IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Methoxyflurane 99.9%, 3 ml inhalation vapour, liquid, from Mundipharma Pharmaceuticals Ltd on 18.09.2020 for the emergency relief of moderate to severe pain in conscious adult patients with trauma and associated pain.

This application for a marketing authorisation was submitted in accordance with Article 10c of Directive 2001/83/EC and is referred to as an 'informed consent' application. This means that the Marketing Authorisation Holder for Penthrox, an authorised medicinal product in Europe, has permitted the applicant to refer to their dossier to obtain an authorisation for Methoxyflurane 99.9%. Methoxyflurane 99.9% has the same qualitative and quantitative composition in terms of actives substances and the same pharmaceutical form as Penthrox.

The product is subject to medical prescription in accordance with S.I. 540 of 2003 , and amended, and can only be marketed to healthcare professionals.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website.

Name of the product	Methoxyflurane 99.9%, 3 ml inhalation vapour, liquid
Name(s) of the active substance(s) (INN)	Methoxyflurane
Pharmacotherapeutic classification (ATC code)	N02BG09
Pharmaceutical form and strength(s)	99.9%, 3 ml Inhalation vapour liquid
Marketing Authorisation Number(s) in Ireland (PA)	PA1688/023/001
Marketing Authorisation Holder	Mundipharma Pharmaceuticals Ltd
MRP/DCP No.	IE/H/0887/001/DC
Reference Member State	IE
Concerned Member State	NL MT EL HU

II. QUALITY ASPECTS

II.1. Introduction

This application is for Methoxyflurane 99.9%, 3 ml inhalation vapour, liquid

II.2 Drug substance

The active substance is methoxyflurane an established active substance and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each bottle contains 3 ml of methoxyflurane 99.9%.

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur. requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Methoxyflurane 99.9%, 3 ml inhalation vapour, liquid.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The HPRA has been assured that GLP standards were followed in an appropriate manner in the studies conducted.

III.2 Pharmacology

The exact mechanism by which methoxyflurane exerts its anaesthetic and analgesic action has not been fully elucidated. No new primary or secondary pharmacology studies have been conducted in support of this application. The applicant has not conducted any pharmacodynamic studies with methoxyflurane. This approach has been justified by citing the history of methoxyflurane use in this indication clinically. This is accepted and no additional non-clinical studies are required. A review of the public scientific literature related to the pharmacodynamic activity of methoxyflurane revealed only limited information. The mechanism mediating methoxyflurane's analgesic effects remains to be elucidated. A study submitted shows that methoxyflurane administration is associated with brain region dependent alterations substance P and ß-endorphin immunoreactivity and CRF concentration in Sprague-Dawley rats. However, as this study did not assess nociceptive endpoints the relationship of these data to its analgesic activity is unknown. A summary of non-clinical studies related the anaesthetic

activity of methoxyflurane are also submitted, showing relatively rapid recovery time following induction of full anaesthesia in non-human primates.

No secondary pharmacodynamics studies have been conducted in support of this application. Methoxyflurane anaesthesia was shown to be associated with an increase plasma free fatty acids which appeared to be mediated via sympathetic nervous system activation as pre-treatment with pan ß- receptor antagonist propranolol attenuated this effect. As these effects were noted after full anaesthesia it is unclear if similar effects can be anticipated with this product. However, as it is designed for single use these potential effects are not considered a significant safety concern.

In general studies sourced from public academic literature relating to safety pharmacology endpoints are submitted in lieu of new studies. A dedicated GLP-compliant in-vitro study assessing the effect of methoxyflurane on hERG tail current ion HEK-293 cells stably transfected with hERG ion channel cDNA. A pilot dose range finding study and GLP-compliant safety pharmacology study were conducted in telemeterised Beagle dogs to assess the effect of inhaled methoxyflurane on cardiac and respiratory safety pharmacology endpoints.

The results of the in-vitro study suggested that methoxyflurane was associated with an inhibition of the hERG potassium channel and hence a potential for QT prolongation. Of note the achieved concentrations in this study are significantly less than the nominal target concentrations, likely related to the volatile nature of methoxyflurane. In the in-vivo study, based on sedation observed in the pilot study at a concentration of 0.5%, a high dose of 0.3% was chosen in the pivotal study. No adverse effects on ECG or respiratory parameters were noted in the pivotal study. These data do not suggest a concern in relation to cardiovascular safety. It should be noted that no toxicokinetic analysis has been conducted and therefore systemic exposure to methoxyflurane in these animals cannot be confirmed.

Literature studies related to the CNS effects of methoxyflurane have been submitted. These report effects on anxiety and reward related behaviour likely related to the primary pharmacological activity of methoxyflurane and can be considered expected. Methoxyflurane is also reported to alter the distribution of blood within the kidney which may in part mediate its nephrotoxic effects. The completed studies in combination with the summary of available literature related to the safety pharmacology assessment of methoxyflurane are considered acceptable.

III.3 Pharmacokinetics

No new PK studies have been conducted and limited information from the literature relating to the non-clinical characterisation of PK is presented. Given the clinical experience with the use of halogenated anaesthetics the applicants approach is considered acceptable. Methoxyflurane is highly lipid soluble. Blood concentrations of methoxyflurane are reported to increase with increasing dose in both rat and dog with age dependent differences in exposure evident in rats. Similarly, clearance appeared to show age dependent differences attributed to sequestration of methoxyflurane in adipose tissue.

There is limited data available on the distribution of methoxyflurane in non-clinical species. Ex-vivo data from human samples is presented showing age dependent differences in tissue/gas partition coefficients. Methoxyflurane has a high oil/gas coefficient hence methoxyflurane is highly lipophilic. Methoxyflurane readily passes through the blood-brain barrier and is presumed to cross the placenta. Clinical data reports that methoxyflurane concentrations of 50-70% maternal levels in the umbilical cord blood.
Methoxyflurane is primarily metabolised via dechlorination and o-demthylation in the liver with methoxydifluoroacetate, fluoride and formaldehyde the primary metabolites. In-vitro data reports that metabolism is primarily mediated by CYP2E1 with a role for CYP1A2. There is some evidence to suggest an accumulation of the fluoride metabolite following prolonged exposure. This is unlikely relevant given the proposed indication and posology of this product. Clinical data relating to the metabolism of methoxyflurane is available and discussed in the clinical assessment report.

No non-clinical mass balance data has been submitted. Excretion is primarily through the lung and urine. Part of the inhaled dose is excreted through the lungs with the relatively high blood/tissue solubility of methoxyflurane resulting relatively (to other inhaled anaesthetics) low clearance via this route. The primary urinary metabolite of methoxyflurane is methoxydifluoroacetate. There does not appear to be significant faecal excretion. No data on potential excretion in milk has been presented.

The metabolism of methoxyflurane is increased following pre-treatment with enzyme inducing drug phenobarbital. Co-administration of methoxyflurane with gentamicin, tetracyclines, ethanol and isoniazid may result in increased metabolism which has been linked to an increase in kidney toxicity related to an increase in fluoride metabolite excretion.

III.4 Toxicology

7-week inhalation administration toxicity studies in Wistar rat, guinea pig and rabbit were conducted. Animals were administered subanaesthetic doses of methoxyflurane (200 ppm, for 7 h/day for 5 days/week). Liver was identified as a target organ in all species. Effects observed were fatty metamorphosis in all species which was associated with elevated serum liver enzyme levels in rabbit. In F344 rats liver fatty metamorphosis was associated with reduced hepatic CYP P450 levels and foci of hepatocellular degeneration and necrosis and associated with elevated serum liver enzyme levels. These effects appeared recoverable following a 4-week drug free period. No NOAEL for these effects was established. Based on the safety margin calculations provided by the applicant these effects may be expected within the exposure range anticipated clinically. It is acknowledged that such effects were observed following repeat exposures while the proposed posology for this product is for short term treatment of analgesia and thus the clinical relevance of these results is questionable. Appropriate information on the risk of hepatotoxicity and the differences in exposures in these studies is included in section 5.3 of the SmPC, this is considered acceptable.

Methoxyflurane was negative in GLP compliant Ames test conducted in the presence and absence of metabolic activation. Methoxyflurane did not induce an increase in micronuclei in polychromatic erythrocytes when administered to Sprague-Dawley rats at a dose of up to 50 mg/kg IV. It should be noted that in this study the high dose was set at 100 mg/kg, but this was found not to be tolerated and tissue from these animals was not assessed. This is accepted. Literature data is submitted in place of an in-vitro assessment of methoxyflurane induced chromosomal damage in mammalian cells. Based on the data provided it is accepted that methoxyflurane is not genotoxic.

In-silico results for DCFME via CAESAR and SARPY systems were equivocal and the applicant states that the instability in this compound precludes conducting an Ames test. The submitted expert statement concludes that DCFME is not genotoxic based on an analysis of genotoxicity data for structurally related compounds. This is accepted. Separate GLP-compliant Ames tests have been submitted for two of these impurities (halomer and methyl dichloroacetate). Both tests were negative both in presence and absence of metabolic activation. It is accepted that based on the weight of evidence submitted these impurities are not genotoxic.

No long term carcinogenicity data have been provided with this application. Data sourced from the literature on short-term studies have been presented. These studies were not conducted to GLP and only limited information on their design is available, hence their relevance for the assessment of carcinogenic risk in humans is questionable. The applicant's justification that as this product is designed for short-term use in an emergency setting in line with ICH S1 guidance such studies are not warranted is accepted.

Very limited data is submitted relating to the effects of methoxyflurane on fertility. Inhalation administration to mice was not associated with any effect on sperm. Data from related halogenated inhalable anaesthetics are also presented which did not identify any effects on fertility. The relevance of these data to potential methoxyflurane related effects are unknown.
Data submitted from the published scientific literature reports that methoxyflurane crosses the placenta but is not associated with embryotoxicity or teratogenicity. Decreased foetal body weight was observed at all dose levels following administration to pregnant Sprague-Dawley dams with the highest dose associated with a decrease in fore-limb ossification. These studies were not conducted to GLP but appear to be of good quality. The exposure margin calculations submitted show that there are no margins between the NOAEL identified in these studies and predicted clinical exposures. These data are included in section 5.3 of the proposed SmPC and are considered acceptable.

No dedicated studies assessing pre and post-natal development have been found in the scientific literature. It is noted that in a short term carcinogenicity study in which swiss mice were exposed in utero to from GD 5 to 10 weeks of age there were no effects on the percentage of dams that delivered or the number of pups per litter. Clinical data following methoxyflurane's use as an anaesthetic in obstetrics is available and has been submitted.

III.5 Ecotoxicity/environmental risk assessment

Phase I screening showed the PECsurfacewater value exceeded the action limit of 0.01 µg/L and log Kow = 2.29. Therefore, Phase II-Tier A assessment was carried out. Methoxyflurane is not PBT. A summary of these data is included in the table below:

Substance (INN/Invented Name): Methoxyflurane						
CAS-number:						

76-38-0						
PBT screening		Result			**Conclusion**	
Bioaccumulation potential- log K_{ow}	OECD107	log K_{ow} = 2.29			Below 4.5 threshold, no PBT screening warranted	
PBT-assessment						
PBT-assessment						
Parameter	**Result relevant for conclusion**					**Conclusion**
Bioaccumulation	log K_{ow}	= 2.29				Not Bioaccumulative
Persistence		Not readily biodegradable Not persistent				Not Persistent
PBT-statement :	The compound is not considered as PBT nor vPvB					
Phase I						
Calculation	**Value**	**Unit**			**Conclusion**	
PEC $_{surface\ water}$, Default	1.343	mg/L			> 0.01 threshold Action limit exceed, proceed to Phase II	
Other concerns					None	
Phase II Physical-chemical properties and fate						
Study type	**Test protocol**	**Results**			**Remarks**	
Adsorption-Desorption	OECD 106	Sludge K_{oc} = 44 ml/g 50 ml/g			2 sludge types, <10000 L/Kg Terrestrial studies not triggered	
Ready Biodegradability Test	OECD 310	Not readily biodegradable				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	River $DT_{50\ (12°C),}$ water= 27 days $DT_{50\ (12°C),}$ total system= 37 days % shifting to sediment = 1.8 Pond $DT_{50\ (12°C)}$, water = 15.8 $DT_{50\ (12°C)}$, total system = 16.2 % shifting to sediment = 0.7			Methoxyflurane is not persistent under semi-continuous aeration conditions. Phase IIb sediment toxicity study not triggered NER 3/3.4% for river and pond system respectively	
Phase IIa Effect studies						

Study type	Test protocol	Endpoint	value	Unit	Remarks	
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	12	mg/L	Growth rate	
Daphnia sp. Reproduction Test	OECD 211	NOEC NOEC	10 10	mg/L	Body lenght Reproduction	
Fish, Early Life Stage Toxicity Test/ *Brachydanio rerio*	OECD 210	NOEC	0.69	mg/L	Fish dry weight	

Considering the above data Penthrox is not expected to pose a risk to the environment. Penthrox should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

III.6 Discussion on the non-clinical aspects

The submitted non-clinical data summarised above were considered sufficient to support the marketing authorisation of Penthrox.

IV. CLINICAL ASPECTS

Introduction

Methoxyflurane is a well-known active substance with established efficacy and tolerability. This medicinal product is the same as Penthrox on the European market. The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product.

Pharmacokinetics

No new clinical pharmacokinetic (PK) studies/data have been provided by the Applicant for methoxyflurane administered with the inhaler, and none are required. The Applicant has provided a review of published data on the pharmacokinetics based predominantly on anaesthetic use of methoxyflurane (anaesthesia is now a contraindication). The available PK data from published literature is considered adequate to support the proposed use of methoxyflurane.

A brief summary of the PK 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%.

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

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.

Methoxyflurane is metabolised via two main pathways, 0-demethylation and dechlorination. The dechlorination pathway leads to the formation of methoxydifluoroacetate, in addition to chloride, fluoride and oxalate. The 0-demethylation pathway produces formaldehyde, fluoride and dichloroacetate. Dichloroacetate is further metabolised to oxalate and other products.

Methoxyflurane is metabolised faster in the body than any other commonly used volatile anaesthetic agents, and the metabolism and biotransformation of methoxyflurane has been studied and reviewed in detail. Biodegradation of methoxyflurane begins immediately after the onset of exposure and continues until any storage depots of the intact drug are depleted. The principal enzyme responsible for the metabolism of methoxyflurane in humans is cytochrome CYP (P450) 2E1

with a contribution from CYP 2A6 which together account for the majority of its metabolism via dechlorination and demethylation pathways. There are also some non CYP dependent pathways of metabolism.

Studies have been performed *in vitro* and in man (both healthy volunteers and patients receiving methoxyflurane for anaesthesia or analgesia), demonstrating that as much as 50- 70% of the absorbed dose of methoxyflurane is metabolised to inorganic fluoride ion, oxalic acid, 2,2-difluoromethoxyacetic acid and dichloroacetic acid. Thus, metabolic elimination is the primary route of elimination. Excretion is via both exhalation of unaltered methoxyflurane and C02, and through the urinary excretion of methoxyflurane metabolites.

Fluoride ions and nephrotoxicity
While the cause of the nephrotoxicity subsequent to methoxyflurane anaesthesia is not fully elucidated, what is clear is that the nephrotoxicity is associated with inorganic fluoride levels and is dose related. Investigations have suggested that renal necrosis may be due to the combination of fluoride and dichloroacetic acid.

Methoxyflurane, administered at doses below 2 MAC (Minimum Alveolar Concentration) hours have led to peak serum inorganic fluoride levels of <40 micromole that were not associated with subclinical or clinical nephrotoxicity. Above this level, subclinical but reversible 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 micromole. 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 micromole. The level of metabolism of methoxyflurane is dose related and when used in the recommended low dose of 3-6 ml for analgesia, the low concentrations of metabolites do not result in the side effects seen following anaesthesia.

As the vapour produced from the maximum dose of 6 ml of liquid methoxyflurane (approximately 1200 ml of vapour from two administrations) to provide analgesia via the inhaler, lasts approximately 50-55 min, 1 MAC hour cannot be achieved. 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. When compared to the use of methoxyflurane as an anaesthetic, the lower doses of methoxyflurane used for analgesia are associated with low serum levels of inorganic fluoride ion. In most cases, these correspond to less than half the level associated with subclinical toxicity.

Special populations

Impaired renal function
The degree of nephrotoxicity can be correlated both with methoxyflurane dose and the serum inorganic fluoride concentration. Methoxyflurane nephrotoxicity has been attributed to certain breakdown products of methoxyflurane, especially inorganic fluoride and oxalic acid. It has been reported that methoxyflurane nephrotoxicity is classically associated with plasma inorganic fluoride concentrations exceeding 50 micromole.

Nephrotoxicity has only been associated when methoxyflurane is administered in large doses during general anaesthesia. Importantly there is no evidence of nephrotoxicity associated with sub-anaesthetic doses of methoxyflurane (even when administered every 1-2 days) and the biochemical evidence demonstrates that the resulting levels of metabolites are well below levels associated with subclinical toxicity (50-80 micromole) and decrease quickly.

Impaired hepatic function
Methoxyflurane in sub anaesthetic doses has also been reported to produce hepatitis (though these are few) therefore precautions are also listed for the use of methoxyflurane in patients with liver disease or who have previously shown signs of liver damage after previous methoxyflurane or halothane anaesthesia. Methoxyflurane hepatitis is thought to be an idiosyncratic hypersensitivity reaction.

Low dose exposure to methoxyflurane such as that required to produce brief analgesia has carried an extremely low risk of inducing hepatotoxicity. The clinical and pathological features of this rare adverse reaction suggest that any risk of its occurrence might be best be avoided by not administering methoxyflurane to any patient previously known to have developed hepatotoxicity after inhalation either of methoxyflurane or halothane.

Elderly
Potential effects on blood pressure and heart rate are known class-effects of high dose methoxyflurane used in anaesthesia and other anaesthetics. They do not appear to be significant at the analgesic doses. However, as the risk may potentially be increased for older people with hypotension and bradycardia, caution should be exercised in the elderly due to possible reduction in blood pressure.

Children
A PIP for methoxyflurane is currently in operation, and the results from this will guide any posology in this population. Studies from Western Australia show that in a large number of cases over many years, administration of Penthrox inhaler to children in the same manner and using the same inhaler as adults produces analgesia which is somewhat better than in adults. No significant problems were reported other than occasional drowsiness, rapidly reversed by temporarily discontinuing administration.

Overall comments on pharmacokineticins pecial populations.
The Applicant has adequately reflected concerns with regard to use in special populations in the SmPC. Caution has been advised in the case of the elderly because of the potential cardiovascular risks and the product is indicated for use in persons ≥18 years. With regard to patients with renal failure and hepatic failure, the Applicant has taken a conservative approach in the SmPC, which is acceptable.

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, based on published literature in support of the application. A brief summary of the pharmacodynamic characteristics of methoxyflurane as originally 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. No papers were identified which specifically investigated or defined the mode of action of methoxyflurane as an analgesic.

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. The MAC for methoxyflurane anaesthesia is 0.16%, which is equivalent to a concentration of 13.4 mg/100 mL in arterial blood, whereas conscious methoxyflurane analgesia is associated with blood levels of 1-8 mg/100 ml.

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 micromole, a level that is not associated with sub clinical 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 micromole. 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 mmol/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 mmol/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 there was no clinical or laboratory evidence of renal dysfunction.

Hepatotoxicity: The other serious adverse event associated with methoxyflurane administered in sub-anaesthetic doses is hepatitis, although only three cases have been reported in the literature in association with the analgesic use of methoxyflurane. It is suggested, from the evidence presented, and the frequency of the reports, that, at least in low doses, this is an idiosyncratic response which may result from a hypersensitivity reaction.

At analgesic concentrations of methoxyflurane there is no clinical depression of respiration or circulation. In one report on methoxyflurane use for emergency rescue, when the patient's haemodynamic condition was initially impaired, there was an appreciable improvement following methoxyflurane administration, with an increased differential BP and stronger heartbeats reported. In a retrospective observational study 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) 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 may 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.

Clinical efficacy
No new dose-response studies were submitted with this application. The studies submitted to support this application are the same studies as those submitted to support the previous applications. Full details of these studies can be found in the original Assessment reports, but these have been found to be acceptable in the procedures to date.

To support the application, the following were submitted:
a) Three prospective clinical studies - two studies, which provide clinical evidence of efficacy of methoxyflurane 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 evidence from the clinical studies was submitted to establish methoxyflurane's analgesic activity. The 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 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 aim did not receive study treatment.

The base-line level of pain (NRS between 4 and 7) is largely moderate to severe pain that interferes significantly with activities of daily living and in an acute setting is an appropriate population to demonstrate the analgesic properties of an active substance.

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 were 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 end point
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 end points
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 end point
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 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.

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. 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 were 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.

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 as 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 (methoxyflurane) 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 end point
The primary endpoint was worst pain during BMB, determined from highest pain score recorded at two time points: pain during aspirate and pain during core biopsy. 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 end points
Use of rescue medication
Only one patient in the placebo used rescue medication and no patients in the methoxyflurane 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.

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. 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-Study2
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.
As Penthrox® and Analgizer® inhalers are similar devices (to one another and to the proposed product), the published data for both devices were considered for review. In total 29566 patients received methoxyflurane via the Penthrox® inhaler on 29543 occasions. 416 Patients received methoxyflurane via the Analgizer® inhaler on 465 occasions (this excludes patients from the study conducted by Packer (1972) as it is unclear as to how many patients used the Analgizer® in this study).

In addition to the above publication, there are a number of publications with the use of methoxyflurane, especially via the Analgizer device.

In this application, the Applicant has applied for the indication of "emergency relief of moderate to severe pain in conscious adult patients (age 18 years and older) with trauma and associated pain", which is aligned with the previously approved Penthrox product Efficacy Study 1 and the supportive literature support this indication.

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 rather provide supportive evidence on the efficacy of methoxyflurane as an analgesic.
These studies cover a number of indications like pre-hospital emergency treatment, burns, dental analgesia, operative analgesia, post-operative analgesia and obstetric analgesia. These 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 department 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, particularly when dose of fentanyl/morphine are adjusted.

Overall conclusion on efficacy
Taken together, the evidence from clinical studies and published literature 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, based on the evidence from the two prospective clinical studies and the published literature it can be agreed that methoxyflurane has analgesic efficacy and can be useful in providing rapid but short duration of pain relief in patients with trauma and associated pain.

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) 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 therapeutic 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 QTc-F 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. 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.

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 (QTc-F), the analysis of covariance showed a statistically significant increase in mean QTc-F at the 15min time point (QTc-F 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, QTc-F, 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 QTc-F values exceeding 480 msec, and (for methoxyflurane and placebo) and only a few exceeding 450 msec. Only one subject had more than one instance of a triplicate mean QTc-F 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 QTc-F 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 15minutes 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/QTc 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 (12 ml) 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 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 (8 events), headache (7 events), hypotension (4 events) and nausea (4 events).

For the drug-related TEAEs relating to dizziness (including light-headedness, woozy, 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.

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 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.

Summary Pharmacovigilance system

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

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 Methoxyflurane 99.9%, 3 ml Inhalation vapour, liquid.

As this is an informed consent application ,many of the aspects of the applicant RMP reflect those already agreed for the originally authorized product, Penthrox, and so may be repeated here.

Safety specification

Summary of safety concerns	
Important identified risks	• Hepatotoxicity
Important potential risks	• Nephrotoxicity • Cardiovascular system effects • Respiratory system effects • Central nervous system effects • Malignant hyperthermia • Abuse potential • Interaction with CYP enzyme inducing drugs • Environmental exposure to methoxyflurane by administering healthcare professionals
Missing information	• Use in pregnancy and breast feeding

Pharmacovigilance Plan
Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

Additional pharmacovigilance activities

1. *Post Authorisation Safety Study (PASS) to Evaluate the Risks of Hepatotoxicity and Nephrotoxicity from Administration of Methoxyflurane (Penthrox) for Pain Relief in Hospital Accident & Emergency Departments in the United Kingdom (Category 3 study)*

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

The secondary objective is to assess whether there is an increased risk of nephrotoxicity.

The exploratory objectives are to:

- Assess whether there is an increased risk of hepatotoxicity or nephrotoxicity in patients who present with crush injury, heavy bleeding, low blood pressure and diabetes.
- Assess whether there is an increased risk of hepatotoxicity or nephrotoxicity in patients who are treated with contrast media or anaesthesia with sevoflurane following methoxyflurane administration.
- Estimate use in patients with a history of drug and alcohol abuse.
- Assess whether there is off-label use of methoxyflurane according to the contraindications listed in the SmPC.
- Assess whether there is any overdosage of methoxyflurane based on the doses specified in the SmPC.

Study design:

A primary data collection prospective cohort study with methoxyflurane, a concurrent control group and a non-concurrent control group.

Study population:
The study will be conducted in UK A&E units for the exposure and concurrent control cohorts and in the THIN database for the non-concurrent controls. A total of eight A&E centres in the UK which administer methoxyflurane and those which do not administer methoxyflurane and are willing to participate will be included in the study. Patients in the exposure and concurrent control cohorts will be selected through systematic consecutive enrolment in participating centres who meet eligibility criteria.

Milestones:
Protocol approved 26 November 2015; Final study report within 3 months after study finish.

2. *Evaluation of the effectiveness of Penthrox (methoxyflurane) educational tools adopted as additional risk minimisation measures: Healthcare professional and Patient Survey. (Category 3 study).*

The primary objective of the study is to measure awareness, usage, readability, knowledge and understanding of the messages, and impact on behavioural implementation of key safety information contained in the HCP administration guide and checklist, and in the patient alert card.

A secondary objective of the survey is to identify major determinants of awareness, usage, readability, knowledge and understanding of the messages, and impact on behavioural implementation of key messages among HCPs and patients. Additionally, the study will correlate measures of awareness, usage, readability, knowledge, understanding and behaviour reported by HCPs and patients in the survey with clinical data collected in the context of the twin PASS.

Study design:
Observational cross-sectional survey of HCPs and patients enrolled in 16 study sites in the UK, six (6) months after launch of Penthrox and implementation of aRMMs.

Study population:
The study target is to enrol 16 sites spread geographically in the UK. The characteristics of the study sites will be diverse so that the study can provide a representative picture of the effectiveness of the aRMMs nationwide. The population for the HCP survey will consist of physicians, nurses and paramedics responsible for the administration of Methoxyflurane in A&E departments and ambulances. The patient population will include patients treated with Methoxyflurane in emergency rooms and ambulances.

Milestones:
Protocol submitted 3 December 2015; Final study report within 2 months after survey finish

Risk minimisation measures

Additional risk minimisation measures targeting both patients and healthcare professionals are required to minimise the following safety concerns:

- Hepatotoxicity
- Nephrotoxicity
- Cardiovascular effects
- Respiratory effects
- Central nervous system effects
- Malignant hyperthermia
- Abuse potential
- Interaction with CYP enzyme inducing drugs
- Occupational exposure

The additional risk minimisation measures targeting healthcare professionals comprise a Methoxyflurane Administration Checklist and a Methoxyflurane Administration Guide. A Patient Alert Card is required to be provided to all patients receiving Methoxyflurane. Details of these aRMMs are outlined below:

Methoxyflurane Administration Checklist

Objectives: To raise awareness about potential hepatotoxicity, thereby reducing the risk of those events occurring and to ensure that healthcare professionals do not administer methoxyflurane to patients where its use is contraindicated.

Methoxyflurane is administered only to patient not known to have:
- Cardiovascular instability
- Hypersensitivity to methoxyflurane (or any fluorinated anaesthetic)
- Elevated temperature from an anaesthetic (malignant hyperthermia)
- Consciousness reduced (including due to alcohol)
- Kidney impairment
- Age below 18 years
- Lung or respiratory impairment
- Liver impairment
- Last administration of methoxyflurane

Ensure lowest required dose is administered and maximum dose of 6ml (2 vials) is not exceeded and patient is not taking:
- CYP-450 enzyme inducers (e.g. alcohol, isoniazid, phenobarbital or rifampicin).
- Antibiotics with known nephrotoxic effect (e.g. tetracycline, gentamicin, colistin, polymyxin B or amphotericin B).
Concomitant use of methoxyflurane with CNS depressants may produce additive depressant effects and patients should be observed closely.

Rationale for the additional risk minimisation activity:
To ensure the safe and effective use of methoxyflurane and appropriate management of important selected risk.

Target audience and planned distribution path:
The educational materials are intended for healthcare professionals administrating the medicinal product. Educational materials (aRMMs) will be available in hard copies as well as online on the emedicines compendium website.

Methoxyflurane Administration Guide - HCP Use

Objectives: to ensure the appropriate management of the following risks:
- Hepatotoxicity
- Nephrotoxicity
- Cardiovascular effects
- Respiratory effects
- Central nervous system effects
- Malignant hyperthermia
- Abuse potential
- Interaction with CYP enzyme inducing drugs
- Occupational exposure

Rationale for the additional risk minimisation activity:
To deliver guidance how should Methoxyflurane be administered, to inform HCPs of the safe and effective use of methoxyflurane and to ensure appropriate management of important selected risks

Target audience and planned distribution path:
The educational materials are intended for healthcare professionals administrating the medicinal product. Educational materials (aRMMs) will be available in hard copies as well as online on the emedicines compendium website.

Methoxyflurane Patient Alert Card

Objectives: To raise awareness about potential hepatotoxicity and nephrotoxicity, thereby reducing the risk of those events occurring and to ensure that the patient is aware of the signs and symptoms of the liver and kidney 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 your right stomach area (below the ribs)
- Reduced or excessive urination
- Swelling of feet or lower legs

Rationale for the additional risk minimisation activity:
To deliver recommendations on the use and/or contraindication(s) and/or warnings associated with Methoxyflurane and the specific important risks needing additional risk minimisation measures

Target audience and planned distribution path:
Intended for patients treated with methoxyflurane. Educational materials (aRMMs) will be available in hard copies as well as online on the e-medicines compendium website.

V. OVERALL CONCLUSIONS

Assessor's overall conclusions on the Risk Management Plan

The current approved RMP in place for Methoxyflurane is RMP version 2.4, with 08 July 2018 as the date of final sign-off. This RMP was approved on 27 September 2018, in accordance with revision 2 of GVP Module V. The summary of safety concerns identified by the Applicant adequately reflects the risks associated with the use of methoxyflurane in the indicated population. Additional pharmacovigilance activities in the form of two PASS to (1) evaluate the risks of hepatotoxicity and nephrotoxicity and to (2) evaluate the effectiveness of the additional risk minimisation measures are required for this product. The PASS protocol, version 7.0, (dated 11/11/2015), to evaluate the risks of hepatotoxicity and nephrotoxicity was approved in November 2015. According to the current information available, the clinical study report is anticipated in January 2020. The PASS protocol, version 3.0 (dated 14/12/2015) to evaluate the effectiveness of the additional risk minimisation measures was approved in January 2016.

A number of outstanding administrative issues were identified by the RMS during the assessment. However, as the RMP submitted with this application is identical to that submitted in a number of different DC procedures, during the first clock-stop period the applicant submitted a request to update the RMP across the different DCPs within three months of receiving the MA, to ensure that the RMPs used by the MAH and its partner are kept aligned. In view of the signed undertaking submitted with the responses, stating that an updated RMP, addressing all of the requested administrative amendments outlined in the Day 70 AR and Day 120 AR will be submitted within 3 months of receiving the MA, the RMP can be considered acceptable as it relates to this application.

The submitted Risk Management Plan, version 2.4 signed 08/07/2018 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The proposed common renewal date is 5 years from the End of Procedure date.

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

The evidence from two prospective clinical (one pivotal, one supportive) studies, published literature and post marketing data, taken together, is considered sufficient to support the efficacy of Methoxyflurane 99.9% as an analgesic for emergency pain relief in patients with trauma associated pain.

It is accepted that methoxyflurane by inhalation provides rapid (within 30 seconds) but moderate pain-relief (less than fentanyl/morphine) for a short duration. At the maximum use of 6ml/day, the dose would provide 1-2 hours of pain relief.

The significant safety concerns of methoxyflurane include nephrotoxicity, hepatotoxicity, malignant hyperthermia and cardiorespiratory depression. Nephrotoxicity appears to be concentration and rate of metabolism related and unlikely at the proposed analgesic doses. Hepatotoxicity has not been well characterised and there have been some reports at the analgesic doses which is a concern. However, based on the incidence rates of these events observed in Australia where the duration of use (since 1975) and extent of use is approximately known, the level of risk is considered acceptable

From the results of the thorough QTc study, at the proposed dose, there is negligible risk of clinically significant QTc prolongation with methoxyflurane, particularly as repeated dosing is not being considered.

Taking the overall evidence on efficacy and safety, the RMS is of the opinion that the benefit-risk profile for Methoxyflurane 99.9% in the proposed use is positive.

VI. REVISION DATE

February 2021

VII. UPDATES

Procedure number	Product Information affected	Date of start of procedure	Date of end of procedure	Approval/non approval
CRN00C2PH MA Transfer	SPC section 7, 8 Package Leaflet New MA Holder: Medical Developments MD&P Limited, 13A Ballyhoy Avenue, Raheny, Dublin 5, D05K068, Ireland New MA number: PA22745/003/001	26/02/2021	26/02/2021	Approved