1 PRODUCT NAME

Piramal Sevoflurane Liquid for Inhalation 100 % v/v

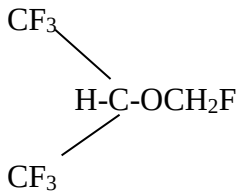
2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 250 mL bottle contains sevoflurane 100 % v/v.

3 PHARMACEUTICAL FORM

Sevoflurane is a fluorinated derivative of methyl isopropyl ether. The chemical name is fluoromethyl 2, 2, 2-trifluoro-1-(trifluoromethyl) ethyl ether.

The structural formula is:



Molecular weight: 200.05

CAS Number: 28523-86-6

Sevoflurane is a non-flammable and non-explosive liquid administered by vaporisation. Piramal Sevoflurane is a clear, colourless, non-pungent and stable liquid. Not more than 130ppm of water is present to provide protection from environmental Lewis acids. No other additives or chemical stabilisers are used. It is miscible with ethanol, ether, chloroform and petroleum benzene and is slightly soluble in water. Some physical constants of the compound are:

Specific gravity at 20°C	1.520 - 1.525
Boiling point (760 mmHg)	58.6°C
Vapour pressure in mmHg	157 mmHg at 20°C 197mmHg at 25°C 317mmHg at 36°C

Distribution Partition Coefficients at 37°C:

Blood / Gas	0.63 - 0.69
Water / Gas	0.36
Olive Oil / Gas	47.2 - 53.9
Brain / Gas	1.15

Mean Component / Gas Partition Coefficient at 25°C:

Conductive rubber	14.0
Butyl rubber	7.7
Polyvinyl chloride	17.4
Polyethylene	1.3

Sevoflurane is non-flammable and non-explosive as defined by the requirements of International Electrotechnical Commission 601-2-13.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Piramal Sevoflurane may be used for induction and maintenance of general anaesthesia in adult and paediatric patients undergoing surgery.

4.2 Dose and method of administration

The concentration of sevoflurane being delivered from a vaporiser during anaesthesia should be known. This may be accomplished by using a vaporiser calibrated specifically for sevoflurane. Filling occurs directly from the bottle with an integrated adaptor, multi-component closure or, in case of a bottle without integrated adaptor multi-component closure, with the use of an appropriate adaptor calibrated specifically to fit the sevoflurane vaporiser.

Premedication

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

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. For induction of anaesthesia, inspired concentrations of up to 8% sevoflurane usually produces surgical anaesthesia in less than two minutes in both adults and children.

Maintenance

Surgical levels of anaesthesia may be sustained with concentrations of 0.5-3% sevoflurane with or without the concomitant use of nitrous oxide (see table).

MAC Values for Adults and Paediatric Patients According to Age		
Age of Patient (Years)	**Sevoflurane in Oxygen**	**Sevoflurane in 65% N_20/35% 0_2**
0 - 1 months*	3.3%	
1 - <6 months	3.0%	
6 months - <3 years	2.8%	2.0% @
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 3 - <5 year-old and 1 - <3 year-old paediatric patients, 60% N20/40% 0_2 was used [1]		

Elderly: As with other inhalation agents, lesser concentrations of sevoflurane are normally required to maintain anaesthesia.

Emergence

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

Hepatic Impairment

Sevoflurane is effective and well-tolerated when used as the primary agent for the maintenance of anaesthesia in patients with impaired hepatic function, Child-Pugh Class A and B. Sevoflurane did not exacerbate pre-existing hepatic impairment.

Renal Impairment

See section 4.4.

4.3 Contraindications

Sevoflurane should not be used in patients with known sensitivity to sevoflurane or to other halogenated agents (e.g. history of hepatotoxicity, usually including elevated liver enzymes, fever, leucocytosis and/or eosinophilia temporally related to anaesthesia with one of these agents) or with known or suspected genetic susceptibility to malignant hyperthermia.

4.4 Special warnings and precautions for use

Sevoflurane is contraindicated in patients in whom general anaesthesia is contraindicated. 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 and oxygen enrichment and circulatory resuscitation must be immediately available.

Since levels of anaesthesia may be altered easily and rapidly, only vaporizers specifically calibrated for sevoflurane should be used. Hypotension and respiratory depression increase as anaesthesia is deepened.

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, such as elderly and patients diagnosed with congenital QTc prolongation.

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.

Sevoflurane should be used with caution in patients with Myasthenia Gravis.

During 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, maintenance of haemodynamic stability is important to the avoidance of myocardial ischaemia in patients with coronary artery disease.

The recovery from general anaesthesia should be assessed carefully before patients are discharged from the post-anaesthesia care unit.

Replacement of Desiccated CO_2 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 vaporizer setting may be associated with excessive heating of the CO_2 absorbent canister.

An exothermic reaction, enhanced sevoflurane degradation, and production of degradation products (see section 3) 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 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.

When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced before administration of sevoflurane. The colour indicator of most CO_2 absorbents does not necessarily change as a result of desiccation. 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.

Compound A

The LC50 of compound A in Wistar rats was 1050-1090 ppm in animals exposed for 1hour and 400-420 ppm in animals exposed for 3 hours (median lethal concentrations were approximately 1070 and 330-490 ppm, respectively). In rats exposed to 30, 60, or 120 ppm of Compound A in an 8-week chronic toxicity study (24 exposures, 3hours/exposure), no apparent evidence of toxicity was observed other than loss of body weight in females on the last study day.

Sprague-Dawley rats were administered Compound A via nose-only inhalation exposure in an open system (25, 50, 100 or 200 ppm [0.0025-0.02%] of Compound A). Control groups were exposed to air. The threshold, at which reversible alterations in urinary and clinical parameters indicative of renal changes (concentration-dependent increases in BUN, creatinine, glucose, protein/creatinine ratios and N-acetyl-glucosamidase/creatinine ratios) were observed, was 114 ppm of Compound A. Histological lesions were all reversible.

Since the uptake of inhalational agents in small rodents is substantially higher than in humans, higher levels of medicine, Compound A (degradant of sevoflurane) or 2-bromo-2-chloro-1, 1-difluoro ethylene (BCDFE) (degradant/metabolite of halothane) would be expected in rodents. Also, the activity of the key enzyme (β-lyase) involved in haloalkene nephrotoxicity is ten-fold greater in the rat than it is in humans.

Compound A concentrations are reported to increase with increasing absorber temperature, increasing sevoflurane concentrations and with decreasing fresh gas flowrates. It has been reported

that the concentration of Compound A increases significantly with prolonged dehydration of Baralyme®. In the clinical situation, the highest concentration of Compound A in the anaesthesia circuit with soda lime as the CO_2 absorbent was 15 ppm in paediatrics and 32 ppm in adults. However, concentrations to 61 ppm have been observed in patients attached to systems with Baralyme® as the CO_2 absorbent.

The level of Compound A at which toxicity occurs in humans is not known. Although exposure to sevoflurane in low flow systems is limited, there has been no evidence of renal dysfunction attributable to Compound A.

Compound B

In the clinical situation, the concentration of Compound B detected in the anaesthesia circuit did not exceed 1.5 ppm. Inhalation exposure to Compound B at concentrations of up to 2400 ppm (0.24%) for 3 hours resulted in no adverse effects on renal parameters or tissue histology in Wistar rats.

Malignant Hyperthermia

In susceptible individuals, potent inhalation anaesthetic agents including sevoflurane, may trigger a skeletal muscle hyper-metabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The clinical syndrome is signal led by hypercapnia, and may include muscle rigidity, tachycardia, tachypnoea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these non-specific 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 post-marketing reports of malignant hyperthermia. Some of these reports have been fatal.

Treatment of malignant hyperthermia 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.

Hyperkalaemic Cardiac Arrest in Paediatric Patients

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 hyper-metabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Carcinogenicity / Mutagenicity

Studies on carcinogenesis have not been performed. No mutagenic effect was noted in the Ames test and no chromosomal aberrations were induced in cultured mammalian cells.

Paediatric population

Paediatric neurotoxicity

Published juvenile animal studies demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive defects when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans.

Some published studies in children suggest that similar deficits may occur after repeated or prolonged exposures to anaesthetic agents early in life and may result in adverse cognitive or behavioural effects. These studies have substantial limitations and it is not clear if the observed effects are due to the anaesthetic/sedative agent administration or other factors such as the surgery or underlying illness.

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks (also see section 4.6).

The use of sevoflurane had 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 (also see section 4.8).

A significantly higher prevalence and degree of bradycardia has been reported in children with Down syndrome during and following sevoflurane induction.

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.

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.

Hepatic Impairment

Very rare cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice have been reported from post-marketing 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 (see section 4.8).

It has been reported that previous exposure to halogenated hydrocarbon anaesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury.

Neurosurgery

In patients at risk for elevations of intracranial pressure (ICP), sevoflurane should be administered cautiously in conjunction with ICP-reducing manoeuvres such as hyperventilation.

Seizures

Rare cases of seizures have been reported in association with sevoflurane use (see above - Paediatric Population and section 4.8).

4.5 Interaction with other medicines and other forms of interaction

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.

Non-selective MAO-inhibitors: Risk of crisis during the operation. It is generally recommended that treatment should be stopped 2 weeks prior to surgery.

Sevoflurane may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivates.

Caution should be exercised when calcium antagonists are used concomitantly with inhalation anaesthetics due to the risk of additive negative inotropic effect.

Concomitant use of succinylcholine with 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 post-operative period.

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 medicines, smooth muscle relaxants, anti-infective agents including aminoglycosides, hormones and synthetic substitutes, blood derivatives and cardiovascular medicines including epinephrine [1]. 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 anaesthetic 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.

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 (see section 5.2 - Pharmacokinetics of Fluoride Ion).

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, 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 suxamethonium chloride and the duration of depolarising neuromuscular blockade have 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. The requirements for non-depolarising muscle relaxants: (1) for endotracheal intubation, do not reduce the dose of non-depolarising muscle relaxants, (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

Risk summary statement

Anaesthetic and sedative agents are a necessary part of the care of children and pregnant women needing surgery, other procedures or tests that cannot be delayed, and no specific medicines have been shown to be safer than any other. Decisions regarding the timing of any elective procedures requiring anaesthesia should take into consideration the benefits of the procedure weighed against the potential risks.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sevoflurane should be used during pregnancy only if clearly needed.

The safety of sevoflurane has been demonstrated in a clinical trial of anaesthesia for caesarean section. The safety of sevoflurane in labour and vaginal delivery has not been demonstrated.

Sevoflurane, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgment should be observed when using sevoflurane during obstetric anaesthesia.

Preclinical data

Published studies in pregnant primates demonstrate that the administration of anaesthetic and sedative agents that block NMDA receptors and/or potentiate GABA activity during the period of peak brain development increases neuronal apoptosis in the developing brain of the offspring when

used for longer than 3 hours. There are no data on pregnancy exposures in primates corresponding to periods prior to the third trimester in humans (also see section 5.3).

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

Use in Lactation

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.

4.7 Effects on ability to drive and use machines

Patients should be advised that performance of activities requiring mental alertness, such as driving or 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

Clinical Trials
As with all potent inhaled anaesthetics, sevoflurane may cause dose-dependent cardio-respiratory depression. Most adverse events are mild or moderate in severity and transient in duration. Nausea, vomiting and delirium have been observed in the postoperative period, common sequelae of surgery and general anaesthesia, which may be due to inhalational anaesthetic, other agents administered intra-operatively or post-operatively and to the patient's response to the surgical procedure.

The most frequent adverse events (≥ 10%) considered to be probably related to sevoflurane administration overall were: nausea, vomiting, increased cough and hypotension. In adult patients, the most frequent adverse events (≥ 10%) were: nausea, vomiting and hypotension. In elderly patients' the most frequent adverse events (≥ 10%) were: hypotension, nausea and bradycardia. In paediatric patients, the most frequent adverse events (≥ 10%) were: vomiting, agitation, increased cough, and nausea. The type, severity and frequency of adverse events in sevoflurane patients were comparable to adverse events in reference medicine patients.

All events, at least possibly related to sevoflurane from clinical trials, are displayed in the Table below by MedDRA System Organ Class, Preferred Term and frequency. The following frequency groupings are used: very common (≥ 1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000); very rare (<1/10,000), including isolated reports. The type, severity, and frequency of adverse events in sevoflurane patients were comparable to adverse events in reference-drug patients.

Summary of Most Frequent Adverse Drug Reactions in Sevoflurane Clinical Trials		
System Organ Class	**Frequency**	**Adverse Effects**
Psychiatric disorders	Very common	Agitation
Nervous system disorders	Common	Somnolence Dizziness Headache
Cardiac/Vascular disorders	Very Common Common	Bradycardia Hypotension Tachycardia Hypertension

	Uncommon Unknown	Atrioventricular block complete QT prolongation associated with Torsade
Respiratory, thoracic and mediastinal disorders	Very Common Common	Cough Respiratory disorder Laryngismus
Gastrointestinal disorders	Very Common Common	Nausea Vomiting Increased salivation
General disorders and administration site conditions	Common	Chills Pyrexia
Investigations	Common	Blood glucose elevation Liver function test abnormal White blood cell count elevation
Injury, poisoning and procedural complications	Common	Hypothermia

In clinical studies administration of sevoflurane has not been associated with any clinically significant effect on liver or kidney function in a wide variety of patient populations including children, adults, elderly, renally impaired, hepatically impaired, obese, patients undergoing cardiac bypass surgery, patients treated with aminoglycosides or metabolic inducers, patients exposed to repeat surgeries, patients undergoing surgeries 6 hours in duration.

Post-marketing Experience

Adverse events 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 or establish a causal relationship to sevoflurane exposure.

Summary of Post-Marketing Adverse Drug Events	
System Organ Class	Adverse Events
Immune system disorders	Anaphylactic reaction*** Anaphylactoid reaction Hypersensitivity***
Nervous system disorders	Convulsion Dystonia
Cardiac disorders	Cardiac Arrest#
Respiratory, thoracic and mediastinal disorders	Bronchospasm Dyspnoea*** Wheezing***
Hepato-biliary disorders	Hepatitis Hepatic failure Hepatic necrosis
Skin and subcutaneous tissue disorders	Rash*** Urticaria Pruritus Dermatitis contact***

	Swelling Face***
General disorders and administration site conditions	Hyperthermia malignant Chest discomfort***
***May be associated with hypersensitivity reactions, particularly in association with long-term occupational exposure to inhaled anaesthetic agents #There have been very rare post-marketing reports of cardiac arrest in the setting of sevoflurane use.	

Seizure-like activity may occur on extremely rare occasions following sevoflurane administration. Reported events were of short duration and there was no evidence of any abnormality during emergence from anaesthesia or in the postoperative period.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Symptoms of overdose include respiratory depression and circulatory insufficiency. In the event of overdosage, the following action should be taken: discontinue administration of sevoflurane, maintain a patent airway, initiate assisted or controlled ventilation with oxygen and maintain adequate cardiovascular function. For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Sevoflurane has been demonstrated to be a fast-acting, non-irritating agent in a variety of animal species and in humans. Administration has been associated with a smooth, rapid loss of consciousness during inhalation induction and a rapid recovery following discontinuation of anaesthesia.

Induction is accomplished, with a minimum of excitement or of signs of upper respiratory irritation, no evidence of excessive secretions within the tracheo bronchial tree and no central nervous system stimulation. In paediatric studies in which mask induction was performed, the incidence of coughing was statistically significantly lower with sevoflurane than with halothane. The times for induction and recovery were also reduced in these patients.

Like other potent inhalational anaesthetics, sevoflurane depresses respiratory function and blood pressure in a dose-related manner. Sevoflurane has been demonstrated to be an appropriate agent for use in neurosurgery, caesarean section, coronary artery bypass surgery and in non-cardiac patients at risk for myocardial ischaemia.

The adrenaline-induced arrhythmogenic threshold for sevoflurane is comparable to that of isoflurane and higher than that of halothane. Studies in dogs have demonstrated that sevoflurane does not reduce collateral myocardial perfusion. In clinical studies, the incidence of myocardial ischaemia and myocardial infarction in patients at risk for myocardial ischaemia was comparable between sevoflurane and isoflurane.

Animal studies have shown that regional blood flow (e.g., hepatic, renal, cerebral circulations) is well maintained with sevoflurane. In both animal studies (dogs, rabbits) and clinical studies, changes in

neurohemodynamics (intracranial pressure, cerebral blood flow/blood flow velocity, cerebral metabolic rate for oxygen, and cerebral perfusion pressure) were comparable between sevoflurane and isoflurane. Sevoflurane has minimal effect on intra-cranial pressure and preserves CO_2 responsiveness.

Sevoflurane does not affect renal concentrating ability, even after prolonged anaesthetic exposure of up to approximately 9 hours.

For MAC equivalents for sevoflurane for various age groups, see section 4.2. As with other halogenated agents, minimum alveolar concentration (MAC) decreases with age and with the addition of nitrous oxide.

5.2 Pharmacokinetic properties

Solubility

The low solubility of sevoflurane in blood would suggest that alveolar concentrations should rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent. This was confirmed in a clinical study where inspired and end-tidal concentrations (FI and FA) were measured. The FA/FI (wash in) value at 30 minutes for sevoflurane was 0.85. The FA/FAO (wash out) value at 5 minutes was 0.15.

Distribution

The effects of sevoflurane on the displacement of medicines from serum and tissue proteins have not been investigated. Other fluorinated volatile anaesthetics have been shown to displace medicines from serum and tissue proteins in vitro. The clinical significance of this is unknown. Clinical studies have shown no untoward effects when sevoflurane is administered to patients taking medicines that are highly bound and have a small volume of distribution (e.g. phenytoin).

Metabolism

The rapid pulmonary elimination of sevoflurane minimises the amount of anaesthetic available for metabolism. In humans <5% of sevoflurane absorbed is metabolised to hexa fluoro isopropanol (HFIP), with release of inorganic fluoride and carbon dioxide (or a one carbon fragment). Once formed HFIP is rapidly conjugated with glucuronic acid and eliminated. No other metabolic pathways for sevoflurane have been identified. It is the only fluorinated volatile anaesthetic that is not metabolised to trifluoroacetic acid.

Fluoride Ion

Fluoride ion concentrations are influenced by the duration of anaesthesia, the concentration of sevoflurane administered, and the composition of the anaesthetic gas mixture.

Inorganic fluoride concentrations peak within two hours of the end of sevoflurane anaesthesia and return to baseline concentrations within 48 hours' post anaesthesia. Approximately 7% of adults evaluated for inorganic fluoride concentrations in clinical studies experienced concentrations greater than 50 µM; no clinically significant effect on renal function was observed in any of these individuals (see section 4.5 - Inducers of CYP2E1).

The defluorination of sevoflurane is not inducible by barbiturates.

5.3 Preclinical safety data

Animal toxicology and/or pharmacology
Published studies in animals demonstrate that the use of anaesthetic and sedative agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, exposure to 3 hours of an anaesthetic regimen that produced a light surgical plane of anaesthesia did not increase neuronal cell loss, however, treatment regimens of 5 hours or longer increased neuronal cell loss. Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with prolonged cognitive deficits in learning and memory.

In a published study conducted on rhesus monkeys, administration of an anaesthetic dose of ketamine for 24 hours on gestation day 122 increased neuronal apoptosis in the developing brain of the foetus. In other published studies, administration of either isoflurane or propofol for 5 hours on gestation day 120 resulted in increased neuronal and oligodendrocyte apoptosis in the developing brain of the offspring of rhesus macaques. With respect to brain development, this time period corresponds to the third trimester of gestation in the human. The clinical significance of these findings is not clear, however, studies in juvenile animals suggest neuroapoptosis correlates with long-term cognitive deficits. Healthcare providers should balance the benefits of appropriate anaesthesia in pregnant women, neonates and young children who require procedures with the potential risks suggested by the nonclinical data.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

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 penta fluoro isopropanyl 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 hexa fluoro isopropanol (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

The shelf-life of Piramal Sevoflurane is 5 years when stored below 25°C.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

Piramal Sevoflurane™ inhalation containing sevoflurane 100%v/v is packaged in 250 mL amber-coloured glass bottles (with or without an external PVC coating) with two component screw cap or amber coloured glass bottle (with or without an external PVC coating) with an integrated adaptor multi-component closure.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MEDICINE SCHEDULE

Prescription Only Medicine.

8 SPONSOR

Device Technologies New Zealand Ltd
47 Arrenway Drive
Albany, Auckland
New Zealand
Telephone: +64 9 913 2000
Fax: +64 9 913 2009
Email: sales@device.co.nz

9 DATE OF FIRST APPROVAL

26th March 2015.

10 DATE OF REVISION OF THE TEXT

10th November 2020.

Version 6.

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[1] International Medical Datasheet Update – Navarro R et al. Humans anaesthetised with sevoflurane or isoflurane have similar arrhythmic response to epinephrine. Anaesthesiology 1994 Mar; 80 (3): 545-9.

SUMMARY TABLE OF CHANGES

Section Changed	**Summary of New Information**
All sections	Updated to reflect originator product's Data Sheet (Sevorane) (Version 2)
8 Sponsor	Include NZ Sponsor details (Version 3)
4.4 Special warnings and precautions for use / Paediatric Population 4.6 Fertility, pregnancy and lactation 5.3 Preclinical safety data	Additional safety information relating to use in paediatric and pregnant populations Adopted new Medsafe Data Sheet SmPC-style format and content requirements in accordance with NZDS Explanatory Guide, effective 1 March 2017. (Version 4)
4.2 Dose and Method of Administration 6.5 Nature and Contents of Container	Include description of additional new integrated adaptor multi-component closure. Include Summary Table of Changes. (Version 5)
4.3 Contraindications 4.4 Special warnings and precautions for use 4.5 Interaction with other medicines and other forms of interaction 4.9 Overdose	Updated safety information regarding contraindications and special warnings and precautions. Updated information on interactions with other medicines. Additional safety information for overdose.