Public Assessment Report

Decentralised Procedure

Methoxyflurane 99.9% Mundipharma 3 ml inhalation vapour, liquid

(methoxyflurane)

Procedure No: UK/H/6350/001/DC

UK Licence No: PL 16950/0355

Napp Pharmaceuticals Limited
LAY SUMMARY

Methoxyflurane 99.9% Mundipharma 3 ml inhalation vapour, liquid (methoxyflurane)

This is a summary of the Public Assessment Report (PAR) for Methoxyflurane 99.9% Mundipharma 3 ml inhalation vapour, liquid (PL 16950/0355; UK/H/6350/001/DC). For ease of reading, the product will be referred to as Methoxyflurane 99.9% Mundipharma in this lay summary. The lay summary explains how the application for Methoxyflurane 99.9% Mundipharma 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 Methoxyflurane 99.9% Mundipharma.

For practical information about using Methoxyflurane 99.9% Mundipharma, patients should read the package leaflet or contact their doctor or pharmacist.

What is Methoxyflurane 99.9% Mundipharma and what is it used for?
Methoxyflurane 99.9% Mundipharma 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 Methoxyflurane 99.9% Mundipharma Inhaler. Methoxyflurane 99.9% Mundipharma is intended to reduce the severity of pain, rather than stop it completely.

How does Methoxyflurane 99.9% Mundipharma work?
Methoxyflurane 99.9% Mundipharma contains the active substance methoxyflurane which reduces pain when inhaled at low concentrations.

How is Methoxyflurane 99.9% Mundipharma used?
Methoxyflurane 99.9% Mundipharma 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 Methoxyflurane 99.9% Mundipharma 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 Methoxyflurane 99.9% Mundipharma Inhaler, under the supervision of a healthcare professional. The patient’s healthcare professional will prepare the Methoxyflurane 99.9% Mundipharma Inhaler and give it to the patient.

Adults
One or two 3 ml bottles of Methoxyflurane 99.9% Mundipharma can be used per administration. The patient should not inhale more than the maximum dose of two 3 ml 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.

Methoxyflurane 99.9% Mundipharma should not be used in children under 18 years.
This medicine can only be obtained with a prescription.

**What benefits of Methoxyflurane 99.9% Mundipharma have been shown in studies?**

Methoxyflurane 99.9% Mundipharma is a duplicate product to Penthrox (methoxyflurane) 3mL inhalation vapour, liquid (Medical Developments UK Limited), which is already approved in the European Union. The company, Napp Pharmaceuticals Limited provided some data on efficacy and safety of methoxyflurane from prospective studies previously provided by Medical Development UK Limited for Penthrox. In addition, data has been provided from the published literature on methoxyflurane. These studies have shown that Methoxyflurane 99.9% Mundipharma is effective in the proposed indication to reduce pain in adults 18 years and older.

**What are the possible side effects of Methoxyflurane 99.9% Mundipharma?**

Like all medicines, Methoxyflurane 99.9% Mundipharma 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
- Feeling of extreme happiness
- Difficulty in speaking
- Memory loss
- Anxiety or depression
- Taste disturbance, loss of taste or dry mouth
- Headache
- Nausea
- Numbness
- Low blood pressure
- Coughing
- Feeling drunk
- Sweating

For the full list of all side effects reported with Methoxyflurane 99.9% Mundipharma see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Methoxyflurane 99.9% Mundipharma.

**Why is Methoxyflurane 99.9% Mundipharma approved?**

It was concluded that, in accordance with EU requirements that, for Methoxyflurane 99.9% Mundipharma, 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 Methoxyflurane 99.9% Mundipharma?

A Risk Management Plan (RMP) has been developed to ensure that Methoxyflurane 99.9% Mundipharma 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 Methoxyflurane 99.9% Mundipharma, including the appropriate precautions to be followed by healthcare professionals and patients. In addition to the safety information provided in the Methoxyflurane 99.9% Mundipharma product information, the RMP includes educational activities/training and materials for healthcare professionals to ensure the safe and effective use of Methoxyflurane 99.9% Mundipharma. 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 and kidney following methoxyflurane administration.

Other information about Methoxyflurane 99.9% Mundipharma

Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Croatia, Iceland, Italy, Lithuania, Luxembourg, Latvia, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovak Republic and the UK agreed to grant a Marketing Authorisation for Methoxyflurane 99.9% Mundipharma on 11 December 2017. A Marketing Authorisation for Methoxyflurane 99.9% Mundipharma was granted in the UK to Napp Pharmaceuticals Limited on 18 January 2018.

The full PAR for Methoxyflurane 99.9% Mundipharma follows this summary.

For more information about treatment with Methoxyflurane 99.9% Mundipharma, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in April 2018.
SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Introduction</td>
<td>6</td>
</tr>
<tr>
<td>II</td>
<td>Quality aspects</td>
<td>7</td>
</tr>
<tr>
<td>III</td>
<td>Non-clinical aspects</td>
<td>9</td>
</tr>
<tr>
<td>IV</td>
<td>Clinical aspects</td>
<td>13</td>
</tr>
<tr>
<td>V</td>
<td>User consultation</td>
<td>41</td>
</tr>
<tr>
<td>VI</td>
<td>Overall conclusion, benefit/risk assessment and recommendation</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Annex 1- Table of content of the PAR update for MRP and DCP</td>
<td>53</td>
</tr>
</tbody>
</table>
Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Methoxyflurane 99.9% Mundipharma 3 ml inhalation vapour, liquid (PL 16950/0355; UK/H/6350/001/DC) could be approved. The product will be referred to as ‘Methoxyflurane 99.9% Mundipharma’ in this scientific discussion.

Methoxyflurane 99.9% Mundipharma 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. Methoxyflurane 99.9% Mundipharma is self-administered under the supervision (with assistance if necessary) of a healthcare professional using the hand-held Methoxyflurane 99.9% Mundipharma Inhaler. The healthcare professional must prepare the inhaler for use and give it to the patient. The proposed dosage regimen is one 3 ml dose. A second 3 ml bottle of methoxyflurane can be given to extend the period of pain relief. The maximum dose to be used is two bottles of 3 ml, and this should not be exceeded.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Germany, Denmark, Estonia, Spain, Finland, France, Croatia, Iceland, Italy, Lithuania, Luxembourg, Latvia, Norway, Poland, Portugal, Romania, Sweden, Slovenia and the Slovak Republic 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. This is the second DCP application in the European Union for methoxyflurane in the proposed indication. The first DCP (UK/H/5542/001/DC; with UK as Reference Member State and Ireland, Belgium and France as CMS) was submitted by Medical Developments UK Limited for Penthrox 3 mL inhalation vapour liquid, under Article 8(3) of Directive 2001/83/EC, as amended, as a new active substance; the procedure concluded in 2015. For ease of reading Penthrox 3 mL inhalation vapour liquid, will be referred to as ‘Penthrox’ in this scientific discussion.

The Applicant, Napp Pharmaceuticals Limited (and the Mundipharma Group of companies) have a License, Development and Commercialisation Agreement for Penthrox with the Medical Developments UK Limited in Europe (but not the UK). This submission for Methoxyflurane 99.9% Mundipharma is essentially a duplicate of the initial submission, although there are updates to the current dossier and there have subsequently been a number of variations to that initial submission. The updated dossier submitted by the Applicant in this DCP is, overall, very similar to the dossier submitted for the previous application for Penthrox (methoxyflurane) approved in 2015.

Although there is published literature on the use of methoxyflurane for analgesia in children and is licensed for use in children in Australia, the 2015 DCP approval in Europe restricted the use of methoxyflurane to adults in Europe. The Marketing Authorisation Holder (MAH) of the first DCP is yet to complete a clinical study in children in accordance to the agreed Paediatric Investigation Plan (PIP). The current application is also proposed to be restricted to adult use.

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 cardiovascular safety pharmacology studies and four genotoxicity studies being conducted by the Applicant for Penthrox, which is acceptable in line with the Guideline on the non-clinical documentation for mixed marketing authorisation applications (CPMP/SWP/799/95).

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 Penthrox in Australia. 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.

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.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 11 December 2017. After a subsequent national phase, a Marketing Authorisation was granted in the UK to Napp Pharmaceuticals Limited on 18 January 2018.

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, Methoxyflurane 99.9% Mundipharma, is a clear, almost colourless, volatile liquid (for oral inhalation), with a characteristic fruity odour.

Each bottle of Methoxyflurane 99.9% Mundipharma contains 3 ml of methoxyflurane 99.9%. Methoxyflurane 99.9% Mundipharma 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 Methoxyflurane 99.9% Mundipharma 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 Methoxyflurane 99.9% Mundipharma 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: C₃H₄Cl₂F₂O
Structure

M₉: 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 (3 ml) 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. This product does not contain or consist of genetically modified organisms (GMO).

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 Methoxyflurane 99.9% Mundipharma, from a quality point of view.

III NON-CLINICAL ASPECTS
III.1 Introduction
The non-clinical dossier is largely based on available data in the published literature with three cardiovascular safety pharmacology studies and four genotoxicity studies having been conducted in support of the application for Penthrox. 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 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 antinociceptive 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 for 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 and the Applicant has presented the safety margins for hepatic effects based on administered dose. Given that safety margins have been calculated using data from cited toxicity studies with significantly higher exposures and dosing durations than can be expected through normal clinical use of the proposed product the use of these to form any conclusions on clinical relevance may not be appropriate. The SmPC adequately describes the hepatotoxicity findings. Clinical data are available on the number and nature of hepatic adverse events in relation to analgesic and anaesthetic use and are discussed in the Clinical aspects section of this report.

A risk assessment has been provided for the excipient butylated hydroxytoluene (BHT) and its inclusion in the proposed product does not raise any safety concerns.

References are made to in vitro (Ames) and in vivo genotoxicity (micronucleus) studies, conducted by the Applicant for Penthrox, 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 Methoxyflurane 99.9% Mundipharma is not intended for daily use, the Applicant argues the risk of delayed fetal development is considered very low. The wording of sections 4.6 and 5.3 of the SmPC adequately cover these effects.

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:risks 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.

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 (logKow) 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 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 Methoxyflurane 99.9% Mundipharma is of negligible risk to the environment when used in accordance with the product information.

However, according to the EMA document Questions and Answers on 'Guideline on the environmental risk assessment of medicinal products for human use' (EMA/CHMP/SWP/44609/2010), the log Kow should be
determined experimentally. A calculated value is generally not acceptable. Hence the Applicant has agreed to provide a Phase II environmental risk assessment for methoxyflurane as a post authorisation measure.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Methoxyflurane 99.9% Mundipharma, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction
The application for Methoxyflurane 99.9% Mundipharma 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. These studies are those submitted in the initial submission for Penthrox.
  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 (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%. Methoxyflurane has the following partition coefficients:

- a water/gas coefficient of 4.5,
- a blood/gas coefficient of 13 and
- an oil/gas coefficient of 825

The oil/gas coefficient shows 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.

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.

Methoxyflurane is metabolised via two main pathways, O-demethylation and dechlorination. 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 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 CO2, 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 μmol/l 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 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. 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 50 μmol/l 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 μmol/l.

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 (50-80μM/L) 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 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:** 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 pharmacokinetic in special 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.

**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, based on published 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. 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 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.

Hepatotoxicity: The other serious adverse event associated with methoxyflurane administered in subanaesthetic 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 heart beats reported. 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:

- Hepatic inducers increasing nephrotoxicity of methoxyflurane
- Reduction of renal blood flow and hence anticipated enhanced effect when used in combination with drugs reducing cardiac output
- 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**

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 DCP application for Penthrox (methoxyflurane), which was granted a Marketing Authorisation in 2015.

To support the application, the following were submitted:

- 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.
- Substantial evidence from published literature to support efficacy and safety of methoxyflurane in the proposed dose and method of use.
- 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 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.
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 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:
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></th>
<th>Methoxyflurane (N=149)</th>
<th>Placebo (N=149)</th>
<th>Estimated Treatment Effect (95% CI Confidence Interval)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted* change from baseline</td>
<td>-30.2</td>
<td>+11.9</td>
<td>-18.3 (-22.9,-13.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></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 (-28.0,-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></td>
<td>0.0003</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:
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 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.

Adjusted odds ratios and 95% confidence intervals were provided 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>
<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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mins</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>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>
<td>5.6</td>
</tr>
<tr>
<td>10 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>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>
<td>5.3</td>
</tr>
<tr>
<td>15 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>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>
<td>11.3</td>
</tr>
<tr>
<td>20 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>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>
<td>12</td>
</tr>
<tr>
<td>Placebo (N=149)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 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>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>
<td>0.7</td>
</tr>
<tr>
<td>10 mins</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>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>
<td>1.5</td>
</tr>
<tr>
<td>15 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>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>
<td>4.1</td>
</tr>
<tr>
<td>20 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>64.9</td>
<td>54.4</td>
<td>43.0</td>
<td>36.8</td>
<td>28.9</td>
<td>16.7</td>
<td>10.5</td>
<td>8.8</td>
<td>6.1</td>
<td>4.4</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 (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 endpoint
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 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 12-4: Subject Global Medication Performance Assessment (n=97)

<table>
<thead>
<tr>
<th>Patient rating</th>
<th>Methoxyflurane</th>
<th>Placebo</th>
<th>Overall</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<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.

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.
The below table presents an overview of the published studies on the clinical efficacy of methoxyflurane as an analgesic:

<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 and pre-hospital analgesia</td>
<td>16</td>
<td>&gt;30,000</td>
<td>Penthrox\textsuperscript{a}: 12, Analgizer\textsuperscript{b}: 4, Other: 2</td>
<td>15 months – 98 years</td>
</tr>
<tr>
<td>Burns Analgesia</td>
<td>8</td>
<td>216 (542 occasions)</td>
<td>Penthrox\textsuperscript{a}: 0, Analgizer\textsuperscript{b}: 2, Other: 6 (1 study compared 2 devices)</td>
<td>4 months – 82 years</td>
</tr>
<tr>
<td>Dental Analgesia</td>
<td>4</td>
<td>553 (575 occasions)</td>
<td>Penthrox\textsuperscript{a}: 1, Analgizer\textsuperscript{b}: 0, Other: 3</td>
<td>1-69 (Exclusion: age range not documented for 1 study)</td>
</tr>
<tr>
<td>Analgesia studies in healthy volunteers</td>
<td>3</td>
<td>37</td>
<td>Penthrox\textsuperscript{a}: 0, Analgizer\textsuperscript{b}: 0, Other: 3</td>
<td>29-51 (Exclusion: age range not documented for 1 study)</td>
</tr>
<tr>
<td>Post operative Analgesia</td>
<td>2</td>
<td>60</td>
<td>Penthrox\textsuperscript{a}: 0, Analgizer\textsuperscript{b}: 2, Other: 0</td>
<td>19-78</td>
</tr>
<tr>
<td>Operative Analgesia</td>
<td>2</td>
<td>73</td>
<td>Penthrox\textsuperscript{a}: 1, Analgizer\textsuperscript{b}: 1, Other: 0</td>
<td>15-84</td>
</tr>
</tbody>
</table>
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”, 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 further 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 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, 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.

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) 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/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 (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 (13.3%)</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
The Applicant makes reference to a retrospective, observational study conducted by MDI (the Applicant for the DCP) that investigated in a real life setting whether Penthrox (methoxyflurane), 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. The observations indicated that, in this otherwise unselected, large group of cases who had received methoxyflurane for pain, there were no deleterious effects on pulse rate, systolic blood pressure or respiratory rate.

Besides the Penthrox Vital Signs Report, there have been number of published papers (between 2006 – 2016) focusing on the use of methoxyflurane as an analgesic and presenting adverse events associated with this use in adults and children in different setting with both incident pain and trauma related pain.

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 and was conducted by MDI in conjunction with the University of Western Australia (2010). 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. Recorded health events occurred at a lower or similar rate in the methoxyflurane and non-methoxyflurane groups.

In a separate data linkage study, 247 renal colic patients and 373 patients with hepatic disease being transported to hospital by ambulance were administered methoxyflurane and there was no increased risk reported in these patients.

The literature also 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 minutes approximate duration of the 6 mL methoxyflurane used with the Penthrox Inhaler.

In addition to the record linkage study (2010), 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 6ml 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 (3ml of methoxyflurane per week, for two weeks; recovered with sequela), acute hepatitis, hepatomegaly (3ml methoxyflurane per week for 3 weeks; resolved without sequela), vomiting and jaundice (3ml methoxyflurane in one day; resolved without sequela), dizziness, confusion and hypoxia, among other symptoms (3ml methoxyflurane in one day; resolved without sequela), medication error (6ml methoxyflurane, duration of exposure not known that was resolved without sequel), blood pressure fluctuation (Penthrox outcome unknown), amnesia and affect lability (dose and outcome unknown), increased lipase and pancreatitis (dose and outcome unknown), and altered state of consciousness, nausea and vomiting (dose and outcome unknown).

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.
It has been reported that 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. Oxalate crystals have been reported in the kidneys following methoxyflurane nephrotoxicity, however, the degree of oxalate crystal deposition did not adequately explain the development of renal failure and in animal studies injection of oxalic acid in amounts similar to those resulting from methoxyflurane did not produce polyuria a key feature of methoxyflurane nephrotoxicity. In animal studies, injection of inorganic fluoride produced renal functional and histological changes similar to those seen following high doses of methoxyflurane, except that there were no oxalate crystals. Thus, it was postulated that the inorganic fluoride ion was the prime cause of nephrotoxicity in a dose related manner.

It has been reported that although methoxyflurane nephrotoxicity is classically associated with plasma inorganic fluoride concentrations exceeding 50 μmol/L, sevoflurane, enfurane and isoflurane have not been associated with nephrotoxicity despite plasma fluoride concentrations often exceeding 50 μmol/L. Thus, the high levels of inorganic fluoride ion associated with methoxyflurane toxicity but may not be the only cause. There may be a co-pathogenetic role for dichloroacetic acid that is also produced by metabolism of methoxyflurane in the liver and kidney.

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 methoxyflurane 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 methoxyflurane 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.

It has also been demonstrated that peak serum fluoride levels in paediatric patients were found to be lower than those reported in adults after similar exposure to methoxyflurane and no cases of methoxyflurane nephrotoxicity have been reported in children.

Information on patients with pre-existing renal conditions:
Nephrotoxicity has only been associated when methoxyflurane is administered in large doses during general anaesthesia. One case of renal failure was reported to the TGA. It appears that the patient had both hepatic and renal failure following repeated use of methoxyflurane for dental analgesia. Repeated follow-up by MDI failed to elucidate any further details to clarify the details of any confounders or course of events. There is a possibility that the renal failure was secondary to hepatic failure (which required transplantation). Importantly there is no evidence of nephrotoxicity associated with subanaesthetic 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- 80μmol/L) and decrease quickly.

MDI has conducted a meta-analysis of 8 studies with matching data on serum inorganic fluoride levels before and after methoxyflurane analgesia during labour and delivery, and comparing them with levels in controls. The result confirmed that prolonged administration of methoxyflurane resulted in elevated levels.
of serum inorganic fluoride. The mean plasma fluoride < 20 μmol/L in patients given methoxyflurane for analgesia was much lower than the minimum level that can result in subclinical nephrotoxicity.

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 methoxyflurane 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.

There is some clinical evidence to show that hepatic damage (hepatitis) may very rarely occur after high dose exposure to methoxyflurane as an anaesthetic, and quite exceptionally after its limited, low dose use to produce brief analgesia. Liver damage has commonly been self-limiting and recoverable provided further exposure was avoided. It has been shown to involve necrosis of hepatocytes and a reactive inflammatory cell infiltrate, sometimes predominantly composed of eosinophils.

The clinical and pathological features of the hepatotoxicity suggest it is a very rare idiosyncratic allergic response, presumably an autoimmune reaction to proteins haptenised by a metabolite of methoxyflurane. This hypothesis depends on an argument by analogy with the well-known halothane-induced allergic autoimmune hepatitis and the potential similarities between their metabolic pathways in the body. There is a quite limited indication that cross- sensitisation between methoxyflurane and halothane may occur. There is no evidence to show whether this reflects a common autoantigen resulting in an immunological cross-reaction.

No evidence of hepatotoxicity was found in the Efficacy Study 1, and the liver function data were similar between methoxyflurane- treated patients and placebo- treated patients. In Efficacy Study 2, laboratory evaluations, none of the abnormal findings or outside of reference range values were considered to be clinically significant, resulted in an AE or required treatment.

In a data linkage study that included 373 hepatic disease patients being transported to hospital by ambulance in Western Australia and administered methoxyflurane, there was no increased risk in patients that received methoxyflurane compared to patients that did not, and the time taken to the first occurrence of disease was similar in the methoxyflurane and non- methoxyflurane treated patients.

According to the Applicant, around 50 cases of hepatotoxicity have been described in literature with anaesthetic use of methoxyflurane, which generally occurred after multiple exposures and higher dose. The damage presented between 2-21 days after administration and most cases recovered in few weeks.

Intensive searching of the published literature including publicly available adverse reaction databases in major regulatory agencies has revealed 10 cases in which hepatotoxicity has been reported after more limited exposure to methoxyflurane, usually as an analgesic. Of the 10 cases, four of them occurred in Australia where Penthrox was the sole product used. Information about the overall extent of exposure was
reported in all 10 cases; in four cases exposure exceeded the proposed recommended dose; in five instances there was also repeated use of methoxyflurane within a few days to a few weeks, including one subject who inhaled it twice daily for 6 weeks.

The clinical and pathological features of this rare adverse reaction suggest that any risk of its occurrence might best be avoided by not administering methoxyflurane to any patient previously known to have developed hepatotoxicity after inhalation either of methoxyflurane or halothane.

The incidence of methoxyflurane-associated liver damage has been very low. Most reports have been of isolated cases, even in the 1960s-1970s when high doses of methoxyflurane were in wide use as an anaesthetic agent, in several countries including Canada and the USA. Investigators sought evidence of hepatic damage in patients given full surgical anaesthesia with methoxyflurane, and did not find any biochemical indication of it in any of their 12 patients.

A formal data linkage study (2010) of 17,629 patients receiving analgesic doses of methoxyflurane did not reveal any instances of liver damage.

The literature reports methoxyflurane inhalation in approximately 6,880 patients and the number of confirmed cases of hepatitis attributed to analgesic levels of methoxyflurane is five. In addition, there have been over 3 million administrations of Penthrox in Australia since 1975. In that time there have only been a handful of adverse events that involved hepatic function.

The Applicant concludes that hepatic damage may rarely occur after high dose and is quite exceptional after low dose use. The liver damage is generally self-limiting and is likely to be due to idiosyncratic response.

**Potential for Abuse/Misuse**

The Applicant refers to the evaluation report presented by MDI on the potential for abuse/misuse of methoxyflurane. The salient features of the report were:

- Penthrox (methoxyflurane) 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 (methoxyflurane) does not trigger key neurotransmitters in key regions of the brain associated with abuse and dependency;
- Penthrox (methoxyflurane) is not listed by any regulatory authority as a drug of abuse or dependence.
- Penthrox (methoxyflurane) is manufactured and packaged to minimise abuse potential and does not have a history of diversion despite widespread use by both professional paramedic/medical staff, first aid providers, veterinary practitioners and biological research staff.

Under these conditions, it is highly unlikely to cause physical dependency.

More than 5 million doses of methoxyflurane have been given/administered since 1975. Drug abuse has not been recorded as a significant risk. Six cases of methoxyflurane abuse (all by health professionals/health professional contacts have been reported from post-marketing data related to anaesthetic use. There is a strong likelihood that the abuse may have been linked with the availability of larger pack sizes (125 ml for anaesthesia and 15 mL for analgesia). In all these cases it was health care professionals or a person
associated with the HCP abusing 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.

With the current packaging and access to methoxyflurane and considering 5 million 3 ml doses have been sold, the abuse potential is considered very rare.

**Malignant hyperthermia**

One clinical case of malignant hyperthermia has been reported (to the TGA) to date with the clinical use of methoxyflurane. In this case, the dose of methoxyflurane was unknown and patient was also receiving 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 and potential for QT-prolongation**

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.

In the retrospective observational study (Penthrox Vital Signs report) on 590 prehospital patients, the administration of low dose methoxyflurane used for analgesia did not produce any deleterious effect on cardiovascular or respiratory parameters. Typically, systolic blood pressure decreased slightly after methoxyflurane administration 0 to 10 minutes after administration and then plateaued between 10 and 30 minutes after administration. Overall, respiratory pulse rate fell continuously over 20 to 30 minutes after methoxyflurane administration.

Methoxyflurane inhibited the hERG tail current in vitro (IC50 ~ 84 μg/ml), indicating a potential for QT-prolongation, a known property of this pharmacological class. However, in Study 3, there was no evidence for any effect of methoxyflurane on heart rate, on the RR interval, PR interval or QRS duration, or on ECG morphology. Clinical experience has not provided any indication that methoxyflurane may cause ventricular tachyarrhythmia or torsades de pointes under conditions of use in analgesia.

In a long-term data linkage study, (2010), it was reported that in patients administered methoxyflurane no increased risk of cardiac disease occurrence was observed when compared with pre-hospital care patients who were not administered methoxyflurane.
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. 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).

The overall extent of use of methoxyflurane has been approximately 5 million units (including European usage since approval of the first DCP). Although there have been a few reported cases of hepatic injury, CNS symptoms, cardiovascular instability and kidney damage, the risk with analgesic doses of methoxyflurane appears low.

No new significant safety concerns have been identified.

**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 Methoxyflurane 99.9% inhalation vapour, liquid.

The Applicant proposes the following Summary of Safety Concerns which is considered to adequately reflect the data available:
**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 and nephrotoxicity 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 a survey to evaluate the effectiveness of Methoxyflurane 99.9% Mundipharma educational tools adopted as additional risk minimisation measures to address the safety concerns: Healthcare Professional (HCP) and Patient survey

**Summary of pharmacovigilance activities:**
**Risk Minimisation Measures**
Routine risk minimisation through warnings in the SmPC and additional risk minimisation through the provision of educational materials and training for HCPs, which will be distributed from the time of launch, are proposed.

The Applicant has committed to maintain a harmonised RMP with the innovator.

In order to maintain a harmonised RMP, it is appropriate that the additional risk minimisation measures remain within the combined RMP for both products. It is also appropriate that these risk minimisation measures apply for the proposed MA in order to ensure that HCPs understand that the risk minimisation measures apply to both the innovator product, Penthrox, and this duplicate product Methoxyflurane 99.9% Mundipharma.

**IV.7 Discussion of the clinical aspects**
It is recommended that a Marketing Authorisation is granted for Methoxyflurane 99.9% Mundipharma, from a clinical point of view.

**V. USER CONSULTATION**
A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to the package leaflet for Penthrox 3mL inhalation vapour liquid (Medical Developments UK Limited). The bridging report submitted by the applicant is acceptable.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-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% Mundipharma 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% Mundipharma in the proposed use is favourable.

The grant of a Marketing Authorisation is, therefore, recommended.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The Marketing Authorisation Holder has submitted the text version only and has committed to submitting mock-up to the regulatory authorities for approval before packs are marketed. The current labelling text is presented below:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON LABEL (10 PACK OF COMBINATION PACKS)

1. NAME OF THE MEDICINAL PRODUCT

*Methoxyflurane 99.9% Mundipharma*, 3 ml inhalation vapour, liquid
methoxyflurane

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bottle contains 3 ml methoxyflurane 99.9%

3. LIST OF EXCIPIENTS

Butylated hydroxytoluene (E321).

4. PHARMACEUTICAL FORM AND CONTENTS

Contains:
10 x combination packs:

Each combination pack contains:
1 bottle containing 3 ml methoxyflurane 99.9%
1 *Methoxyflurane 99.9% Mundipharma* Inhaler
1 Activated Carbon (AC) Chamber

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Inhalation use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 0GW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 16950/0355

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille to be agreed

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier to be included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Methoxyflurane 99.9% Mundipharma 3 ml inhalation vapour, liquid
methoxyflurane

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bottle contains 3 ml methoxyflurane 99.9%

3. LIST OF EXCIPIENTS

Butylated hydroxytoluene (E321).

4. PHARMACEUTICAL FORM AND CONTENTS

Inhalation vapour, liquid

Each pack contains:
1 bottle containing 3 ml methoxyflurane 99.9%
1 Methoxyflurane 99.9% Mundipharma Inhaler
1 Activated Carbon (AC) Chamber

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 0GW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 16950/0355

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille to be agreed.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier to be included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:
Methoxyflurane 99.9% Mundipharma 3 ml inhalation vapour, liquid

PARTICULARS TO APPEAR ON THE INNER PACKAGING

INHALER LABEL (FOR DEVICE LABEL WITHOUT ACTIVE)

1. NAME OF THE MEDICINAL PRODUCT

*Methoxyflurane 99.9% Mundipharma* Inhaler

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For use with *Methoxyflurane 99.9% Mundipharma* (methoxyflurane) only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medical Developments International Ltd
4 Caribbean Drive, Scoresby,
Vic, 3179, Australia

12. MARKETING AUTHORISATION NUMBER(S)
Emergo Europe
Prinsesgracht 20, 2514 AP, The Hague
The Netherlands

13. BATCH NUMBER
LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Disposable: Single patient use.
Read the package leaflet before use

"Or"

Disposable: Single patient use.

Remove the cap of the bottle by hand. Alternatively, use the base of the Methoxyflurane 99.9% Mundipharma Inhaler to loosen the cap with a ½ turn. Separate the Inhaler from the bottle and remove the cap by hand.
Tilt the Methoxyflurane 99.9% Mundipharma inhaler to a 45° angle and pour the total contents of one bottle into the base whilst rotating.
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTTLE LABEL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Methoxyflurane 99.9% Mundipharma</em> 3 ml Inhalation vapour, liquid</td>
</tr>
<tr>
<td>methoxyflurane</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. METHOD OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>inhalation use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. BATCH NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
</table>
**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON LABEL (10 PACK OF BOTTLES)**

1. **NAME OF THE MEDICINAL PRODUCT**

*Methoxyflurane 99.9% Mundipharma* 3 ml inhalation vapour, liquid

methoxyflurane

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

One bottle contains 3 ml of methoxyflurane 99.9%

3. **LIST OF EXCIPIENTS**

Butylated hydroxytoluene (E321).

4. **PHARMACEUTICAL FORM AND CONTENTS**

Contains:
10 x bottles containing 3ml methoxyflurane 99.9%

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.
Inhalation use.

6. **SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

EXP
9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Napp Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 0GW
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

PL 16950/0355

13. BATCH NUMBER

LOT

14. GENERAL CLASSIFICATION FOR SUPPLY

Prescription only medicine

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille to be agreed

17. UNIQUE IDENTIFIER – 2D Barcode

2D barcode carrying the unique identifier to be included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:
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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>