Public Assessment Report

Decentralised Procedure

Sojourn Sevoflurane 100% Inhalation Vapour, Liquid (sevoflurane)

Procedure No: UK/H/4252/001/DC

UK Licence No: PL 29595/0002

Piramal Healthcare UK Limited
LAY SUMMARY

On 21 September 2011, the Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation for the medicinal product Sojourn Sevoflurane 100% Inhalation Vapour, liquid (PL 29595/0002; UK/H/4252/001/DC) to Piramal Healthcare UK Limited. This is a prescription-only medicine (POM).

Sojourn Sevoflurane 100% Inhalation Vapour, liquid is an inhaled general anaesthetic used for surgical operations and other procedures. It causes the patient to fall into a deep sleep (induction of anaesthesia), and it also maintains a deep painless sleep during which the patient can undergo surgery (maintenance of anaesthesia).

Sojourn Sevoflurane 100% Inhalation Vapour, liquid contains the active ingredient sevoflurane, which is a general anaesthetic.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Sojourn Sevoflurane 100% Inhalation Vapour, liquid (PL 29595/0002; UK/H/4252/001/DC) outweigh the risks; hence a Marketing Authorisation was granted.
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# Module 1
**Information about the initial procedure**

<table>
<thead>
<tr>
<th><strong>Product Name(s)</strong></th>
<th>Sojourn Sevoflurane 100% Inhalation Vapour, liquid</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
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<td><strong>Active Substances</strong></td>
<td>Sevoflurane</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Inhalation vapour, liquid</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>100%</td>
</tr>
</tbody>
</table>
| **MA Holder** | Piramal Healthcare UK Limited  
1st Floor, Alpine House,  
Unit II, Honeypot Lane,  
London NW9 9RX,  
United Kingdom |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia and Slovak Republic |
| **Procedure Number(s)** | UK/H/4252/001/DC |
| **Timetable** | Day 210 – 24 August 2011 |
Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Sojourn Sevoflurane 100% Inhalation Vapour, liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Sevoflurane 100%. The finished product is comprised only of the active ingredient,

3 PHARMACEUTICAL FORM
Inhalation vapour, liquid
Clear, colourless, volatile liquid

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Induction and maintenance of general anaesthesia in adult and paediatric patients of all ages, including full term neonates (see section 4.2 for age details).

4.2 Posology and method of administration
Sevoflurane should be delivered via a vaporizer specifically calibrated for use with Sevoflurane so that the concentration delivered can be accurately controlled. MAC (minimum alveolar concentration) values for sevoflurane decrease as the patient’s age increases and with the addition of nitrous oxide. Dosage should be individualised and titrated to the desired effect according to the patient’s age and clinical status.

<table>
<thead>
<tr>
<th>Age of Patient (years)</th>
<th>Sevoflurane 100% Inhalation Vapour, liquid in Oxygen</th>
<th>Sevoflurane 100% Inhalation Vapour, liquid in 65% N₂O/35% O₂ *</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 1 months</td>
<td>3.3 %</td>
<td>2.0 %</td>
</tr>
<tr>
<td>1 - &lt; 6 months</td>
<td>3.0 %</td>
<td></td>
</tr>
<tr>
<td>6 months - &lt; 3 years</td>
<td>2.8 %</td>
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<tr>
<td>3 – 12</td>
<td>2.5 %</td>
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<tr>
<td>25</td>
<td>2.6 %</td>
<td>1.4 %</td>
</tr>
<tr>
<td>40</td>
<td>2.1 %</td>
<td>1.1 %</td>
</tr>
<tr>
<td>60</td>
<td>1.7 %</td>
<td>0.9 %</td>
</tr>
<tr>
<td>80</td>
<td>1.4 %</td>
<td>0.7 %</td>
</tr>
</tbody>
</table>

* Neonates are full term gestational age. MAC in premature infants has not been determined.
** In 1 – 3 year old paediatric patients, 60% N₂O/40% O₂ was used.

Anaesthesia Induction
A short acting barbiturate or other intravenous induction agent may be administered followed by inhalation of sevoflurane.

Induction with sevoflurane only may be achieved by inhalation of 0.5-1.0% sevoflurane in oxygen (O₂) with or without nitrous oxide (N₂O), increasing by increments of 0.5-1.0% sevoflurane, to a maximum of 8% in adults and children until the required depth of anaesthesia is achieved.

In adults inspired concentrations of up to 5% sevoflurane usually produce surgical anaesthesia in less than two minutes. In children, inspired concentrations of up to 7% sevoflurane usually produce surgical anaesthesia in less than two minutes.

Maintenance of Anaesthesia
Surgical levels of anaesthesia may be maintained by inhalation of 0.5-3% sevoflurane in O₂ with or without N₂O.
Emergence:
Emergence times are generally short following Sevoflurane anaesthesia. Therefore, patients may require early post operative pain relief.

As with other halogenated inhalational anaesthetic agents repeated use within a short period of time should be performed only with caution

Hepatic Dysfunction:
Sevoflurane should not be used in patients with a history of unexplained moderate/severe hepatic dysfunction with jaundice, fever, and/or eosinophilia in association with halogenated anesthetics.

Renal Insufficiency:
Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 133 μmol/litre) studied, the safety of sevoflurane administration in this group has not been fully established. Therefore, sevoflurane should be used with caution in patients with renal insufficiency. In some studies in rats, nephrotoxicity was seen in animals exposed to levels of Compound A (pentafluoroisopropenyl fluoromethyl ether (PIFE) in excess of those usually seen in routine clinical practice. The mechanism of this renal toxicity in rats is unknown and its relevance to man has not been established. (See Section 5.3, Preclinical Safety Data for further details.). Post-operative monitoring of the renal function is recommended in renal patients.

Route of Administration:
Inhalation use. Sevoflurane has to be administered either via face mask or via endotracheal tube. Sevoflurane should be administered only by persons trained in the administration of general anaesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and circulatory resuscitation must be immediately available. Sevoflurane should be delivered via a vaporiser specifically calibrated for use with sevoflurane so that the concentration delivered can be accurately controlled. If the carbon dioxide absorbent may be desiccated, it must be replaced before the use of sevoflurane (see section 4.4.).

4.3 Contraindications
Sevoflurane should not be used in patients with known hypersensitivity to sevoflurane or other halogenated anaesthetics.

Sevoflurane is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

Sevoflurane should not be used in patients with a history of unexplained moderate/severe hepatic dysfunction with jaundice, fever, and/or eosinophilia in association with halogenated anesthetics.

4.4 Special warnings and precautions for use
Hypotension and respiratory depression increase as anaesthesia is deepened.

During the maintenance of anaesthesia, increasing the concentration of sevoflurane produces dose-dependent decreases in blood pressure. Excessive decrease in blood pressure may be related to depth of anaesthesia and in such instances may be corrected by decreasing the inspired concentration of sevoflurane.

As with all anaesthetics, particular care should be taken when selecting the dose for hypovolaemic, hypotensive or weakened patients.

As with all anaesthetics, maintenance of haemodynamic stability is important to avoid myocardial ischaemia in patients with coronary artery disease.

In patients at risk from elevation of intra-cranial pressure, sevoflurane should be administered cautiously in conjunction with techniques to lower intra-cranial pressure (e.g. hyperventilation).

Caution should be observed when using sevoflurane during obstetric anaesthesia because the relaxant effect on the uterus could increase the risk of uterine bleeding (see section 4.6).

Malignant Hyperthermia: In susceptible individuals, potent inhalation anaesthetic agents may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known
as malignant hyperthermia. Treatment includes discontinuation of triggering agents (e.g. sevoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Renal failure may appear later, and urine flow should be monitored and sustained if possible.

Use of inhaled anaesthetic agents has been associated with very rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in children during the postoperative period. The condition has been described in patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy. Use of suxamethonium has been associated with most, but not all of these cases. These patients showed evidence of muscle damage with increased serum creatine kinase concentration and myoglobinuria. These patients did NOT have classical signs of malignant hyperthermia such as muscle rigidity, rapid increase in body temperature, or increased oxygen uptake and carbon dioxide production. Prompt and vigorous treatment for hyperkalaemia and arrhythmias is recommended. Subsequent evaluation for latent neuromuscular disease is indicated.

Isolated cases of ventricular arrhythmia were reported in paediatric patients with Pompe's disease.

Observe caution in patients with underlying liver disease (including viral hepatitis) (see sections 4.3 and 4.8). Patients with repeated exposures to halogenated hydrocarbons, including sevoflurane, within a relatively short interval may have an increased risk of hepatic injury.

Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 133 μmol/litre) studied, the safety of sevoflurane administration in this group has not been fully established. Therefore, sevoflurane should be used with caution in patients with renal insufficiency. In some studies in rats, nephrotoxicity was seen in animals exposed to levels of Compound A (pentafluorosopropenyl fluoromethyl ether (PIFE) in excess of those usually seen in routine clinical practice. The mechanism of this renal toxicity in rats is unknown and its relevance to man has not been established. (See Section 5.3, Preclinical Safety Data for further details.). Post-operative monitoring of the renal function is recommended in renal patients.

Use of sevoflurane has been an association with seizures occurring in children and young adults as well as older adults with and without predisposing risk factors. Clinical judgment is necessary before sevoflurane is used in patients at risk of seizures. In children the depth of anaesthesia should be limited. EEG may permit the optimization of sevoflurane dose and help avoid the development of seizure activity in patients with a predisposition for seizures (section 4.8).

Dystonic movements in children have been observed (see section 4.8).

The recovery from general anaesthesia should be assessed carefully before patients are discharged from the recovery room. Rapid emergence from anaesthesia is generally seen with sevoflurane so early relief of postoperative pain may be required. Rapid emergence in children may be associated with agitation and lack of co-operation (in about 25% of cases).

Experience with repeat exposure to sevoflurane is very limited. However, there were no obvious differences in adverse events between first and subsequent exposures.

Sevoflurane should be used with caution in patients with Myasthenia Gravis. Like other halogenated anaesthetics, sevoflurane may cause cough during induction. Sevoflurane could cause QTc prolongation. In clinical practice, this rarely leads to Torsade des Pointes. Sevoflurane should be administered with caution to patients at risk, such as elderly and patients diagnosed with congenital QTc prolongation.

Potential Interactions with CO₂ Absorbents
An exothermic reaction with degradation of volatile anaesthetics can occur when the carbon dioxide absorbent in the vaporizer becomes desiccated following an extended period of use as a result of dry gas flow through the circuit. Rare cases of extreme heat, smoke, and/or spontaneous fire in the anaesthesia machine have been reported during sevoflurane use in conjunction with the use of desiccated CO₂ absorbent, specifically those containing potassium hydroxide (e.g Baralyme). An unusually delayed rise or unexpected decline of inspired sevoflurane concentration compared to the vaporizer setting may be associated with excessive heating of the CO₂ absorbent canister.

Sevoflurane degradants were observed in the respiratory circuit of an experimental anaesthesia machine using desiccated CO₂ absorbents and maximum sevoflurane concentrations (8%) for extended
periods of time (2 hours). Concentrations of formaldehyde observed at the anaesthesia respiratory circuit (using sodium hydroxide containing absorbents) were consistent with levels known to cause mild respiratory irritation. The clinical relevance of the degradants observed under this extreme experimental model is unknown.

It must be taken into account that the colour indicator does not always change after desiccation has taken place. The carbon dioxide absorbent should be routinely replaced irrespectively of the status. If a health care professional suspects that the carbon dioxide absorbent has become desiccated, it must be replaced before subsequent use of volatile anesthetics (such as sevoflurane).

4.5 Interaction with other medicinal products and other forms of interaction

The action of non-depolarising muscle relaxants is potentiated with sevoflurane, therefore, when administered with sevoflurane, dosage adjustments of these agents should be made.

Sevoflurane is similar to isoflurane in the sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline.

MAC values for sevoflurane decrease with the addition of nitrous oxide as indicated in the table on ‘Effect of Age on MAC of sevoflurane’ (see Dosage and Method of Administration).

Benzodiazepines and opiates are expected to reduce sevoflurane MAC. Opioids (e.g. alfentanil and sufentanil), used concomitantly with sevoflurane, may lead to a synergistic fall in heart rate, blood pressure and respiratory rate.

As with other agents, lesser concentrations of sevoflurane may be required following use of an intravenous anaesthetic e.g. propofol.

The metabolism of sevoflurane may be increased by known inducers of CYP2E1 (e.g. isoniazid and alcohol), but it is not inducible by barbiturates.

Significant increases in plasma fluoride concentrations have been observed following the increased activity of CYP2E1.

Sevoflurane may increase the negative inotropic, chronotropic and dromotropic effects of beta blockers (by blocking cardiovascular compensatory mechanisms). Patients should be warned against interruption of beta-blockers and in any case abrupt interruption of the medication is to be avoided. The anaesthetist should be informed of beta-blocker therapy.

The dosage of adrenaline and noradrenaline utilised for local haemostatic action by subcutaneous or-gingival injections should be limited to, for example, 0.1 mg epinephrine within 10 minutes or 0.3 mg within one hour in adults. Parenteral administration of adrenaline and noradrenaline is not recommended.

Serious rhythm disturbances are associated with the use of isoprenaline (increased cardiovascular reactivity). Not recommended.

The use of amphetamines and derivatives as well as of ephedrine and derivatives can cause preoperative hypertensive crisis. It is preferable to interrupt treatments some days before surgery.

Concomitant use of MAO inhibitors: A risk of intraoperative collapse cannot be excluded as this has been observed with other halogenated inhalational anaesthetic agents.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Sevoflurane should only be used in pregnancy if clearly indicated.

It has a relaxant effect on the uterus, which can lead to increased uterine bleeding, as was reported in a study of its use during termination of pregnancy. Use during labour and delivery is limited to one small study in Caesarian section.

Animal studies indicate that sevoflurane is not teratogenic.
Reproduction studies in rats and rabbits (doses up to 1 MAC) showed no effect on male and female reproductive capability. Reduced fetal body weight, with increased skeletal anomalies, were noted in rats at maternally toxic concentrations but no adverse fetal effects were noted in rabbit.

**Lactation**
Caution should be exercised when sevoflurane is administered to nursing mothers as it is not known whether it is excreted in human milk.

**4.7 Effects on ability to drive and use machines**
As with other agents, patients should be advised that performance of activities requiring mental alertness, such as operating hazardous machinery, may be impaired for some time after general anaesthesia.

Patients should not be allowed to drive for a suitable period after sevoflurane anaesthesia.

**4.8 Undesirable effects**
As with all potent inhaled anaesthetics, sevoflurane may cause dose-dependent cardio-respiratory depression. Most adverse events are mild to moderate in severity and are transient in duration. Nausea and vomiting are commonly observed in the post-operative period, at a similar incidence to those found with other inhalation anaesthetics. These effects are common sequelae of surgery and general anaesthesia which may be due to the inhalational anaesthetic, other agents administered intraoperatively or post-operatively and to the patient's response to the surgical procedure.

Adverse event data are derived from controlled clinical trials conducted in the United States and Europe in over 3,200 patients. The type, severity and frequency of adverse events in sevoflurane patients were comparable to adverse events in patients treated with other inhalation anaesthetics.

The most frequent adverse events associated with sevoflurane overall were nausea (24%) and vomiting (17%). Agitation occurred frequently in children (23%).

All adverse reactions at least possibly relating to sevoflurane from clinical trials are presented in the following table by body system and frequency. The following frequency categories are used:
- Very common (≥1/10)
- Uncommon (≥1/1,000 to <1/100)
- Rare (≥1/10,000 to <1/1,000)
- Very rare (<1/10,000)
- Not known (cannot be estimated from the available data)

The type, severity and frequency of adverse reactions in sevoflurane patients were comparable to adverse reactions in reference-drug patients.

**Post-marketing Experience**
Adverse reactions have been spontaneously reported during post-approval use of sevoflurane. These events are reported voluntarily from a population of an unknown rate of exposure. Therefore it is not possible to estimate the true incidence of adverse events.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Reactions</th>
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</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
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<td>Leukopenia</td>
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<tr>
<td></td>
<td></td>
<td>Leukocytosis</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Common*</td>
<td>Agitation</td>
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<td>Uncommon</td>
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<td>Nervous system disorders</td>
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<td>Somnolence</td>
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<td>Dizziness</td>
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<td>Headache</td>
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<td>Tachycardia</td>
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<td>Atrioventricular block complete</td>
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<tr>
<td></td>
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<td>Atrial fibrillation</td>
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<td></td>
<td></td>
<td>Arrhythmia</td>
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<td>Ventricular extrasystoles</td>
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<td>Vascular disorders</td>
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<td>disorders</td>
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<td>Laryngospasm</td>
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<td>Nausea</td>
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<td>Common</td>
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<td>Glycosuria</td>
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<td>Liver function test abnormal**</td>
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<td>White blood cell count abnormal</td>
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<td>Alanine aminotransferase increased</td>
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<td>Blood creatinine increased</td>
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<td>Blood lactate dehydrogenase increased</td>
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<td>Post Marketing Experience</td>
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<tr>
<td>Immune system disorders</td>
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<td>Anaphylactic reaction****</td>
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<tr>
<td></td>
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<td>Dyspnoea ****</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wheezing ****</td>
</tr>
</tbody>
</table>
4.9 Overdose
Symptoms of overdose include respiratory depression and circulatory insufficiency. In the event of overdosage, the following action should be taken: Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen and maintain adequate cardiovascular function.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmaco-therapeutic group: Halogenated hydrocarbons
ATC code: N01AB08
Changes in the clinical effects of sevoflurane rapidly follow changes in the inspired concentration.

Cardiovascular Effects
As with all other inhalation agents, sevoflurane depresses cardiovascular function in a dose related fashion. In one volunteer study, increases in sevoflurane concentration resulted in decrease in mean arterial pressure, but there was no change in heart rate. Sevoflurane did not alter plasma noradrenaline concentrations in this study.

Nervous System Effects
In patients with normal intracranial pressure (ICP), sevoflurane had minimal effect on ICP and preserved CO2 responsiveness. The safety of sevoflurane has not been investigated in patients with a raised ICP. In patients at risk for elevations of ICP, sevoflurane should be administered cautiously in conjunction with ICP-reducing manoeuvres.

5.2 Pharmacokinetic properties
The low solubility of sevoflurane in blood should result in alveolar concentrations which rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent.

In humans <5% of the absorbed sevoflurane is metabolised. The rapid and extensive pulmonary elimination of sevoflurane minimises the amount of anaesthetic available for metabolism. sevoflurane is defluorinated via cytochrome p450(CYP)2E1 resulting in the production of hexafluoroisopropanol (HFIP) with release of inorganic fluoride and carbon dioxide (or a one carbon fragment). HFIP is then rapidly conjugated with glucuronic acid and excreted in the urine.

The metabolism of sevoflurane may be increased by known inducers of CYP2E1 (e.g. isoniazid and alcohol), but it is not inducible by barbiturates. Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anaesthesia. Generally, concentrations of inorganic fluoride
peak within 2 hours of the end of sevoflurane anaesthesia and return within 48 hours to preoperative levels.

5.3 Preclinical safety data
Animal studies have shown that hepatic and renal circulation are well maintained with sevoflurane.

Sevoflurane decreases the cerebral metabolic rate for oxygen (CMRO₂) in a fashion analogous to that seen with isoflurane. An approximately 50% reduction of CMRO₂ is observed at concentrations approaching 2.0 MAC. Animal studies have demonstrated that sevoflurane does not have a significant effect on cerebral blood flow.

In animals, sevoflurane significantly suppresses electroencephalographic (EEG) activity comparable to equipotent doses of isoflurane. There is no evidence that sevoflurane is associated with epileptiform activity during normocapnia or hypocapnia. In contrast to enflurane, attempts to elicit seizure-like EEG activity during hypocapnia with rhythmic auditory stimuli have been negative.

Compound A was minimally nephrotoxic at concentrations of 50-114 ppm for 3 hours in a range of studies in rats. The toxicity was characterised by sporadic single cell necrosis of the proximal tubule cells. The mechanism of this renal toxicity in rats is unknown and its relevance to man has not been established. Comparable human thresholds for Compound A-related nephrotoxicity would be predicted to be 150-200 ppm. The concentrations of Compound A found in routine clinical practice are on average 19 ppm in adults (maximum 32 ppm) with use of Soda lime as the CO₂ absorbent.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
None.

6.2 Incompatibilities
Sevoflurane is stable when stored under normal room lighting conditions. No discernible degradation of sevoflurane occurs in the presence of strong acids or heat. sevoflurane is not corrosive to stainless steel, brass, aluminium, nickel-plated brass, chrome-plated brass or copper beryllium alloy.

Chemical degradation can occur upon exposure of inhaled anaesthetics to CO₂ absorbent within the anaesthesia machine. When used as directed with fresh absorbents, degradation of sevoflurane is minimal and degradants are undetectable or non-toxic. Sevoflurane degradation and subsequent degradant formation are enhanced by increasing absorbent temperature, desiccated CO₂ absorbent (especially potassium hydroxide-containing, e.g. Baralyme®), increased sevoflurane concentration and decreased fresh gas flow. Sevoflurane can undergo alkaline degradation by two pathways. The first results from the loss of hydrogen fluoride, with the formation of pentafluoroisopropanyl fluoromethyl ether (PIFE or more commonly known as Compound A). The second pathway for degradation of sevoflurane occurs only in the presence of desiccated CO₂ absorbents and leads to the dissociation of sevoflurane into hexafluoroisopropanol (HFIP) and formaldehyde. HFIP is inactive, non-genotoxic, rapidly glucuronidated, cleared and has toxicity comparable to sevoflurane. Formaldehyde is present during normal metabolic processes. Upon exposure to a highly desiccated absorbent, formaldehyde can further degrade into methanol and formate. Formate can contribute to the formation of carbon monoxide in the presence of high temperature. Methanol can react with compound A to form the methoxy addition product Compound B. Compound B can undergo further HF elimination to form Compounds C,D and E. With highly desiccated absorbents, especially those containing potassium hydroxide (e.g Baralyme®) the formation of formaldehyde, methanol, carbon monoxide, Compound A and perhaps some of its degradants, Compounds B, C and D may occur.

6.3 Shelf life
5 years.

6.4 Special precautions for storage
Do not store above 25°C. Do not refrigerate. Keep bottle cap tightly closed due to the volatile nature of the anaesthetic. Store the bottle in an upright position.

6.5 Nature and contents of container
Type III, 250 ml amber coloured glass bottles with two component screw cap made up of outer black phenolic cover and inner translucent low density polyethylene cone. The pack is provided with an LDPE yellow-coloured collar.
6.6 Special precautions for disposal and other handling
Sevoflurane should be administered via a vaporiser calibrated specifically for sevoflurane using a key filling system designed for sevoflurane specific vaporisers or other appropriate sevoflurane specific vaporiser filling systems. Carbon dioxide absorbents should not be allowed to dry out when inhalational anaesthetics are being administered. Some halogenated anaesthetics have been reported to interact with dry carbon dioxide absorbent to form carbon monoxide.

However, in order to minimise the risk of formation of carbon monoxide in rebreathing circuits and the possibility of elevated carboxyhaemoglobin levels, CO₂ absorbents should not be allowed to dry out. There have been rare cases of excessive heat production, smoke and fire in the anaesthetic machine when sevoflurane has been used in conjunction with a desiccated (dried out) CO₂ absorbent. If the CO₂ absorbent is suspected to be desiccated it should be replaced. Only bottles without a pungent odour should be used. The complete contents of a bottle are normally transferred to the vaporiser. In the event that a partially used bottle remains at the end of the procedure, the contents should be discarded. Any unused product or waste material should be disposed of in accordance with local requirements.
Module 3

Sojourn Sevoflurane 100% Inhalation Vapour, liquid

Tell your doctor before you are given Sevoflurane:
- you have previously had general anaesthetics, particularly if repeated over a short period of time.
- you may have an increased risk of hyperalgesia
- you are suffering from a high blood pressure, or have a family history of high blood pressure
- you have had surgery (including dental surgery) within the last 2 weeks
- you are pregnant or breast feeding.

Taking in other medicines
Tell your doctor if you are taking or have recently taken any of the following:
- medicines that affect the heart rate such as adrenalin or beta-blockers
- tranquilizers or benzodiazepines
- anticonvulsants such as phenytion or carbamazepine
- muscle relaxants
- antidepressants or mood stabilizers
- other anaesthetics, e.g. nitrous oxide, propofol, epidurals (e.g. fentanyl and sufentanyl), as Sevoflurane may affect the way they work. They are given as same time.

Tell your doctor or nurse if you are having or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast feeding
Tell your doctor or anaesthetist if you are pregnant or think you may be pregnant. You should not receive Sevoflurane if you are pregnant unless it is essential.

Sevoflurane may cause increased blood loss after operations involving the wound.

Caution should be exercised when Sevoflurane is administered to nursing mothers as it is not known whether Sevoflurane is present in human milk after anaesthesia.

Driving and using machines
You should not drive or use machinery for at least 24 hours after you have had general anaesthesia.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Sevoflurane can cause side effects, although not everyone gets them. It is however, important to consult your ward doctor, nurse or anaesthetist if you are experiencing any.

Serious side effects:

The following side effects are serious and you may need immediate medical attention. Hospital staff will monitor you throughout your anaesthesia and will give immediate assistance when necessary.

Examples of these serious side effects include:
- allergic reactions, which can be severe, with swelling of the face, tongue and throat and difficulty breathing
- allergic reactions (hay fever, asthma) which may require immediate care and may be fatal. This condition may occur in families
- increased potassium levels in the blood (hyperkalaemia), which may result in abnormal heart rhythms and can be fatal in children during the preoperative phase. This has been seen in patients with neurological disease, particularly Duchenne muscular dystrophy.
- high blood pressure
- nausea and vomiting.

Uncommon side effects [1 to 3 patients in 1,000]
- allergic reactions (rash, hives) in children
- blood pressure may be lowered
- increased blood sugar level, liver function test or white blood cell count
- increased blood flow.

If you experience any of the following, tell your doctor or nurse immediately:
- allergic reactions, which can be severe, with swelling of the face, tongue and throat and difficulty breathing
- allergic reactions (hay fever, asthma) which may require immediate care and may be fatal. This condition may occur in families
- increased potassium levels in the blood (hyperkalaemia), which may result in abnormal heart rhythms and can be fatal in children during the preoperative phase. This has been seen in patients with neurological disease, particularly Duchenne muscular dystrophy.

Tell the doctor or nurse immediately if you have any of the following:
- high blood pressure
- nausea and vomiting.

Common side effects (1 to 10 patients in 100)
- common side effects (rash, hives) in adults
- blood pressure may be lowered
- allergic reactions (rash, hives) in children
- blood pressure may be lowered
- increased blood sugar level, liver function test or white blood cell count
- increased blood flow.

If you have any side effects not listed in this leaflet, please tell your doctor or nurse.

5. HOW TO STORE SEVOFLURANE

Do not refrigerate.

Keep bottle cap tightly closed due to the volatile nature of anaesthetic.

Store the bottle in an upright position.

Keep out of reach and sight of children.

Do not use Sevoflurane after the expiry date (MAF27T)

This leaflet was last approved in 1991.

FURTHER INFORMATION

Sojourn contains 100% of the active ingredient Sevoflurane.

Sojourn looks like a contents liquid available in 250ml amber coloured glass bottles.

Marketing Authorisation Holder and Manufacturer

Piramal Healthcare UK Limited
1 Primrose Avenue, Unit B4 Kings Park, London NW9 8OL, United Kingdom

This medicinal product is authorised in the Member States of the EEA under the following names:

This leaflet was last approved in 1991.
Sojourn Sevoflurane 100% Inhalation Vapour, liquid

MAC (minimum alveolar concentration) values for sevoflurane decrease as the patients age increases and with the addition of nitrous oxide. Dosage should be individualized and linked to the benzodiazepine according to the patient's age and clinical status. MAC values for Adults and Paediatric patients according to Age of Patient: Sevoflurane 100% MAC Inhalation Vapour; Sevoflurane 100% MAC Inhalation Vapour in Nitrogen.<br><br>0-1 months 3.3%<br>1-6 months 3.0%<br>6 months- 2 years 2.0%<br>2-6 years 2.0%<br>6-12 years 2.0%<br>12-18 years 1.4%<br>Adolescents 2.1%<br>Adults 1.4%<br>MAC is the concentration of sevoflurane inhaled, with nitrous oxide being used for maintenance of anaesthesia. (Note: For 1-year-old paediatric patients, 0.6% N2O/0.4% sevoflurane was used.)

Anesthesiologist should avoid anaesthesia with lidocaine, propofol, or other inhaled anesthetics. Sevoflurane is administered in combination with inhalational sevoflurane only. Induction of anesthesia with sevoflurane only may be achieved by inhalation of sevoflurane in 100% oxygen, with or without nitrous oxide (N2O), increasing by increments of 0.5-1.0% sevoflurane, to a maximum of 8% adults and children and the required amount of anesthetic administered. Sevoflurane in 100% oxygen in nitrous oxide (N2O) is used for induction of anesthesia in adult, pediatric, and adolescent patients. (Note: For 1-year-old paediatric patients, 0.6% N2O/0.4% sevoflurane was used.) Post-operative monitoring of the renal function is required in neonates.

Sevoflurane should be administered in the operating room environment and the patient should be conscious at all times during the procedure. Sevoflurane should not be used in patients with known or suspected hypersensitivity to sevoflurane or other volatile anesthetics. Sevoflurane is also contraindicated in patients with known or suspected endotracheal intubation under local anaesthesia. Sevoflurane should not be used in patients with a history of unexplained moderate/severe hepatic dysfunction with jaundice, fever, and/or eosinophilia in association with hepatic alterations.

4.1 Indications: Sevoflurane is generally used in the preoperative, intraoperative, and postoperative phases of anesthesia.

4.2 Precautions: Sevoflurane should be used in patients with a history of unexplained moderate/severe hepatic dysfunction with jaundice, fever, and/or eosinophilia in association with hepatic alterations.

4.3 Contraindications: Sevoflurane should not be used in patients with known or suspected hypersensitivity to sevoflurane or other volatile anesthetics.

4.4 Warnings and Precautions: Sevoflurane can cause coughing, bronchospasm, and hypotension. Sevoflurane should be used cautiously in patients with known or suspected endotracheal intubation under local anaesthesia. Sevoflurane should not be used in patients with a history of unexplained moderate/severe hepatic dysfunction with jaundice, fever, and/or eosinophilia in association with hepatic alterations.

4.5 Interaction with other medicinal products and other forms of interaction: The action of non-depolarizing muscle relaxants is potentiated with sevoflurane, therefore, when administered with sevoflurane, dosage adjustments of these agents should be considered. Sevoflurane is similar to isoflurane in the sensitization of the myocardium to the arrhythmic effects of isoflurane. MAC values for sevoflurane decrease with the addition of nitrous oxide to isoflurane in patients with acute myocardial infarction. Sevoflurane should be used with caution in patients with pre-existing cardiovagal reflexes. Sevoflurane should be used with caution in patients with pre-existing cardiovascular diseases. Sevoflurane should be used with caution in patients with pre-existing cardiovascular diseases. Sevoflurane should be used with caution in patients with pre-existing cardiovascular diseases. Sevoflurane should be used with caution in patients with pre-existing cardiovascular diseases.
Sojourn Sevoflurane 100% Inhalation Vapour, liquid

Sevoflurane is a potent short-acting inhalational anesthetic. It is used for surgical procedures and other medical interventions requiring sedation and analgesia. Sevoflurane is often administered in combination with other drugs to enhance its efficacy and reduce side effects.

4. Effects on the ability to drive and use machines
As with other agents, patients should be advised that, if performance of activities requiring mental alertness, such as driving, may be impaired for some time after general anesthesia, care should be taken.

5. Undesirable Effects
Sevoflurane may cause dose-dependent cardiovascular depression. Most adverse events are mild to moderate in severity and are transient in duration. However, some adverse effects may be severe and require immediate attention.

6. Overdose
Symptoms of overdosage include respiratory depression and circulatory instability. In the event of oxidative injury, the following symptoms should be noted:

5. Pharmacological Properties
Sevoflurane is a potent short-acting inhalational anesthetic.
Sojourn Sevoflurane 100% Inhalation Vapour, liquid

Changes in the clinical effects of sevoflurane rapidly follow changes in the inspired concentration.

Cardiovascular Effects
As with all other inhalation agents, sevoflurane depresses cardiovascular function in a dose-related fashion. In one volunteer study, increases in sevoflurane concentration resulted in decreases in mean arterial pressure, but there was no change in heart rate. Sevoflurane did not alter plasma renin activity or angiotensin-converting enzyme activity.

Respiratory System Effects
Sevoflurane decreases the minimal inspiratory pressure (IP), decreases the minimal expiratory pressure (PE), increases the respiratory minute volume, and decreases the peak airway pressure. The safety of sevoflurane has not been investigated in patients with impaired IP and/or PE, nor for elevations of IP. Sevoflurane should be administered cautiously in conjunction with CPAP reducing maneuvers.

5.2 Pharmacokinetic/Performance
The total solubility of sevoflurane in blood should result in alveolar concentrations which rapidly increase on inspiration and rapidly decrease upon termination of the infusion.

Animals: 4% of the absorbed sevoflurane is metabolized.

The rapid and extensive pulmonary elimination of sevoflurane minimizes the amount of cardiovascular available for redistribution; sevoflurane is inhaled as a single-chamber circuit is established.

5.3 Precautions for Use

6.3 Special hazards for disposal

6.4 Special precautions for storage

7. Marketing Authorisation Holder

8. Marketing Authorisation Number(S):

9. Date of First Authorisation/Reauthorization of the Authorisation:

10. Date of revision of the text:
Module 4
Labelling

Do not store above 25°C.
Do not refrigerate.
Keep bottle cap tightly closed due to the volatile nature of the anaesthetic.
Keep out of the reach and sight of children.
Read the package Leaflet before use.
Inhalation use.
Store the bottle in an upright position.
PL 29595/0002

MA Holder:
Piramal Healthcare UK Limited
1st Floor, Alpine House, Unit II, Honeypot Lane, London NW6 9BX, United Kingdom

Contains Sevoflurane 100%
Non flammable. Non explosive.
Module 5  
Scientific discussion during initial procedure

I  INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Sojourn Sevoflurane 100% Inhalation Vapour, liquid (PL 29595/0002; UK/H/4252/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated for induction and maintenance of general anaesthesia in adult and paediatric patients of all ages, including full-term neonates.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia and Slovak Republic as Concerned Member States (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Sevoflurane (Abbott Laboratories Limited, UK), which was first authorised in the UK on 01 September 1995.

The active ingredient, sevoflurane, is a highly fluorinated methyl-isopropyl ether used for the induction and maintenance of general anaesthesia. Sevoflurane induces muscle relaxation and reduces pain sensitivity by altering tissue excitability. It does so by decreasing the extent of gap junction mediated cell-cell coupling and altering the activity of the channels that underlie the action potential.

No new non-clinical or clinical data have been submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years. A bioequivalence study is not required to support this application due to the nature of the dosage form (inhalation vapour, liquid), which is administered via a respiratory route and has no systemic activity. Essential similarity with the originator product is based on the comparative quality attributes of the product.

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, satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or 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 24 August 2011. After a subsequent national phase, a licence was granted in the UK on 21 September 2011.
### II. ABOUT THE PRODUCT

| Names of the product in the Reference Member State | Sojourn Sevoflurane 100% Inhalation Vapour, liquid |
| Name of the active substance (INN) | Sevoflurane |
| Pharmacotherapeutic classification (ATC code) | Halogenated hydrocarbons (ATC Code: N01AB08) |
| Pharmaceutical form and strength | Inhalation vapour, liquid |
| Reference number for the Decentralised Procedure | UK/H/4252/001/DC |
| Reference Member State (RMS) | United Kingdom |
| Concerned Member States (CMS) | Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia and Slovak Republic |
| Marketing Authorisation Number | PL 29595/0002 |
| Name and address of the authorisation holder | Piramal Healthcare UK Limited 1st Floor, Alpine House, Unit II, Honeypot Lane, London NW9 9RX, United Kingdom |
III  SCIENTIFIC OVERVIEW AND DISCUSSION
III.1  QUALITY ASPECTS
ACTIVE SUBSTANCE
INN:  Sevoflurane
Chemical name:  1,1,1,3,3,3-Hexafluoro-2-(fluoromethoxy)propane;
Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether;
Propane, 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)-Fluoromethyl
2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether.

Structure:

```
F       H       F
|       |       |
F  -  C  -  C  -  F
|       |       |
F       O       F
     |       |
     CH₂F
```

Molecular formula:  C₄H₃F₇O
Molecular mass:  200.05
Appearance:  A clear, colourless, volatile liquid, slightly soluble in water, miscible with ethanol (96%).

Sevoflurane is 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.

Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification limits. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

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

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
MEDICINAL PRODUCT

Other Ingredients
There are no pharmaceutical excipients in this product.

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable product that could be considered a generic medicinal product of the originator product, Sevoflurane (Abbott Laboratories Limited, UK).

Suitable pharmaceutical development data have been provided for this application.

Comparable analysis data have been provided for this product and the originator product Sevoflurane (Abbott Laboratories, UK), which show comparable chemical parameters.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, together with an appropriate account 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 proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished product is supplied in Type III, 250 ml amber-coloured, glass bottles, with two component screw caps made up of outer black phenolic covers and inner translucent low-density polyethylene (LDPE) cones. The pack is provided with an LDPE yellow-coloured collar.

Satisfactory specifications and Certificates of Analysis for all packaging material have been provided for all packaging used. All primary packaging complies with the requirements of Directive 2002/72/EC. In addition, the glass bottles are compliant with the Type III requirements of European Pharmacopoeia monograph 3.2.1 ‘Glass containers for pharmaceutical use’.

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. The data from these studies support a shelf-life of 5 years, with the storage conditions “Do not store above 25°C. Do not refrigerate. Keep bottle cap tightly closed due to the volatile nature of the anaesthetic. Store the bottle in an upright position.”

Absence of an in-use shelf life is justified as partially used bottles are discarded at the end of a procedure.

Bioequivalence/Bioavailability
No bioequivalence study has been conducted as this product, being an inhalation anaesthetic, is administered via a respiratory route and has no systemic activity. The justification for a biowaiver is considered acceptable.
Summary of Product Characteristics (SmPC), Product Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Form
The MAA form is pharmaceutically satisfactory.

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

Conclusion
The grant of a Marketing Authorisation is recommended.
III.2 NON-CLINICAL ASPECTS
NON-CLINICAL DATA
As the pharmacodynamic, pharmacokinetic and toxicological properties of sevoflurane are well-known, no new non-clinical data have been submitted and none are required.

NON-CLINICAL EXPERT REPORT
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.

ENVIRONMENTAL RISK ASSESSMENT
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this product is intended for generic substitution with a product that is already marketed, no increase in environmental burden is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
III.3  CLINICAL ASPECTS

CLINICAL PHARMACOLOGY
The clinical pharmacology of sevoflurane is well-known.

No clinical studies have been conducted to support the application. Essential similarity with the originator product is based on the comparative quality attributes of the product. No bioequivalence study has been conducted as this product, being an inhalation anaesthetic, is administered via a respiratory route and has no systemic activity. The justification for a biowaiver is acceptable.

EFFICACY
The efficacy of sevoflurane is well-known. No new efficacy data have been submitted and none are required for this application.

SAFETY
The safety profile of sevoflurane is well-known. No new safety data have been submitted with this application and none are required.

PHARMACOVIGILANCE SYSTEM AND RISK MANAGEMENT PLAN
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for this product.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC), PATIENT INFORMATION LEAFLET (PIL) AND LABELLING
The SmPC, PIL and labelling are clinically acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the details in the SmPC and in-line with the current guidelines. The labelling is in-line with the current guidelines.

CLINICAL EXPERT REPORT
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

CONCLUSION
The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT
QUALITY
The important quality characteristics of Sojourn Sevoflurane 100% Inhalation Vapour, liquid are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted. As the pharmacokinetics, pharmacodynamics and toxicology of sevoflurane are well-known, no additional data were required.

EFFICACY
Essential similarity with the originator product is based on the comparative quality attributes of the product. No bioequivalence study has been conducted as this product, being an inhalation anaesthetic, it is administered via respiratory route and has no systemic activity. The justification for a biowaiver is acceptable.

SAFETY
The safety profile of sevoflurane is well-known. No new safety data were submitted and none were required for this application.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with those for the originator product, where appropriate, and consistent with current guidelines.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with sevoflurane is considered to have demonstrated the therapeutic value of the product. The benefit/risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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