Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sevoflurane 100% Inhalation Vapour, liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sevoflurane 100%.

Excipient with known effect: None

The finished product is comprised only of the active ingredient, see section 6.1.

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

Premedication should be selected according to the need of the individual patient, and at the discretion of the anaesthetist.

Surgical Anaesthesia:
Sevoflurane should be delivered via a vaporiser specifically calibrated for use with Sevoflurane so that the concentration delivered can be accurately controlled.
MAC (minimum alveolar concentration) values for sevoflurane decrease with age 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. The table below indicates average MAC values for different age groups.

Table 1: MAC values for Adults and Paediatric patients according to age		
Age of Patient (years)	Sevoflurane 100% Inhalation Vapour, liquid in Oxygen	Sevoflurane 100% Inhalation Vapour, liquid in 65% N2O/35% O2
0 – 1 months*	3.3%	2.0%**
1 - < 6 months	3.0%	
6 months - < 3 years	2.8%	
3 – 12	2.5%	
25	2.6%	1.4%
40	2.1%	1.1%
60	1.7%	0.9%
80	1.4%	0.7%

* Neonates are full term gestational age. MAC in premature infants has not been determined.
** In 1 – <3 year old paediatric patients, 60% N_2O/40% O_2 was used.

Anaesthesia 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 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 2 minutes. In children, inspired concentrations of up to 7% sevoflurane usually produce surgical anaesthesia in less than 2 minutes.

Maintenance of Anaesthesia
Surgical levels of anaesthesia may be maintained by inhalation of 0.5-3% sevoflurane in O_2 with or without concomitant use of N_2O.

Emergence:
Emergence times are generally short following sevoflurane anaesthesia. Therefore, patients may require early postoperative pain relief. When all anaesthetic administration has been stopped, the patient's airways should be ventilated with 100% oxygen until complete awakening

Elderly people:
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 when used in oxygen with or without concomitant use of nitrous oxide.

Impaired kidney function
Due to the small number of patients with renal impairment (baseline serum creatinine greater than 1.5 mg / dl) studied, the safety of sevoflurane administration in this group has not been fully established. Sevoflurane should therefore be administered with caution in patients with renal impairment.

Method 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 or suspected hypersensitivity 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.

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 anaesthetics.

Sevoflurane should not be used in patients with a history of confirmed hepatitis due to a halogenated inhalational anaesthetic or a history of unexplained moderate to severe hepatic dysfunction with jaundice, fever, and eosinophilia after anaesthesia with sevoflurane.

4.4 Special warnings and precautions for use

Sevoflurane may cause respiratory depression, which may be augmented by narcotic premedication or other agents causing respiratory depression. Respiration should be supervised and if necessary, assisted.
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. All patients anaesthetised with sevoflurane should be constantly monitored, including electrocardiogram (ECG), blood pressure (BP), oxygen saturation and end tidal carbon dioxide (CO_2.)
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.
During the use of halogenated inhalational anaesthetics such as sevoflurane, an AV junctional rhythm may develop in isolated cases, especially when a vagolytic drug such as atropine has been given beforehand.
Awakening delirium is about 2-3 times more common in young children under six years of age than in adults. Agitation in awakening anaesthesia in young children has been reported more frequently with short-awakening anaesthetics such as sevoflurane compared to some other anaesthetics with longer awakening durations, such as propofol and halothane. Rapid emergence in children may be associated with agitation and lack of co-operation (in about 25% of cases).
As with other halogenated inhalational anaesthetics, sevoflurane has a dilating effect on the systemic and coronary arterial system. Therefore, sevoflurane should be used with caution in patients with coronary heart disease and it is important to maintain normal haemodynamics to avoid myocardial ischemia in these patients.

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. 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.

Perioperative Hyperkalaemia
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. If a neuromuscular disease is suspected, further evaluation should take place.

Isolated reports of QT prolongation, very rarely associated with Torsades 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 post-operative 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. In patients who have experienced hepatic injury, jaundice, unexplained fever or eosinophilia after administration of other inhalation anaesthetics, it is recommended to avoid administration of sevoflurane if anaesthesia with intravenous medicinal products or regional anaesthesia is possible (see section 4.8).

Patients with repeated exposures to halogenated hydrocarbons, including sevoflurane, within a relatively short interval may have an increased risk of hepatic injury.

General
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. Due to sevoflurane's insolubility in blood, hemodynamic changes may occur more rapidly than with some other volatile anaesthetics. Particular care must be taken when selecting the dosage for patients who are hypovolaemic, hypotensive, or otherwise hemodynamically compromised, e.g., due to concomitant medications.
As with all anaesthetics, maintenance of haemodynamic stability is important to avoid myocardial ischaemia in patients with coronary artery disease.
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).
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. Although recovery of consciousness following sevoflurane administration generally occurs within minutes, the impact on intellectual function for two or three days following anaesthesia has not been studied. As with other anaesthetics, small changes in moods may persist for several days following administration (see section 4.7).

Replacement of Desiccated CO2 Absorbents:

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 CO_2 absorbent, specifically those containing potassium hydroxide (e.g. Baralyme). An unusually delayed rise or unexpected decline of inspired sevoflurane concentration compared to the vaporiser setting may be associated with excessive heating of the CO_2 absorbent canister.
An exothermic reaction, enhanced sevoflurane degradation, and production of degradation products can occur when the CO_2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO_2 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 CO_2 absorbents and maximum sevoflurane concentrations (8%) for extended periods of time (2: 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 CO_2 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. CO_2 absorbents should be replaced routinely regardless of the state of the colour indicator (see Section 6.6).

Renal Impairment:
Although data from controlled clinical studies at low flow rates are limited, findings taken from patient and animal studies suggest there is a potential for renal injury, which is presumed due to Compound A. Therefore, sevoflurane should be used with caution in patients with renal insufficiency. Animal and human studies demonstrate that sevoflurane administered for more than 2 MAC hours and at fresh gas flow rates of <2 L/min may be associated with proteinuria and glycosuria. Also see Section 5.1.
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. Consider all of the factors leading to Compound A exposure in humans, especially duration of exposure, fresh gas flow rate, and concentration of sevoflurane. Inspired sevoflurane concentration and fresh gas flow rate should be adjusted to minimize exposure to Compound A. Sevoflurane exposure should not exceed 2 MAC hours at flow rates of 1 to <2 L/min. Fresh gas flow rates <1 L/min are not recommended.
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.)
Sevoflurane should be administered with caution to patients with impaired renal function (GFR :S 60 ml/min); renal function should be monitored postoperatively.

Neurosurgery & Neuromuscular Impairment:

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).

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 (see section 4.4- Paediatric population).

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 (see section 4.4 – Seizures).
Dystonic movements in children have been observed (see section 4.8).

Down syndrome
A significantly higher prevalence and degree of bradycardia has been reported in children with Down syndrome during and following sevoflurane induction.
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 lead to Torsades de Pointes. Sevoflurane should be administered with caution to patients at risk, such as elderly and patients diagnosed with congenital QTc prolongation.

4.5 Interaction 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.

Beta-sympathomimetic, and Alpha and Beta-sympathomimetic agents
Beta-sympathomimetic agents like isoprenaline and alpha- and beta- sympathomimetic agents like adrenaline and noradrenaline should be used with caution during sevoflurane narcosis, due to a potential risk of ventricular arrhythmia. 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.

Succinylcholine
Concomitant use of succinylcholine with inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the post-operative period.

Amphetamine derivatives
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.

Non-selective MAO inhibitors
Risk of crisis intraoperative collapse cannot be excluded as this has been observed with other halogenated inhalational anaesthetic agents. It is generally recommended that treatment should be stopped 2 weeks prior to surgery.

Calcium Antagonists
Sevoflurane may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivatives.
Caution should be exercised when calcium antagonists are used concomitantly with inhalation anesthetics due to the risk of additive negative inotropic effect.

Epinephrine/Adrenaline

Sevoflurane is similar to isoflurane in the sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline, the threshold dose of adrenaline producing multiple ventricular arrhythmias has been established at 5 microgram per Kg.

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

Beta blockers
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.

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. Due to possible induction of metabolism, isoniazid treatment should be discontinued 1 week before surgery and not restarted until 15 days after surgery.

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, propofol and other commonly used intravenous anaesthetics. Lower concentrations of sevoflurane may be required following use of an intravenous anaesthetic.

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.

Opioids such as alfentanil and sufentanil, when combined with sevoflurane, may lead to a synergistic fall in heart rate, blood pressure and respiratory rate.

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 (see section 4.2 – Maintenance).

Neuromuscular Blocking Agents
As with other inhalational anaesthetic agents, sevoflurane affects both the intensity and duration of neuromuscular blockade by non-depolarising muscle relaxants. When used to supplement alfentanil-N_2O 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.
The action of non-depolarizing muscle relaxants can be antagonized with neostigmine.
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 N_2O/opioid anaesthesia. Administration of supplemental doses of muscle relaxants should be guided by the response to nerve stimulation.

4.6 Fertility, pregnancy and lactation

Pregnancy
Studies in animals have shown reproductive toxicity (see section 5.3). 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. Caution should be exercised in obstetric anaesthesia due to the relaxant effect of sevoflurane on the uterus and increase in uterine haemorrhage.

Breastfeeding
It is not known whether sevoflurane or its metabolites are excreted in human milk. Caution should be exercised when sevoflurane is administered to nursing mothers

Fertility
Reproduction studies in rats and rabbits at doses up to 1 MAC have revealed no evidence of impaired fertility due to sevoflurane.
Sevoflurane should only be used in pregnancy if clearly indicated. The increased risk for uterus bleeding due to a relaxation effect of sevoflurane on the uterus. Use during labour and delivery is limited to one small study in Caesarean 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. No sign of foetal toxicity was seen in animal studies.

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 a motor vehicle or hazardous machinery, may be impaired for some time after general anaesthesia (see section 4.4).
Patients should not be allowed to drive for a suitable period after sevoflurane anaesthesia.

4.8 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

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 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.

Adverse Reaction Data Derived From Clinical Trials and Post-marketing Experience

Summary of Most Frequent Adverse Drug Reactions in sevoflurane Clinical Trials and Post-marketing Experience		
System Organ Class	**Frequency**	**Adverse Reactions**

Immune system disorders	Unknown	Anaphylactic reaction [1] Anaphylactoid reaction Hypersensitivity [1]
Blood and lymphatic system disorders	Uncommon	Leukopenia Leukocytosis
Psychiatric disorders	Very Common Uncommon	Agitation Confusional state
Nervous system disorders	Common Unknown	Somnolence Dizziness Headache Convulsion [2, 3] Dystonia Increased intracranial pressure
Cardiac disorders	Very Common Common Uncommon Unknown	Bradycardia Tachycardia Atrioventricular block complete, Cardiac arrhythmias (including ventricular arrhythmias), Atrial fibrillation Arrhythmia Ventricular extrasystoles Supraventricular extrasystoles Extrasystoles (ventricular, supra-ventricular, bigeminy-linked), Cardiac arrest [4] Ventricular fibrillation Torsades de Pointes Ventricular tachycardia, Electrocardiogram QT prolonged
Vascular disorders	Very Common Common	Hypotension Hypertension
Respiratory, thoracic and mediastinal disorders	Very Common Common Uncommon Unknown	Cough Respiratory disorder Respiratory depression Laryngospasm Airway obstruction Pulmonary oedema Apnoea Hypoxia Asthma Bronchospasm Dyspnoea [1] Wheezing [1] Breath holding
Gastrointestinal disorders	Very Common Common Unknown	Vomiting Nausea Salivary hypersecretion Pancreatitis
Metabolism And Nutrition Disorders	Unknown	Hyperkalaemia
Renal and urinary disorders	Uncommon Unknown	Urinary retention Glycosuria Tubulointerstitial nephritis
Hepato-biliary disorders	Unknown	Hepatitis [1, 2]

		Hepatic failure [1, 2] Hepatic necrosis [1, 2] Jaundice
Skin and subcutaneous tissue disorders	Unknown	Dermatitis contact [1] Pruritus Rash [1] Swelling face [1] Urticaria
Musculoskeletal and connective tissue disorders	Unknown	Muscle rigidity
General disorders and administration site conditions	Common Unknown	Chills Pyrexia Chest discomfort [1] Hyperthermia malignant [1, 2] Oedema
Investigations	Common Uncommon	Blood glucose abnormal Liver function test abnormal [5] White blood cell count abnormal Blood fluoride increased[1] Aspartate aminotransferase increased Serum Creatinine increased Alanine aminotransferase increased Blood lactate dehydrogenase increased
Injury, poisoning and procedural complications	Common	Hypothermia

[1] See section 4.8 – Description of selected adverse reactions.
[2] See section 4.4.
[3] See section 4.8 – 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.

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 (see section 4.4).
Rare reports of hypersensitivity (including contact dermatitis, rash, dyspnoea, wheezing, chest discomfort, swelling face, eyelid oedema, erythema, urticaria, pruritus bronchospasm, anaphylactic or anaphylactoid reactions) 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 (see section 4.4).

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. Several cases reported no concomitant medications, and at least one case was confirmed by electroencephalography (EEG). Although many cases were single seizures that resolved spontaneously or after treatment, cases of multiple seizures have also been reported. Seizures have occurred during, or soon after sevoflurane induction, during emergence, and during post operative recovery up to a day following anaesthesia. Clinical judgment should be exercised when using sevoflurane in patients who may be at risk for seizures (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2, Tel: +353 1 6764971, Fax: +353 1 6762517, Website: www.hpra.ie, e-mail: medsafety@hpra.ie.

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: anaesthetics, general; Halogenated hydrocarbons ATC code: N01 AB08
Changes in the clinical effects of sevoflurane rapidly follow changes in the inspired concentration. Sevoflurane is a halogenated methyl isopropyl ether inhalational anaesthetic which produces a rapid induction and recovery phase. MAC (minimum alveolar concentration) is age specific (see Section 4.2).

Sevoflurane produces loss of consciousness, reversible abolition of pain and motor activity, diminution of autonomic reflexes, respiratory and cardiovascular depression. These effects are dose-dependent.

Sevoflurane has a low blood/gas partition coefficient (0.65) leading to a rapid recovery from anaesthesia.

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. Sevoflurane produces a sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered epinephrine. This sensitisation is similar to that produced by isoflurane.

Nervous System Effects
In patients with normal intracranial pressure (ICP), sevoflurane had minimal effect on ICP and preserved CO_2 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. The FA / FI (wash-in) value after 30 minutes for sevoflurane is 0.85. The FA / FAO (wash-out) value after 5 minutes is 0.15.

In humans <5% of the absorbed sevoflurane is metabolised sevoflurane is defluorinated via cytochrome p450$(CYP)_2E_1$ in the liver, 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 rapid and extensive pulmonary elimination of sevoflurane minimises the quantity available for metabolism.

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 pre-operative levels.

5.3 Preclinical safety data

Preclinical data on single and repeated dose toxicity of sevoflurane showed no specific organ toxicity.

Reproductive studies: Studies on fertility performed in rats indicated a decrease in implantation and pregnancy rates after repeated exposure to anaesthetic doses. Developmental toxicity studies performed in rats and rabbits did not reveal any teratogenic effect. In sub-anaesthetic concentrations during the perinatal phase rats showed a prolongation of gestation.

Extensive in-vitro and in-vivo mutagenicity studies with sevoflurane yielded negative results. Carcinogenicity studies were not performed.
Effects on circulatory function and oxygen consumption: The results of studies conducted in dogs indicate that sevoflurane does not cause any coronary steal syndrome and does not exacerbate a pre-existing myocardial ischaemia. Animal studies have shown that hepatic and renal circulation are well maintained with sevoflurane.

Sevoflurane decreases the cerebral metabolic rate for oxygen ($CMRO_2$) in a fashion analogous to that seen with isoflurane. An approximately 50% reduction of $CMRO_2$ 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: Compound A is a degradation product of sevoflurane, which is generated in CO_2-absorbers. Its concentration increases normally with increasing absorber temperature, sevoflurane concentration and lowering of the fresh gas flow rate.

Studies performed in rats have shown a dose and duration of exposure dependent, reversible, nephrotoxicity (single cell necrosis of the proximal tubule cells). In the rat evidence for nephrotoxicity could be found at 25-50 ppm following 6 and 12 hours exposure. The relevance to humans is unknown.

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these nonclinical findings in not known.

In clinical studies the highest concentration of Compound A (using soda lime as CO_2 absorbents in the circuit) was 15 ppm in children and 32 ppm in adults. In systems using barium lime as CO_2 absorbents concentrations of up to 61 ppm were found. Although the experience with low-flow anaesthesia is limited, to date there is no evidence of kidney impairment due to Compound A.

Compound B: Inhalation exposure to Compound B at concentrations up to 2400 ppm (0.24%) for a duration of three hours resulted in no adverse effects on renal parameters or tissue histology in Wistar rats.

Carcinogenesis
No carcinogenicity studies have been performed. No mutagenic effect was found in the Ames test and no chromosomal aberrations were induced in cultivated mammalian cells. Reproduction studies in rats and rabbits at doses up to 1 MAC have not provided evidence of impaired fertility or harm to the fetus due to sevoflurane

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, alumimum, nickel- plated brass, chrome-plated brass or copper beryllium alloy.

Chemical degradation can occur upon exposure of inhaled anaesthetics to CO_2 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 CO_2 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 CO_2 absorbents and leads to the dissociation of sevoflurane into hexafluoroisopropanol (HFIP) and formaldehyde. HFIP is inactive,

non-genotoxic, rapidly glucoronidated, 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 fomation 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 for amber glass bottles with screw cap.
3 years for amber glass bottles with an integrated adaptor, multi-component closure.
Once opened, the contents of the bottle should be used within 8 weeks.

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 glass bottles (with or without an external PVC coating) 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.
OR
Type III, 250 ml amber glass bottle (with or without an external PVC coating) with an integrated adaptor multi-component closure (HDPE, EPDM rubber, stainless steel) attached to the bottle with an aluminium crimp ring.

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 re-breathing circuits and the possibility of elevated carboxyhaemoglobin levels, CO_2 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) CO_2 absorbent. If the CO_2 absorbent is suspected to be desiccated it should be replaced. Sevoflurane has been found to undergo degradation in the presence of strong Lewis acids that may be formed on metal or glass surfaces under harsh conditions, and the use of vaporisers that contain such strong Lewis acids, or that may form them under conditions of normal use, must be avoided. Only bottles without a pungent odour should be used.

In the event that a partially used bottle remains at the end of the procedure, the contents may be used for a period of up to 8 weeks.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Piramal Critical Care B.V.
Rouboslaan 32 (ground floor)
2252 TR
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8 MARKETING AUTHORISATION NUMBER

PA22583/003/001

10 DATE OF REVISION OF THE TEXT

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