Penthrox correctly and can instruct the patient to use Penthrox correctly in order to reduce risk to the patient and to themselves (through possible environmental exposure)

iv) ensure that healthcare professionals are aware of the important safety concerns and associated warnings and precautions for use.

v) ensure that healthcare professionals know the importance of safe storage and appropriate disposal of the product (abuse potential).

vi) remind healthcare professionals to advise patients accordingly.

The Applicant also proposes that the effectiveness of the proposed additional risk minimisation measures will be evaluated through surveys conducted at approximately 6-months following launch and finishes at approximately 4 months after survey start.

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Penthrox.

V. USER CONSULTATION

A package leaflet (Patient Information Leaflet and Information for Use) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION QUALITY

The important quality characteristics of PENTHROX inhalation vapour, liquid are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL

The non-clinical dossier is largely based on available data in the published literature with only three safety
pharmacology studies and four genotoxicity studies being conducted by the Applicant. Given the extensive clinical experience with methoxyflurane as both an analgesic and anaesthetic some omissions in non-clinical data can be accepted in line with the Guideline on the non-clinical documentation for mixed marketing authorisation applications (CPMP/SWP/799/95). The Non-clinical Overview covers all expected Module 4 headings and attempts to justify the absence of any specific type of data.

**EFFICACY**

This application is supported by two prospective clinical efficacy studies (one study is considered pivotal and the other supportive), evidence from the literature and evidence of Penthrox’s continued clinical use in Australia.

The pivotal efficacy study was a randomized, double-blind, placebo controlled study in which patients with a baseline pain score between 4 and 7 (on a numerical rating scale 0-10) were randomized to methoxyflurane or placebo; efficacy was measured by pain intensity score on VAS. The results showed that overall change from baseline in the methoxyflurane was -30.2 as compared to -15.2 in the placebo arm. The estimated treatment difference of -15.1 (95% CI -19.2 -11.0) was statistically significant and clinically relevant. The secondary endpoints and ancillary analyses were also supportive. The proportion of patients with a 30% improvement from baseline was also significantly more in the methoxyflurane group (52.8 - 76.1%) as compared to placebo (24.5 – 43%) at all evaluated time-points.

The second efficacy study compared the efficacy of methoxyflurane against placebo on incident pain of bone marrow biopsy. The study showed moderate efficacy for methoxyflurane as compared to placebo. On the primary endpoint of worst pain, the results in the methoxyflurane treatment arm were more favourable (worst score of 4.9) as compared to the placebo group (worst score of 6.0). This difference of 1.1 between treatments on the 11 point scale is around a 10% better efficacy than placebo which is not conclusive of a clinically relevant effect on pain. The results on the secondary endpoint also reflected the results from the primary endpoint. It is pertinent to note that though a clinically relevant effect was not shown in this study, the results tend to favour methoxyflurane and as such the study can be considered supportive.

Evidence of efficacy in the literature includes a number of published studies (approximately 21,902 patients). However, most of the studies were from retrospective observational studies and so cannot be considered to provide conclusive evidence. Two randomized double-blind placebo controlled studies suggested a similar efficacy as that inferred in pivotal prospective efficacy study, however the full reports of these studies are not available. Therefore, the published studies can be considered as supportive evidence only.

The Applicant also presented evidence from the clinical use of Penthrox in countries where it is authorised, in particular from Australia where Penthrox has been used extensively (5 million 3mL units sold since the 1970s). The evidence includes published literature, clinical guidelines for use of Penthrox in the hospital practice, clinical guidelines for use of Penthrox in the ambulance and testimonials from its users. Overall, the situation and type of cases for which Penthrox is proposed to be used in the European Union are similar to those for which Penthrox is currently used in clinical practice in Australia. Hence, the experience from Australia is considered relevant and applicable to the European setting. The applicant has also enclosed statements from clinical practitioners in the UK who have had prior experience with Penthrox to support its relevance to the clinical situation seen in Europe.

The Applicant has acknowledged that there are no prospective studies in which Penthrox has been compared to the analgesics (such as morphine, fentanyl and Entonox) currently used in the proposed setting.
in Europe. However, the Applicant has conducted an extensive literature search and provided a cross-study comparison of the relative efficacy and safety of Penthrox and other analgesics (that is, i.v. morphine, intra-nasal fentanyl and inhaled Entonox). A cross-study comparison of randomised controlled trials is not ideal or very robust; nevertheless a cautious interpretation of the data supports the conclusion that Penthrox has acceptable analgesic activity. However some features of treatment with Penthrox, such as, the ease of transport (as compared to Entonox), ease of administration (as compared to i.v access needed for morphine), quick onset of action and quick offset of action all provide obvious advantages in some specific situations for short-term emergency treatment of pain associated with trauma.

Overall, the evidence from the two prospective clinical studies, literature and evidence of its continued clinical use in Australia taken together is considered sufficient to support the efficacy of Penthrox as an analgesic for emergency pain relief in patients with trauma associated pain.

SAFETY
The safety data on Penthrox is presented from the two efficacy studies (n=199), a thorough QTc study (n=39), data from published literature (n = 21902 approximately and includes other methoxyflurane products used for analgesia) and the pharmacovigilance activity (including reports to regulatory authorities) in the countries where it is authorised, especially Australia. In addition, there is published information from other methoxyflurane products (for example, Analgizer device) used as an analgesic as well as from the use of methoxyflurane as an anaesthetic.

From the controlled clinical studies the identified adverse events include dizziness and somnolence. From published literature with use of methoxyflurane as an analgesic the most common adverse events include dizziness, euphoria, hallucinations, headache, nausea vomiting, back pain, upper respiratory tract infection, fatigue, pain, constipation, somnolence and dry mouth.

The significant safety concerns associated with methoxyflurane (either from analgesic or anaesthetic use) from the overall data includes nephrotoxicity, malignant hyperthermia, cardio-respiratory depression, hepatotoxicity and potential for abuse.

Of these significant safety concerns, it is known that nephrotoxicity with methoxyflurane use is dose-related and occurs at the higher anaesthetic doses. It has been determined that methoxyflurane, when administered in large doses (40-60 mL), is associated with high output renal failure, and so the proposed 3-6 mL use in 24 hours is unlikely to cause nephrotoxicity. Although there were two reports to the US FDA on nephrotoxicity with analgesic use of methoxyflurane, further details on these cases are not available. To date, there has been only one report of renal failure (associated with hepatic failure) with use of Penthrox in Australia (over 5 million units sold). In light of the now established dose-related mechanism of methoxyflurane use and the likelihood that the nephrotoxicity with Penthrox was probably following hepatotoxicity, it is accepted that nephrotoxicity is not significant risk with the use of Penthrox.

There was one report of malignant hyperthermia with use of Penthrox in Australia and this patient was also on propofol, suxamethanium and sevoflurane. Therefore it is agreed that malignant hyperthermia is not a significant risk with use of Penthrox.

A retrospective observational study report (Penthrox Vital signs report) of 590 patients who used Penthrox for analgesia, conducted by the applicant, showed that there were no significant cardiac or respiratory depressant effects. Furthermore, in the three controlled studies conducted by the Applicant, there were no significant cardiac or respiratory depressant effects. The assertion that relevant cardiac or respiratory
depression occurs only at the anaesthetic dose of methoxyflurane is therefore accepted.

Based on literature review by the Applicant, round 50 cases of hepatotoxicity have been described with the anaesthetic use of methoxyflurane. The liver damage occurred between 2-21 days after administration and most cases recovered in few weeks.

A formal published data linkage study (2010) of 17,629 patients receiving analgesic doses of methoxyflurane did not reveal any instances of liver damage. However an intensive literature search found 10 cases of hepatotoxicity reported with use of methoxyflurane at the analgesic dose. Out of a total of 10 cases of liver damage reported after analgesic use of methoxyflurane, four of them occurred in Australia in patients wherein Penthrox was the sole product used and the dose was limited to a maximum of 6 mL/day. Three of the four cases of hepatitis recovered without adverse consequences while one case required liver transplantation. The patient who required transplantation had received 3 mL/week of Penthrox over two times. Of the remaining six cases (four from USA, one from Israel and one from Japan), four cases recovered, one was fatal and the outcome in one case was unknown. There are no details on the fatal case that was reported in 1970 other than that the reported event was cholestatic jaundice and exposure to methoxyflurane was only one day (although the dose is not known, at the time the analgesic doses marketed in US was around 15 mL).

Overall, the data suggest that risk of hepatotoxicity with Penthrox is small and acceptable. However this should be actively monitored in the post-marketing setting.

With regards to the risk of abuse, there are no clinical studies which have evaluated the abuse potential of methoxyflurane. There were six cases of methoxyflurane abuse related to anaesthetic use, from post-marketing data published between 1971 and 1988. Of the six cases identified, four occurred in the US, one in Mexico and one in Japan. In all these cases, the methoxyflurane abuse was carried out by healthcare professionals or a person (s) associated with a health profession. No abuse cases have been identified in the UK or the EU during the same period, when methoxyflurane was supplied as an anaesthetic (125 ml) and analgesic (15 ml). In addition, abuse of methoxyflurane by healthcare professionals/healthcare professional contacts in New Zealand (three) and Australia (three) has also been reported (private communication).

Taking into account the duration for which Penthrox has been available and the level of control and access described above, the risk of abuse is considered small as evidenced by the low numbers of abuse that have been reported.

Overall, from the post-marketing data that is available to date, there has been one case of renal toxicity, four cases of hepatotoxicity (two of which had unacceptable outcomes), two cases of hypoxia and six cases of abuse with the use of Penthrox specifically. From the available details, the events of renal toxicity, hepatic toxicity and hypoxia cannot, with certainty, be solely attributed to Penthrox. Overall, the number and severity of these events are considered an acceptable safety profile given the large context of use from which these reports have emerged.

It is acknowledged that there could be significant under reporting in the post-marketing setting. Therefore the applicant will be required to actively monitor for these safety concerns (hepatotoxicity and abuse) in the post-marketing setting in Europe to ascertain that the actual incidence of these safety events is not higher than currently thought. In addition, there are appropriate warnings and contra-indications and there will be sufficient training prior to product launch to ensure good adherence to the advised precautions.
PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical safety concerns have been identified.

It is agreed that adequate efficacy has been demonstrated and there are certain advantages of Penthrox which make it a useful addition to the current analgesics available for emergency relief of pain associated with trauma.

Overall, of all the safety concerns reported with methoxyflurane, there appears to be a small risk of hepatotoxicity and risk of abuse with the proposed use of Penthrox. However based on the incidence rates of these events observed in Australia where the duration of use (since 1975) and extent of use (five million sold) is approximately known, the level of risk is considered acceptable.

Taking the overall evidence on efficacy and safety, the RMS is of the opinion that the benefit-risk profile for Penthrox in the proposed use is favourable.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:
PENTHROX 3mL inhalation vapour, liquid

Each pack contains:
1 bottle Penthrox® (methoxyflurane 3mL)
1 Penthrox® Inhaler
1 Activated Carbon (AC) Chamber

Combination Pack

For inhalation only

How to use Penthrox®

1. Ensure the Activated Carbon (AC) Chamber is inserted into the dilator 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 ⅓ 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 the 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 anaesthesia. First few breaths should be gentle and then breathe normally through Inhaler.

5. Patient inhales into the Penthrox® Inhaler. The inhaled vapor passes through the AC Chamber to adsorb any inhaled methoxyflurane.

6. If stronger anaesthesia is required, patient can cover dilator hole on the AC Chamber with finger during use.

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

8. Replace cap onto Penthrox® bottle. Place used Penthrox Inhaler and used bottle in sealed plastic bag and dispose of responsibility.
Annex 1 - Table of content of the PAR update for MRP and DCP
Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
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<tbody>
<tr>
<td>To update Section 4.4 (Special warnings) and 4.5 (Interactions) of the SmPC in accordance with the recommendations of RMS Post-Day 210 Assessment Report on Responses to Concerns raised by stakeholders and correspondence with the RMS. Consequently, the PIL and the Risk Management Plan (RMP) have been updated.</td>
<td>UK/H/5542/001/II/004</td>
<td>SmPC PIL</td>
<td>15/01/2016</td>
<td>27/05/2016</td>
<td>Approval</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Annex 1

Our Reference: PL 42467/0001, Application 0004
Product: PENTHROX 3ml inhalation vapour, liquid
Marketing Authorisation Holder: Medical Developments UK Limited
Active Ingredient(s): Methoxyflurane

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type II
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/5542/001/I/004

Reason:
To update Section 4.4 (Special warnings) and 4.5 (Interactions) of the SmPC in accordance with the recommendations of RMS Post-Day 210 Assessment Report on Responses to Concerns raised by stakeholders and correspondence with the RMS. Consequently, the PIL and the Risk Management Plan (RMP) have been updated

Supporting Evidence
Revised SmPC fragments
Updated leaflet.
Revised RMP

Evaluation
The proposed changes to the SmPC, leaflet and RMP are considered satisfactory.

Conclusion
The proposed changes to the SmPC, leaflet and RMP are considered acceptable and there are no objections to approval.

In accordance with Directive 2010/84/EU the SmPCs and PILs for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision
Approved on 05 July 2016.