Induction:
Dosage should be individualised and titrated to the desired effect according to the patient’s age and clinical status. A short acting barbiturate or other intravenous induction agent may be administered followed by inhalation of sevoflurane. Induction with sevoflurane may be achieved in oxygen or in combination with oxygen-nitrous oxide mixtures. In adults inspired concentrations of up to 5% sevoflurane usually produce surgical anaesthesia in less than 2 minutes. In children, inspired concentrations of up to 7% sevoflurane usually produce surgical anaesthesia in less than 2 minutes. Alternatively, for induction of anaesthesia in unpremedicated patients, inspired concentrations of up to 8% sevoflurane may be used.

Maintenance:
Surgical levels of anaesthesia may be sustained with concentrations of 0.5 - 3% sevoflurane with or without the concomitant use of nitrous oxide.

Emergence:
Emergence times are generally short following sevoflurane anaesthesia. Therefore, patients may require early post operative pain relief.

Elderly:
MAC decreases with increasing age. The average concentration of sevoflurane to achieve MAC in an 80 year old is approximately 50% of that required in a 20 year old.

Paediatric population:
Refer to Table 1 for MAC values for paediatric patients according to age.

Contraindications
Sevoflurane should not be used in patients with known or suspected sensitivity to sevoflurane or other halogenated anaesthetics (e.g. history of liver function disorder, fever or leucocytosis of unknown cause after anaesthesia with one of these agents).
Sevoflurane is also contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

Sevoflurane is contraindicated in patients in whom general anaesthesia is contraindicated.

**Special warnings and precautions for use**

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.

The concentration of sevoflurane being delivered from a vaporiser must be known exactly. As volatile anaesthetics differ in their physical properties, only vaporisers specifically calibrated for sevoflurane must be used. The administration of general anaesthesia must be individualised based on the patient’s response. Hypotension and respiratory depression increase as anaesthesia is deepened.

**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.

The clinical syndrome is signalled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anaesthesia, acute hypoxia, hypercapnia and hypovolaemia.

In clinical trials, one case of malignant hyperthermia was reported. In addition, there have been postmarketing reports of malignant hyperthermia. Some of these reports have been fatal.

Treatment includes discontinuation of triggering agents (e.g. sevoflurane), administration of intravenous dantrolene sodium (consult prescribing information for intravenous dantrolene sodium for additional information on patient management), and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base abnormalities. Renal failure may appear later, and urine flow should be monitored and sustained if possible.

**Perioperative Hyperkalemia**

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in paediatric patients during the postoperative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Isolated reports of QT prolongation, very rarely associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering sevoflurane to susceptible patients.

Isolated cases of ventricular arrhythmia were reported in paediatric patients with Pompe’s disease. Caution should be exercised in administering general anaesthesia, including sevoflurane, to patients with mitochondrial disorders.

**Hepatic**

Very rare cases of mild, moderate and severe postoperative hepatic dysfunction or hepatitis with or without jaundice have been reported from postmarketing experiences.

Clinical judgment should be exercised when sevoflurane is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction.

Patients with repeated exposures to halogenated hydrocarbons, including sevoflurane, within a rela-
An exothermic reaction, enhanced sevoflurane degradation, and production of degradation products can occur when the CO2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO2 absorbent canisters. Sevoflurane degradants (methanol, formaldehyde, carbon monoxide, and Compounds A, B, C, and D) 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. If a health care professional suspects that the CO2 absorbent has become desiccated, it must be replaced before subsequent use of volatile anaesthetics (such as sevoflurane). It must be taken into account that the colour indicator does not always change after desiccation has taken place. Therefore, the lack of significant colour change should not be taken as an assurance of adequate hydration. CO2 absorbents should be replaced routinely regardless of the state of the colour indicator.

Renal Impairment:
Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 1.5 mg/dL) 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.

Neurosurgery & Neuromuscular Impairment:
In patients at risk from elevation of intra-cranial pressure, sevoflurane should be administered cau-
tiously in conjunction with techniques to lower intracranial pressure (e.g. hyperventilation).

**Seizures:**
Rare cases of seizures have been reported in association with sevoflurane use.
Use of sevoflurane has been associated 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.

**Paediatric population:**
The use of sevoflurane has been associated with seizures. Many have occurred in children and young adults starting from 2 months of age, most of whom had no predisposing risk factors. Clinical judgment should be exercised when using sevoflurane in patients who may be at risk for seizures. Dystonic movements in children have been observed.

**Interactions with other medicinal products and other forms of interaction**
Sevoflurane has been shown to be safe and effective when administered concurrently with a wide variety of agents commonly encountered in surgical situations such as central nervous system agents, autonomic drugs, skeletal muscle relaxants, anti-infective agents including aminoglycosides, hormones and synthetic substitutes, blood derivatives and cardiovascular drugs, including epinephrine.

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

**Indirect-acting Sympathomimetics**
There is a risk of acute hypertensive episode with the concomitant use of sevoflurane and indirect-acting sympathomimetics products (amphetamines, ephedrine).

**Beta blockers**
Sevoflurane may increase the negative inotropic, chronotropic and dromotropic effects of beta blockers (by blocking cardiovascular compensatory mechanisms).

**Verapamil**
Impairment of atrioventricular conduction was observed when verapamil and sevoflurane were administered at the same time.

**Inducers of CYP2E1**
Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of sevoflurane and lead to significant increases in plasma fluoride concentrations. Concomitant use of sevoflurane and isoniazid can potentiate the hepatotoxic effects of isoniazid.

**St John’s Wort**
Severe hypotension and delayed emergence from anaesthesia with halogenated inhalational anaesthetics have been reported in patients treated long-term with St John’s Wort.

**Barbiturates**
Sevoflurane administration is compatible with barbiturates as commonly used in surgical practice.

**Benzodiazepines and Opioids**
Benzodiazepines and opioids are expected to decrease the MAC of sevoflurane in the same manner as with other inhalational anaesthetics. Sevoflurane administration is compatible with benzodiazepines and opioids as commonly used in surgical practice.

**Nitrous Oxide**
As with other halogenated volatile anaesthetics, the MAC of sevoflurane is decreased when administered in combination with nitrous oxide. The MAC equivalent is reduced approximately 50% in adult and approximately 25% in paediatric patients.

**Neuromuscular Blocking Agents**
As with other inhalational anaesthetic agents, sevo-
flurane affects both the intensity and duration of neuromuscular blockade by non-depolarising muscle relaxants. When used to supplement alfentanil-N2O anaesthesia, sevoflurane potentiates neuromuscular block induced with pancuronium, vecuronium or atracurium. The dosage adjustments for these muscle relaxants when administered with sevoflurane are similar to those required with isoflurane. The effect of sevoflurane on succinylcholine and the duration of depolarising neuromuscular blockade has not been studied.

Dosage reduction of neuromuscular blocking agents during induction of anaesthesia may result in delayed onset of conditions suitable for endotracheal intubation or inadequate muscle relaxation because potentiation of neuromuscular blocking agents is observed a few minutes after the beginning of sevoflurane administration.

Among non-depolarising agents, vecuronium, pancuronium and atracurium interactions have been studied. In the absence of specific guidelines: (1) for endotracheal intubation, do not reduce the dose of non-depolarising muscle relaxants; and, (2) during maintenance of anaesthesia, the dose of non-depolarising muscle relaxants is likely to be reduced compared to that during N2O/opioid anaesthesia. Administration of supplemental doses of muscle relaxants should be guided by the response to nerve stimulation.

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

Significant increases in plasma fluoride concentrations have been observed following the increased activity of CYP 2E1.

Pregnancy and lactation

Pregnancy

Sevoflurane 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 caesarean section.

Reproduction studies in rats and rabbits at doses up to 1 MAC have revealed no evidence of harm to the fetus due to sevoflurane. There are no adequate and well-controlled studies in pregnant women; therefore, sevoflurane should be used during pregnancy only if clearly needed.

Labour and Delivery

In a clinical trial, the safety of sevoflurane was demonstrated for mothers and infants when used for anaesthesia during Caesarean section. The safety of sevoflurane in labour and vaginal delivery has not been demonstrated.

Breastfeeding

It is not known whether sevoflurane or its metabolites are excreted in human milk. Due to the absence of documented experience, women should be advised to skip breast-feeding for 48 hours after administration of sevoflurane and discard milk produced during this period.

Fertility

Reproduction studies in rats and rabbits at doses up to 1 MAC have revealed no evidence of impaired fertility due to sevoflurane.

Effects on the ability to drive and use machines

As with other agents, patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or 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.

Undesirable Effects

Summary of the safety profile

As with all potent inhaled anaesthetics, sevoflurane may cause dose-dependent cardio-respiratory depression. Most adverse reactions 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 intra-operatively or post-operatively and to the patient’s response to the surgical procedure.
The most commonly reported adverse reactions were as follows:
In adult patients: hypotension, nausea and vomiting;
In elderly patients: bradycardia, hypotension and nausea; and
In paediatric patients: agitation, cough, vomiting and nausea.

**Tabulated summary of adverse reactions**

All adverse reactions at least possibly relating to sevoflurane from clinical trials and post-marketing experience are presented in the following table by MedDRA System Organ Class, Preferred Term and frequency. The following frequency categories are used: Very common (>1/10); common (>1/100, <1/10); uncommon (>1/1,000, <1/100); rare (>1/10,000, <1/1,000); very rare (<1/10,000), including isolated reports. Post-marketing adverse reactions are reported voluntarily from a population with an unknown rate of exposure. Therefore it is not possible to estimate the true incidence of adverse events and the frequency is "unknown". The type, severity and frequency of adverse reactions in sevoflurane patients in clinical trials were comparable to adverse reactions in reference-drug patients.

### Summary of Most Frequent Adverse Drug Reactions in sevoflurane Clinical Trials and Post-marketing Experience

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td>Unknown</td>
<td>Anaphylactic reaction ¹ \nAnaphylactoid reaction \nHypersensitivity ¹</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>Leukopenia \nLeukocytosis</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Very Common</td>
<td>Agitation</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td>Confusional state</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Somnolence \nDizziness \nHeadache</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>Convulsion ², ³ \nDystonia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Very Common</td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Tachycardia</td>
</tr>
</tbody>
</table>

| Uncommon | Atrioventricular block complete \nAtrial fibrillation \nArrhythmia \nVentricular extrasystoles \nSupraventricular extrasystoles \nExtrasystoles |
| Unknown | Cardiac arrest ⁴ |

**Vascular disorders**

| Very Common | Hypotension |
| Common | Hypertension |

**Respiratory, thoracic and mediastinal disorders**

| Very Common | Cough |
| Common | Respiratory disorder \nLaryngospasm |
| Uncommon | Apnoea \nHypoxia \nAsthma |
| Unknown | Bronchospasm \nDyspnoea \nWheezing ¹ \nPulmonary oedema |

**Gastrointestinal disorders**

| Very Common | Nausea \nVomiting |
| Common | Salivary hypersecretion |

**Renal and urinary disorders**

| Unknown | Urinary retention |
| Unknown | Glycosuria \nRenal failure acute |

**Hepato-biliary disorders**

| Unknown | Hepatitis ¹, ² \nHepatic failure ¹, ² \nHepatic necrosis ¹, ² |

**Skin and subcutaneous tissue disorders**

| Unknown | Dermatitis contact ¹ \nPruritus \nRash ¹ \nSwelling face ¹ \nUrticaria |

**Musculoskeletal and connective tissue disorders**

| Unknown | Muscle twitching |

**General disorders and administration site conditions**

| Common | Chills \nPyrexia \nHypothermia \nChest discomfort ¹ |
| Unknown | Hyperthermia malignant ¹, ² |

**Investigations**

| Common | Blood glucose abnormal \nLiver function test abnormal ⁵ \nWhite blood cell count abnormal \nAspartate aminotransferase abnormal \nBlood fluoride increased ⁶ \nAlanine aminotransferase increased |
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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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 a 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

No evidence of seizure was observed during the clinical development programme.

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 such as hyperventilation.

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.

Description of selected adverse reactions

Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anaesthesia. Concentrations of inorganic fluoride generally peak within two hours of the end of sevoflurane anaesthesia and return within 48 hours to pre-operative levels. In clinical trials, elevated fluoride concentrations were not associated with impairment of renal function.

Rare reports of post-operative hepatitis exist. In addition, there have been rare post-marketing reports of hepatic failure and hepatic necrosis associated with the use of potent volatile anaesthetic agents, including sevoflurane. However, the actual incidence and relationship of sevoflurane to these events cannot be established with certainty.

Rare reports of hypersensitivity (including contact dermatitis, rash, dyspnoea, wheezing, chest discomfort, swelling face, or anaphylactic reaction) have been received, particularly in association with long-term occupational exposure to inhaled anaesthetic agents, including sevoflurane.

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.

Paediatric population

The use of sevoflurane has been associated with seizures. Many of these have occurred in children and young adults starting from 2 months of age, most of whom had no predisposing risk factors.

Clinical judgment should be exercised when using sevoflurane in patients who may be at risk for seizures.

Uncommon

Blood creatinine increased
Blood lactate dehydrogenase increased

Injury, poisoning and procedural complications

Common

Hypothermia

1 See Undesirable Effects – Description of selected adverse reactions.
2 See Special warnings and precautions for use.
3 See Undesirable Effects – Paediatric population.
4 There have been very rare post-marketing reports of cardiac arrest in the setting of sevoflurane use.
5 Occasional cases of transient changes in hepatic function tests were reported with sevoflurane and reference agents.
6 Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anaesthesia. See Description of selected adverse reactions below.
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.

**PHARMACEUTICAL PARTICULARS**

**List of excipients**
Water (as a Lewis Acid Inhibitor).

**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, aluminum 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.

**Special precautions for storage**
Do not store above 25°C. Do not refrigerate. Keep cap tightly closed.

**Nature and contents of container**
100 ml and 250 ml amber polyethylene naphthalate (PEN) bottles.

**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 re-breathing 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.

**Manufacturer**
See outer pack.
Marketing Authorisation Holder
AbbVie Ltd.
Abbott House, Vanwall Road, Maidenhead
Berks SL6 4XE, UK

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