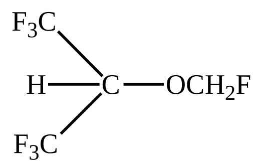
SEVOFLURANE

NAME OF THE MEDICINE:

- Australian Approved Name: Sevoflurane
- Non-proprietary name: fluoromethyl 2,2,2,-trifluoro-1-(trifluoromethyl) ethyl ether
- Chemical structure:



- CAS number: 28523-86-6

DESCRIPTION:

Sevoflurane ($C_4H_3F_7O$), volatile liquid for inhalation, a non-flammable and nonexplosive liquid administered by vaporization, is a halogenated general inhalation anaesthetic drug.

Physical Constants are:

Molecular weight	200.05
Boiling point at 760 mm Hg	58.6°C
Specific gravity at 20°C	1.520 -1.525
Vapour pressure in mm Hg	157 mm Hg at 20°C
	197 mm Hg at 25°C
	317 mm Hg at 36°C

Distribution Partition Coefficients at 37°C:

Blood/Gas	0.63 - 0.69
Water/Gas	0.36
Olive Oil/Gas	47 - 54
Brain/Gas	1.15

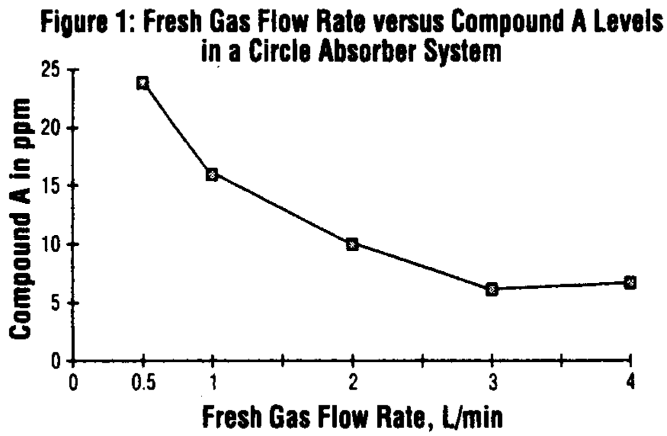
Mean Component/Gas Partition Coefficients at 25°C for Polymers Used Commonly in Medical Applications:

Conductive rubber	14.0
Butyl rubber	7.7
Polyvinylchloride	17.4
Polyethylene	1.3

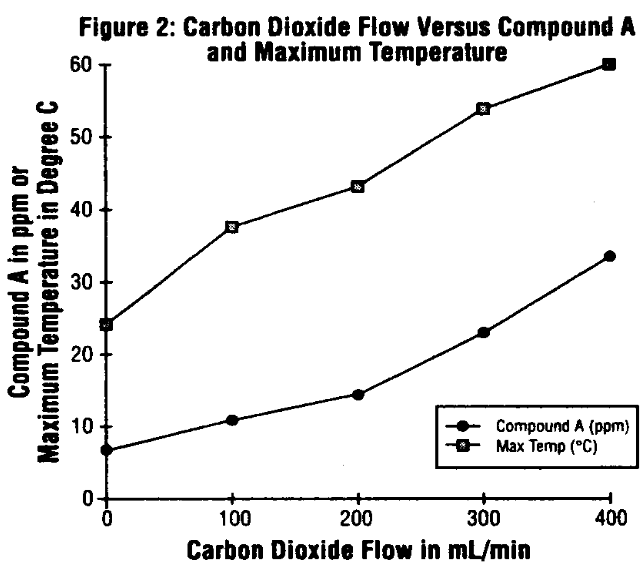
Sevoflurane is a clear, colourless, stable liquid containing no additives or chemical stabilizers. Sevoflurane is nonpungent. It is miscible with ethanol, ether, chloroform and petroleum benzene, and it is slightly soluble in water. Sevoflurane is stable when stored under normal room lighting conditions according to instructions.

Sevoflurane is chemically stable. No discernible degradation occurs in the presence of strong acids or heat. The only known degradation reaction in the clinical setting is through direct contact with CO_2 absorbents (soda lime and Baralyme®) producing pentafluoroisopropenyl fluoromethyl ether, (PIFE, $C_4H_2F_6O$), also known as Compound A, and trace amounts of pentafluoromethoxy isopropyl fluoromethyl ether, (PMFE, $C_5H_6F_6O$), also known as Compound B.

The production of degradants in the anesthesia circuit results from the extraction of the acidic proton in the presence of a strong base (KOH and/or NaOH) forming an alkene (Compound A) from sevoflurane similar to formation of 2-bromo-2-chloro-1,1-difluoro ethylene (BCDFE) from halothane. Baralyme causes more production of Compound A than does soda lime. Laboratory simulations have shown that the concentration of these degradants is inversely correlated with the fresh gas flow rate (See Figure 1).



Sevoflurane degradation in soda lime has been shown to increase with temperature. Since the reaction of carbon dioxide with absorbents is exothermic, this temperature increase will be determined by quantities of CO_2 absorbed, which in turn will depend on fresh gas flow in the anesthesia circle system, metabolic status of the patient, and ventilation. The relationship of temperature produced by varying levels of CO_2 and Compound A production is illustrated in the following *in vitro* simulation where CO_2 was added to a circle absorber system.



Compound A has been shown to be nephrotoxic in rats after exposures that have varied in duration from one to three hours. No histopathologic change was seen at a concentration of up to 270 ppm for one hour. Sporadic single cell necrosis of proximal tubule cells has been reported at a concentration of 114 ppm after a 3-hour exposure to Compound A in rats. The LC_{50} reported at 1 hour is 1050-1090 ppm (male-female) and, at 3 hours, 350-490 ppm (male-female).

At a fresh gas flow rate of 1 L/min, mean maximum concentrations of Compound A in the anesthesia circuit in clinical settings are approximately 20 ppm (0.002%) with soda lime and 30 ppm (0.003%) with Baralyme in adult patients; mean maximum concentrations in paediatric patients with soda lime are about half those found in adults. The highest concentration observed in a single patient with Baralyme was 61 ppm (0.0061%) and 32 ppm (0.0032%) with soda lime. The concentrations of Compound A measured in the anesthesia circuit when sevoflurane is used clinically are not known to be deleterious to humans.
Sevoflurane is not corrosive to stainless steel, brass, aluminium, nickel-plated brass, chrome-plated brass or copper beryllium.

PHARMACOLOGY:

Pharmacodynamics:

Sevoflurane is an inhalation anaesthetic agent for use in induction and maintenance of general anesthesia. Administration has been associated with a smooth, rapid loss of consciousness during inhalation induction and a rapid recovery following discontinuation of anesthesia. Minimum alveolar concentration (MAC) of sevoflurane in oxygen for a 40 year old adult is 2.1%. The MAC of sevoflurane decreases with age and with the addition of nitrous oxide (see **DOSAGE AND ADMINISTRATION** for details).

Induction is accomplished with a minimum of excitement or of signs of upper respiratory irritation, no evidence of excessive secretions within the tracheobronchial tree and no central nervous system stimulation. Changes in the depth of sevoflurane anesthesia rapidly follow changes in the inspired concentration. The times for induction and recovery were reduced in paediatric patients who received sevoflurane in clinical studies.

Some of the recovery variables evaluated in the sevoflurane clinical programme are summarised as follows:

Table 1: Induction and Recovery Variables for Evaluable Paediatric Patients in Two Comparative Studies: Sevoflurane versus Halothane

Time to End-Point (min)	Sevoflurane Mean ± SEM	Halothane Mean ± SEM
Induction	2.0 ± 0.2 (n=294)	2.7 ± 0.2 (n=252)
Emergence	11.3 ± 0.7 (n=293)	15.8 ± 0.8 (n=252)
Response to command	13.7 ± 1.0 (n=271)	19.3 ± 1.1 (n=230)
First analgesia	52.2 ± 8.5 (n=216)	67.6 ± 10.6 (n=150)
Eligible for recovery discharge	76.5 ± 2.0 (n=292)	81.1 ± 1.9 (n=246)

n = number of patients with recording of events.

Table 2: Recovery Variables for Evaluable Adult Patients in Two Comparative Studies: Sevoflurane versus Isoflurane

Time to Parameter: (min)	Sevoflurane Mean ± SEM	Isoflurane Mean ± SEM
Emergence	7.7 ± 0.3 (n=395)	9.1 ± 0.3 (n=348)
Response to command	8.1 ± 0.3 (n=395)	9.7 ± 0.3 (n=345)
First analgesia	42.7 ± 3.0 (n=269)	52.9 ± 4.2 (n=228)
Eligible for recovery discharge	87.6 ± 5.3 (n=244)	79.1 ± 5.2 (n=252)

n = number of patients with recording of recovery events.

Table 3: Meta-Analyses for Induction and Emergence Variables for Evaluable Adult Patients in Comparative Studies: Sevoflurane versus Propofol

Parameter	No. of Studies	Sevoflurane Mean ± SEM	Propofol Mean ± SEM
Mean maintenance anesthesia exposure	3	1.0 MAC•hr. ± 0.8 (n=259)	7.2 mg/kg/hr ± 2.6 (n=258)
Time to induction: (min)	1	3.1 ± 0.18* (n=93)	2.2 ± 0.18** (n=93)
Time to emergence: (min)	3	8.6 ± 0.57 (n=255)	11.0 ± 0.57 (n=260)
Time to respond to command: (min)	3	9.9 ± 0.60 (n=257)	12.1 ± 0.60 (n=260)
Time to first analgesia: (min)	3	43.8 ± 3.79 (n=177)	57.9 ± 3.68 (n=179)
Time to eligibility for recovery discharge: (min)	3	116.0 ± 4.15 (n=257)	115 .6 ± 3.98 (n=261)

*Propofol induction of one sevoflurane group = mean of 178.8mg ± 72.5 SD (n=165)
**Propofol induction of all propofol groups = mean of 170.2mg ± 60.6 SD (n=245)
n = number of patients with recording of events.

Cardiovascular Effects

Sevoflurane was studied in 14 healthy volunteers (18-35 years old) comparing sevoflurane-O_2 (Sevo/O_2) to sevoflurane-N_2O/O_2 (Sevo/N_2O/O_2) during 7 hours of anesthesia. During controlled ventilation, haemodynamic parameters versus minimum alveolar concentration (MAC) were measured for both mixtures (Figures 3-6):

Figure 3: Heart Rate

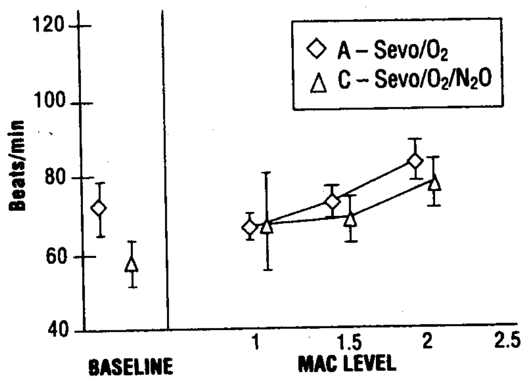


Figure 4: Mean Arterial Pressure

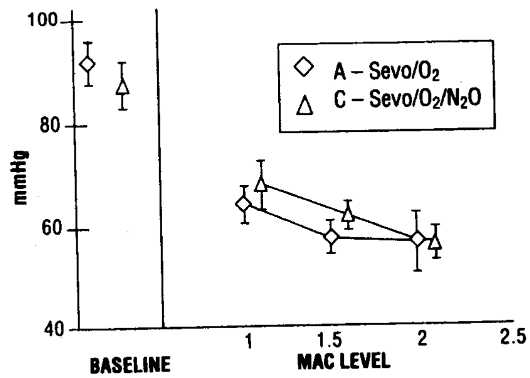


Figure 5: Systemic Vascular Resistance

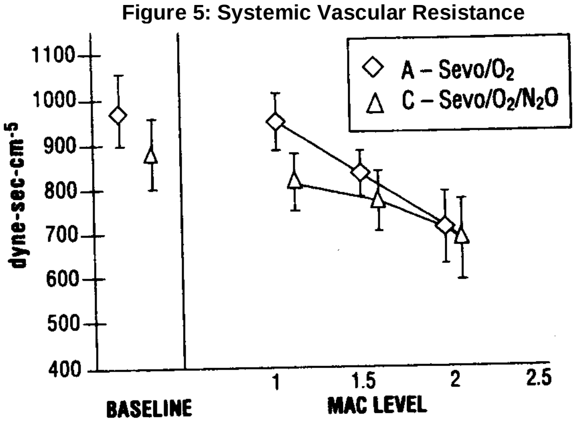
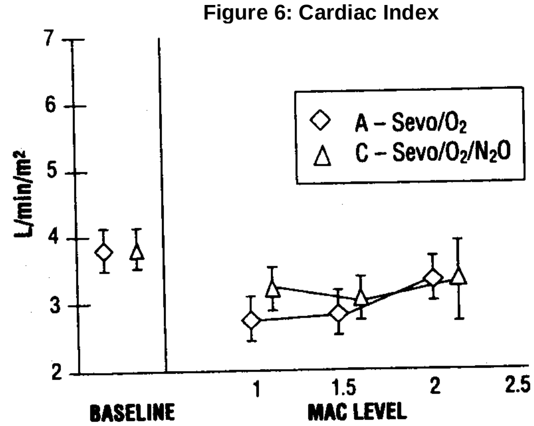


Figure 6: Cardiac Index



Sevoflurane is a dose-related cardiac depressant. Sevoflurane does not produce increases in heart rate at doses less than 2 MAC.

A study investigating the adrenaline induced arrhythmogenic effect of sevoflurane versus isoflurane in adult patients undergoing transsphenoidal hypophysectomy demonstrated that the threshold dose of adrenaline (ie. the dose at which the first sign of arrhythmia was observed) producing multiple ventricular arrhythmias was 5 mcg/kg with both sevoflurane and isoflurane. Consequently, the interaction of sevoflurane with adrenaline appears to be equal to that seen with isoflurane.

Pharmacokinetics:

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 (F_I) and end tidal (F_A) concentrations were measured. The F_A/F_I (wash in) value for sevoflurane at 30 minutes was 0.85 (Figure 7). The F_A/F_{AO} (wash out) value at 5 minutes was 0.15 where F_{AO} is the last alveolar concentration measured immediately before discontinuance of the anaesthetic (Figure 8).

Figure 7: Ratio of Concentration of Anaesthetic in Alveolar Gas to Inspired Gas

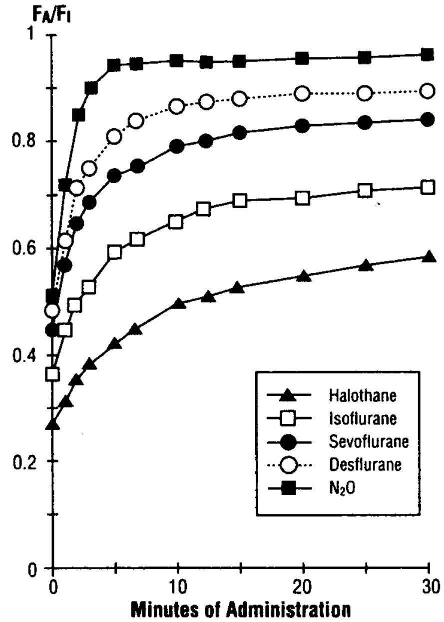
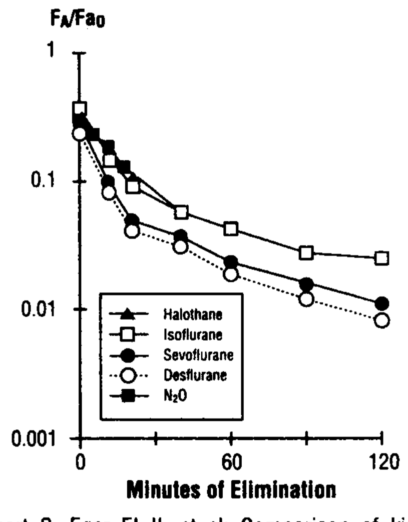


Figure 8: Concentration of Anaesthetic in Alveolar Gas Following Termination of Anaesthesia

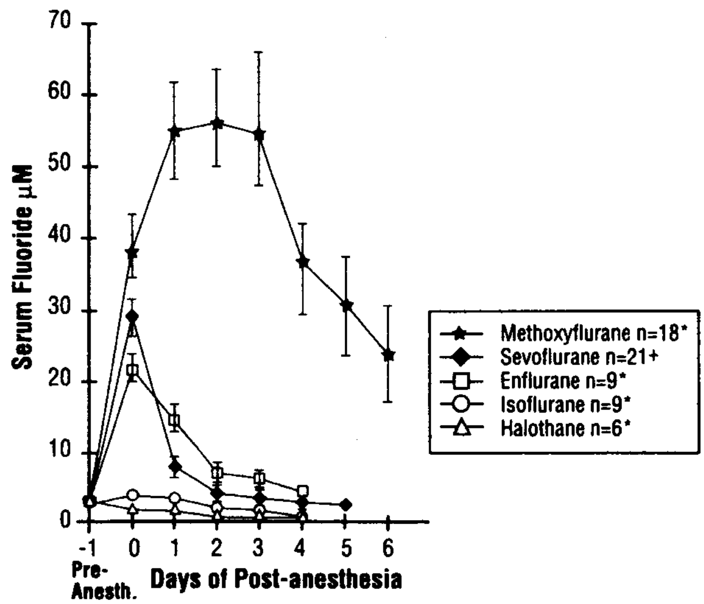


Yasuda N, Lockhart S, Eger EI II, et al: Comparison of kinetics of sevoflurane and isoflurane in humans. Anesth Analg 72:316, 1991.

The rapid pulmonary elimination of sevoflurane minimizes the amount of anaesthetic available for metabolism. In humans, approximately 5% of absorbed sevoflurane is metabolized by cytochrome P450 2E1 to hexafluoroisopropanol (HFIP), with release of inorganic fluoride and CO_2 (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 metabolized to trifluoracetic acid.

Cytochrome P450 2E1 is the principal isoform identified for sevoflurane metabolism and this may be induced by chronic exposure to isoniazid and ethanol. This is similar to the metabolism of isoflurane and enflurane and is distinct from that of methoxyflurane which is metabolised via a variety of cytochrome P450 isoforms (Figure 9).

Figure 9: Serum Inorganic Fluoride Concentrations for Sevoflurane and Other Volatile Anaesthetics



Cousins M.J., Greenstein L.R., Hitt B.A., et al: Metabolism and renal effects of enflurane in man. Anesthesiology 44:44; 1976* and Sevo-93-044+.

Legend:

Pre-Anesth. = Pre-anesthesia

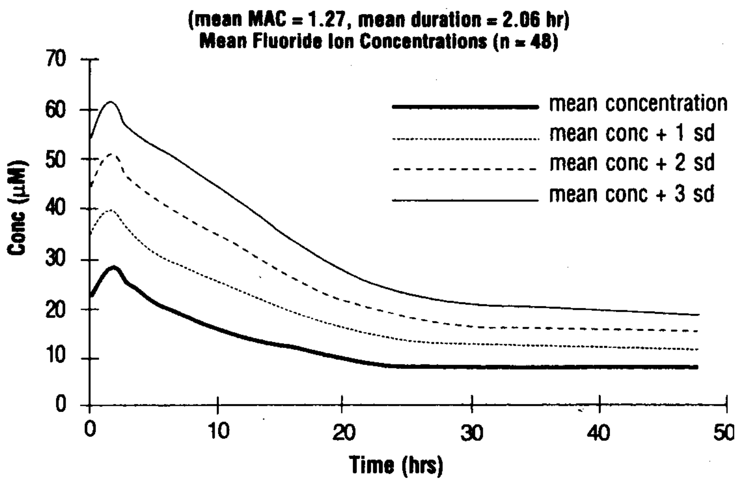
Approximately 7% of patients/volunteers evaluated for inorganic fluoride concentration in clinical studies had fluoride levels >50 µM.

Pharmacokinetics of Fluoride Ion

Fluoride ion concentrations are influenced by the duration of anesthesia, the concentration of sevoflurane administered, and the composition of the anaesthetic gas mixture. In studies where anesthesia was maintained purely with sevoflurane for periods ranging from 1 to 6 hours, peak fluoride concentrations ranged between 12 µM and 90 µM. As shown in Figure 10, peak concentrations occur within 2 hours of the end of anesthesia and are less than 25 µM (475ng/mL) for the majority of the population after 10 hours. The half-life is in the range of 15-23 hours.

It has been reported that following administration of methoxyflurane, serum inorganic fluoride concentrations >50 µM were correlated with the development of vasopressin-resistant, polyuric, renal failure. Inadequate data exist to evaluate the nephrotoxicity of elevated fluoride concentrations with sevoflurane. Isolated examples of mild impairment of concentrating ability have been reported. In clinical trials with sevoflurane, there were no reports of toxicity with elevated fluoride ion levels. Based on animal and human studies, this methoxyflurane derived threshold does not appear valid for sevoflurane, perhaps due to sevoflurane's rapid pulmonary elimination, difference in cytochrome P450 isoforms involved in metabolism, low level of metabolism and lower area under the curve (Figure 9).

Figure 10: Fluoride Ion Concentrations Following Administration of Sevoflurane



Fluoride Concentrations after Repeat Exposure And In Special Populations

Fluoride concentrations have been measured after single, extended, and repeat exposure to sevoflurane in normal surgical and special patient populations, and pharmacokinetic parameters were determined.

Compared with healthy individuals, the fluoride ion half-life was prolonged in patients with renal impairment, but not in the elderly. A study in 8 patients with hepatic impairment suggests a slight prolongation of the half-life. The mean half-life in patients with renal impairment averaged approximately 33 hours (range 21-61 hours) as compared to a mean of approximately 21 hours (range 10-48 hours) in normal healthy individuals. The mean half-life in the elderly (greater than 65 years) approximated 24 hours (range 18-72 hours). The mean half-life in individuals with hepatic impairment was 23 hours (range 16-47 hours). Mean maximal fluoride values (C_{max}) determined in individual studies of special populations are displayed below. Obesity is a risk factor contributing to elevated inorganic fluoride concentrations.

Table 4: Fluoride Ion Estimates in Special Populations Following Administration of Sevoflurane

	n	Age (yr)	Duration (hr)	Dose (MAC•hr)	C_{max} (µM)
PAEDIATRIC PATIENTS					
Anaesthetic					
Sevoflurane-O_2	76	0-11	0.8	1.1	12.6
Sevoflurane-O_2	40	1-11	2.2	3.0	16.0
Sevoflurane/N_2O	25	5-13	1.9	2.4	21.3
Sevoflurane/N_2O	42	0-18	2.4	2.2	18.4
Sevoflurane/N_2O	40	1-11	2.0	2.6	15.5
ELDERLY	33	65-93	2.6	1.4	25.6
RENAL	21	29-83	2.5	1.0	26.1
HEPATIC	8	42-79	3.6	2.2	30.6
OBESE	35	24-73	3.0	1.7	38.0

n = number of patients studied.

Preclinical data suggest that the defluorination of sevoflurane by hepatic enzymes, and hence the production of fluoride, may be increased by agents such as alcohol, isoniazid and barbiturates.

CLINICAL TRIALS:

Cardiovascular surgery/coronary artery bypass graft surgery

Sevoflurane was compared to isoflurane as an adjunct with opioids in a multicentre study of 273 patients undergoing coronary artery bypass graft (CABG) surgery. The average Minimum Alveloar Concentration (MAC) dose was 0.49 for sevoflurane and 0.53 for isoflurane. No statistical differences were observed between the two treatment groups with respect to incidence (sevoflurane 7%, isoflurane 11%) and duration (sevoflurane approximately 18 minutes, isoflurane approximately 17 minutes) of ischaemic events, number of patients with a diagnosis of myocardial infarction (sevoflurane 8%, isoflurane 10%), time to haemodynamic stability (sevoflurane approximately five hours, isoflurane approximately six hours), or use of cardioactive drugs (sevoflurane 53%, isoflurane 47%).

Noncardiac surgery patients at risk for myocardial ischaemia.

Sevoflurane/N_2O was compared to isoflurane/N_2O for maintenance of anesthesia in a multicentre study of 214 patients at mild to moderate risk for myocardial ischaemia who underwent elective noncardiac surgery. The average MAC dose was 0.49 for both drugs. No statistical differences were observed between the treatment groups for the incidence of any haemodynamic variation (tachycardia, bradycardia, hypertension, hypotension, and ischaemia without haemodynamic abnormality). No statistical differences were observed between the two regimens with respect to intraoperative incidence of myocardial ischaemia (sevoflurane 6%, isoflurane 3%) or postoperative incidence of ischaemic events (sevoflurane 10%, isoflurane 16%). No statistical differences were observed between the treatment groups for the incidence of study drug related adverse experiences by body system or by COSTART term (sevoflurane 60%, isoflurane 61%). There was one death in the sevoflurane group and four deaths in the isoflurane group. None of these deaths were considered by the investigator to be drug related.

Paediatric anesthesia

The concentration of sevoflurane required for maintenance of general anesthesia is age dependent (see **Dosage and Administration**). Overall incidences of bradycardia (more than 20 beats/minute less than normal) is lower for sevoflurane (3%) than for halothane (7%). Emergence times for sevoflurane are faster than for halothane (12 versus 19 minutes, respectively). A higher incidence of agitation occurs with sevoflurane (208/837 patients or 25%) when compared with halothane (114/661 patients or 17%).

Neurosurgery

Three studies compared sevoflurane to isoflurane for maintenance of anesthesia during neurosurgical procedures. In a study of 20 patients, there was no difference between sevoflurane and isoflurane with regard to recovery from anesthesia. In two studies, a total of 22 patients with intracranial pressure (ICP) monitors received either sevoflurane or isoflurane. There was no difference between sevoflurane and isoflurane with regard to ICP response to inhalation of 0.5, 1.0 and 1.5 MAC inspired concentrations of volatile agent during N_2O/O_2/fentanyl anesthesia. During progressive hyperventilation from $PaCO_2 = 40$ to $PaCO_2 = 30$, ICP response to hypocarbia was preserved with sevoflurane at both 0.5 and 1.0 MAC concentrations. In patients at risk for elevations of ICP, sevoflurane should be administered cautiously (See **Precautions**).

Caesarean section

Sevoflurane (n = 29) was compared to isoflurane (n = 27) in American Society of Anaesthesiologists (ASA) class I or II patients for the maintenance of anesthesia during caesarean section. Newborn infant evaluations and recovery events were recorded. With both anaesthetics, Apgar scores averaged 8 and 9 at one and five minutes, respectively.

Use of sevoflurane as part of general anesthesia for elective caesarean section produced no untoward effects in mother or neonate. Sevoflurane and isoflurane demonstrated equivalent recovery characteristics. There was no difference between sevoflurane and isoflurane with regard to the effect on the newborn infant, as assessed by Apgar score and neurological and adaptive capacity score (average = 29.5). The safety of sevoflurane in labour and vaginal delivery has not been evaluated.

INDICATIONS:

Sevoflurane is indicated for induction and maintenance of general anesthesia in adult and paediatric patients undergoing surgery.

CONTRAINDICATIONS:

Sevoflurane can cause malignant hyperthermia. It should not be used in patients with known sensitivity to sevoflurane or to other halogenated agents nor in patients with known or suspected susceptibility to malignant hyperthermia.

The use of sevoflurane in anaesthesia apparatus employing rebreathing circuits which contain Baralyme is contraindicated.

It 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 (eg. jaundice associated with fever and/or eosinophilia) after anaesthesia with sevoflurane or other halogenated inhalational anaesthetics.

It should not be used in patients in whom general anaesthesia is contraindicated.

PRECAUTIONS:

All patients anesthetized with sevoflurane must be constantly monitored (eg. monitoring of the ECG, blood pressure, oxygen saturation and end tidal CO_2).

Sevoflurane should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment, and circulatory resuscitation must be immediately available. Since levels of anesthesia may be altered rapidly, only vaporizers producing predictable concentrations of sevoflurane should be used. Hypotension and respiratory depression increase as sevoflurane concentrations increase and anesthesia is deepened.

During the maintenance of anesthesia, increasing the concentration of sevoflurane produces dose-dependent decreases in blood pressure. Due to sevoflurane's insolubility in blood, haemodynamic changes may occur more rapidly than with some other volatile anaesthetics. Excessive decreases in blood pressure or respiratory depression may be related to depth of anesthesia and may be corrected by decreasing the inspired concentration of sevoflurane.

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

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

Sevoflurane exerts a dose-related cardiac depressant effect and causes a dose-related reduction in systemic vascular resistance. Particular care must be taken when selecting the dosage for patients who are hypovolaemic, hypotensive or otherwise haemodynamically compromised eg. due to concomitant medications.

The recovery from general anesthesia should be assessed carefully before a patient is discharged from the post-anesthesia care unit.

Sevoflurane may present an increased risk in patients with known sensitivity to volatile halogenated anaesthetic agents. Caution should be exercised in administering general anaesthesia, including sevoflurane, to patients with mitochondrial disorders.
Rare cases of seizures have been reported in association with sevoflurane use (see **P/ Paediatric Use** and **Adverse Events**).

In patients with or at risk of elevations of Intracranial Pressure (ICP), sevoflurane should be administered cautiously and in conjunction with ICP-reducing manoeures such as hyperventilation.

Compound A:

Although data from controlled clinical studies at low flow rates are limited, findings taken from patient and animal studies suggest that there is a potential for renal injury which is presumed due to Compound A (See **Description**). 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.

While a level of Compound A exposure at which clinical nephrotoxicity might be expected to occur has not been established, it is prudent to consider all of the factors leading to Compound A exposure in humans, especially duration of exposure, fresh gas flow rate, and concentration of sevoflurane. During sevoflurane anesthesia the clinician should adjust inspired concentration and fresh gas flow rate to minimize exposure to Compound A. To minimize exposure to Compound A, sevoflurane exposure should not exceed 2 MAC•hours at flow rates of 1 to <2 L/min. Because of limited clinical experience with sevoflurane in low-flow systems, fresh gas flow rates below 2L/min in a circle absorber system are not recommended.

Malignant Hyperthermia:

In susceptible individuals, potent inhalation anaesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. In genetically susceptible pigs, sevoflurane induced malignant hyperthermia. In clinical studies, sevoflurane has been associated with one case of malignant hyperthermia in 3220 exposures (incidence 0.03%). The patient responded to dantrolene sodium and subsequent muscle biopsy confirmed the patient's susceptibility to this condition. Fatal outcome of malignant hyperthermia has been reported with sevoflurane.

The clinical syndrome is signalled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these non-specific signs may also appear during light anesthesia, acute hypoxia, hypercapnia, and hypovolemia.

Treatment of malignant hyperthermia includes discontinuation of triggering agents (eg. sevoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy (consult Prescribing Information for dantrolene sodium intravenous for additional information on patient management). Renal failure may appear later, and urine flow should be monitored and sustained if possible.

Perioperative hyperkalaemia:

Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias, some fatal, in patients during the postoperative period. Patients with both latent and overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Hyperkalaemic cardiac arrest has also been reported in a child with Duchenne muscular dystrophy after anaesthesia with sevoflurane.

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 or 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.

Renal Function:

Because clinical experience in administering sevoflurane to patients with renal insufficiency (creatinine >1.5 mg/dL) is limited, its safety in these patients has not been established. Limited pharmacology data in these patients appear to suggest that the half-life of sevoflurane may be increased. The clinical significance is unknown at this time. Thus, sevoflurane should be used with caution in these patients and renal function should be monitored postoperatively.

Sevoflurane may be associated with glycosuria and proteinuria when used for long procedures at low flow rates. The safety of low flow sevoflurane on renal function was evaluated in patients with normal preoperative renal function. One study compared sevoflurane (N=98) to an active control (N=90) administered for ≥2 hours at a fresh gas flow rate of ≤1 L/minute. Per study defined criteria (Hou et al.) one patient in the sevoflurane group developed elevations of creatinine, in addition to glycosuria and proteinuria. This patient received sevoflurane at fresh gas flow rates of ≤800 mL/minute. Using these same criteria, there were no patients in the active control group who developed treatment emergent elevations in serum creatinine.

Hepatic Function:
Results of evaluations of laboratory parameters (eg. ALT, AST, alkaline phosphatase, and total bilirubin, etc.), as well as investigator-reported incidence of adverse events relating to liver function, demonstrate that sevoflurane can be administered to patients with normal or mild-to-moderately impaired hepatic function. However, patients with severe hepatic dysfunction were not investigated.

Occasional cases of transient changes in postoperative hepatic function tests were reported with both sevoflurane and reference agents. Sevoflurane was found to be comparable to isoflurane with regard to these changes in hepatic function.

Very rare cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice, including fatal hepatic necrosis and fatal hepatic failure, have been reported from post marketing experiences. Clinical judgement should be exercised when sevoflurane is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction (see **Adverse Events**). Patients with repeated exposures to halogenated hydrocarbons within a relatively short interval may have an increased risk of hepatic injury.

Risks associated with CO_2 Absorbents:
When in contact with alkaline CO_2 absorbents within the anaesthesia machine, sevoflurane can undergo degradation under certain conditions.

Replacement of desiccated CO_2 absorbents:
Sevoflurane should not be used with desiccated CO_2 absorbents.

Potassium hydroxide–containing CO_2 absorbents are not recommended for use with sevoflurane.

The exothermic reaction that occurs with sevoflurane and CO_2 absorbents is increased when the CO_2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO_2 absorbent canisters. Rare cases of extreme heat, smoke and/or spontaneous fire in the anesthesia machine have been reported during sevoflurane use in conjunction with the use of desiccated CO_2 absorbent. 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.

CO_2 absorbents should not be allowed to dry out when inhalational anaesthetics are being administered. 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, following current guidelines for use of anesthesiology equipment.

Formation of Degradation Products:
Degradation and formation of degradation products (methanol, formaldehyde, carbon monoxide, and Compounds A, B, C, D, and E) are increased by desiccated CO_2 absorbents (especially potassium hydroxide–containing absorbents), by increasing absorbent temperature, and by increased sevoflurane concentration.

Hypersensitivity, Headache and Elevated Liver Enzymes in Persons with Occupational Exposure:
Hypersensitivity reactions (manifested by anaphylactic reaction, dyspnoea, wheezing, rash, contact dermatitis, swelling face, chest discomfort), headache and elevated liver enzymes have been reported in persons with occupational exposure to inhaled anaesthetics, including sevoflurane.

Impairment on Fertility:
Potential effects of sevoflurane on male and female fertility have not been adequately investigated. In rats, after repeated administration of anaesthetic doses, there were suggestions of reduced fertility. The significance of these studies for humans is not known.

Reproduction studies have been performed in rats and rabbits at doses up to 2.2% and 1.8% respectively and have revealed no evidence of teratogenicity due to sevoflurane. However, teratogenic potential has not been adequately investigated in rabbits. The significance of these studies for humans is not known.

Use in Pregnancy (Category B2):
There are no adequate and well-controlled studies in pregnant women. Sevoflurane should be used during pregnancy only if clearly needed.

The safety of sevoflurane has been demonstrated in a clinical trial of anesthesia for caesarean section. The safety of sevoflurane in labour and 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.

All general anaesthetics carry the potential to produce central nervous system and respiratory depression in the newborn infant. In routine practice this does not appear to be a problem. However, in the compromised foetus, careful consideration should be given to this potential depression and to the selection of particular anaesthetic drugs, doses and techniques.

Use in Lactation:
It is not known whether sevoflurane is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when sevoflurane is administered to a breast-feeding woman.

Paediatric Use:
The concentration of sevoflurane required for maintenance of general anesthesia is age dependent. When used in combination with nitrous oxide, the MAC equivalent dose of sevoflurane should be reduced in paediatric patients. The sevoflurane MAC in premature infants has not been determined.

The use of sevoflurane has been associated with seizures (see **Adverse Events**). The majority of these have occurred in children and young adults starting from 2 months of age, most of whom had no predisposing risk factors. The epileptiform effect appears to be dose dependent and increases with depth of anaesthesia.

Benefits and risks should be carefully weighed and clinical judgement exercised when using sevoflurane in patients who may be at risk for seizures. The use of cerebral function monitoring (EEG) may permit optimization of sevoflurane dose and may help to avoid burst suppression and major epileptiform manifestations in susceptible patients.

Isolated cases of ventricular arrhythmia were reported in paediatric patients with Pompe disease. Bradycardia has been reported in paediatric patients with Down syndrome who have received sevoflurane.

Frequently, emergence in children may evoke a brief state of agitation that may hinder cooperation.

Use in the 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.

Carcinogenicity/ Genotoxicity:
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.

Effects on ability to drive and operate machinery:
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 anesthesia. Patients should not be allowed to drive for a suitable period after sevoflurane anesthesia.

INTERACTIONS WITH OTHER MEDICINES:

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, smooth muscle relaxants, anti-infective agents including aminoglycosides, hormones and synthetic substitutes, blood derivatives, and cardiovascular drugs.

Intravenous Anaesthetics:
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 would be expected to decrease the MAC of sevoflurane in the same manner as with other inhalation anaesthetics. Sevoflurane administration is compatible with benzodiazepines and opioids as commonly used in surgical practice. Opioids, such as fentanyl, 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 anaesthetic requirement for sevoflurane is decreased when administered in combination with nitrous oxide. Using 50% N_2O, the MAC equivalent dose requirement is reduced approximately 50% in adults, and approximately 25% in paediatric patients (see **Dosage and Administration**).

Neuromuscular Blocking Agents:
As is the case with other volatile anaesthetics, sevoflurane increases both the intensity and duration of neuromuscular blockade induced by nondepolarizing muscle relaxants. When used to supplement alfentanil-N_2O anesthesia, sevoflurane and isoflurane equally potentiate neuromuscular block induced with pancuronium, vecuronium or atracurium. Therefore, during sevoflurane anesthesia, the dosage adjustments for these muscle relaxants are similar to those required with isoflurane.

Potentiation of neuromuscular blocking agents requires equilibration of muscle with delivered partial pressure of sevoflurane. Reduced doses of neuromuscular blocking agents during induction of anesthesia may result in delayed onset of conditions suitable for endotracheal intubation or inadequate muscle relaxation.

Among available nondepolarizing agents, only vecuronium, pancuronium and atracurium interactions have been studied during sevoflurane anesthesia. The requirements for non-depolarizing muscle relaxants:

1. For endotracheal intubation, do not reduce the dose of nondepolarizing muscle relaxants.
2. During maintenance of anesthesia, the required dose of nondepolarizing 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.

The effect of sevoflurane on the duration of depolarizing neuromuscular blockade induced by suxamethonium chloride has not been studied.

Adrenaline
Sevoflurane is similar to isoflurane in the sensitization of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline. Doses of adrenaline >5µg/kg administered submucosally may produce multiple ventricular arrhythmias.

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 ionotropic, chronotropic and dromotropic effects of beta blockers through blockade of cardiovascular compensation 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.

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.

ADVERSE EFFECTS:

As with all potent inhaled anaesthetics, Sevoflurane may cause dose-dependent cardio-respiratory depression. Most adverse events are mild to moderate in severity and are transient. Nausea and vomiting have been observed in the post-operative period, 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.

In clinical trials involving 2906 patients, the incidence of cardiovascular events was reported as less than one percent. The cardiovascular events reported were as follows: arrhythmia, ventricular extrasystoles, supraventricular extrasystoles, complete AV block, bigeminy, inverted T wave, atrial fibrillation, atrial arrhythmia, second degree heart block, S-T depressed.

Adverse events are derived from reference controlled clinical trials in 2906 patients exposed to sevoflurane including 2069 adults and 837 children. Adverse events are presented within each body system in order of decreasing frequency in the following listings.

Adverse Events during the Induction Period (from onset of anaesthesia by mask induction to surgical incision)

Adult Patients (N = 118)
Common (≥1% and <10%)

Cardiovascular:	Bradycardia 5%, Hypotension 4%, Tachycardia 2%
Nervous System:	Agitation 7%
Respiratory System:	Laryngospasm 8%, Airway obstruction 8%, Breath holding 5%, Cough Increased 5%

Paediatric Patients (N = 507)
Very common (≥10%)

Nervous System:	Agitation 15%

Common (≥1% and <10%)

Cardiovascular:	Tachycardia 6%, Hypotension 4%
Respiratory System:	Breath holding 5%, Cough Increased 5%, Laryngospasm 3%, Apnoea 2%
Digestive System:	Increased salivation 2%

Adverse Events during Maintenance and Emergence Periods
All patients (N = 2906)

Very common (≥10%)

Digestive System:	Nausea 25%, Vomiting 18%
Cardiovascular:	Hypotension 11%
Respiratory System:	Cough increased 11%

Common (≥1% and <10%)

Body as a whole:	Fever 1%, Shivering 6%, Hypothermia 1%, Movement 1%, Headache 1%
Cardiovascular:	Hypertension 2%, Bradycardia 5%, Tachycardia 2%
Nervous System:	Somnolence 9%, Agitation 9%, Dizziness 4%, Increased salivation 4%
Respiratory System:	Breath holding 2%, Laryngospasm 2%

Occasional cases of transient changes in hepatic function tests and isolated examples of mild impairment of renal concentrating ability have been reported. Other changes in laboratory tests were consistent with those expected with anesthesia and surgery, and are similar in incidence and magnitude to other inhalational agents.

Adverse Events, All Patients in Clinical Trials (N = 2906), All Anaesthetic Periods, Incidence <1% (reported in 3 or more patients)

Body as a whole:	Asthenia, Pain
Cardiovascular:	Arrhythmia, Extrasystoles, Ventricular Extrasystoles, Supraventricular Extrasystoles, Complete AV Block, Bigeminy, Haemorrhage, Inverted T Wave, Atrial Fibrillation, Atrial Arrhythmia, Second Degree AV Block, Syncope, S-T Depressed
Nervous System:	Crying, Nervousness, Confusion, Hypertonia, Dry Mouth, Insomnia
Respiratory System:	Sputum Increased, Apnoea, Hypoxia, Wheezing, Bronchospasm, Hyperventilation, Pharyngitis, Hiccup, Hypoventilation, Dyspnoea, Stridor
Metabolism and Nutrition:	Increases in LDH, AST, ALT, BUN, Alkaline Phosphatase, Creatinine, Hyperbilirubinaemia, Glycosuria, Fluorosis, Albuminuria, Hypophosphataemia, Acidosis, Hyperglycaemia
Hemic and Lymphatic System:	Leucocytosis, Thrombocytopaenia
Skin and Special Senses:	Amblyopia, Pruritus, Taste Perversion, Dry Mouth, Rash, Conjunctivitis
Urogenital:	Urination Impaired, Urine Abnormality, Urinary Retention, Oliguria, Glycosuria, Albuminuria, Blood urea nitrogen increased, Blood creatinine increased
Hepatobiliary:	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood lactate dehydrogenase increased, hyperbilirubinaemia

Adverse Events During Post-Marketing Experience:

Nervous System Disorders: Post-marketing reports indicate that sevoflurane use has been associated with seizure-like activity (described as convulsions, seizures, tonic-clonic movements and twitching) on very rare occasions. Reported events were of short duration and there was no evidence of any abnormality during emergence from anesthesia or in the post-operative period. The majority of these cases were in children and young adults, most of whom had no medical history of seizures. Several cases reported no concomitant medications, and at least one case was confirmed by 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 anesthesia.

Cases of dystonic movement with spontaneous resolution have been reported in children receiving sevoflurane for induction of anesthesia with an uncertain relationship to sevoflurane.

Cases of increased intracranial pressure have been reported.

Malignant Hyperthermia:
Rare cases of malignant hyperthermia have been reported (see **Contraindications** and **Precautions**).

Hepatobiliary Disorders:
Rare reports of post-operative hepatitis exist. In addition, there have been rare post-marketing reports of hepatic failure, hepatic necrosis and jaundice 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.

Renal and Urinary Disorders:
Very rare events of acute renal failure have been reported with an uncertain relationship to sevoflurane. Tubulointerstitial nephritis has also been reported.

Immune System Disorders:
Rare events of allergic reactions, such as rash, urticaria, pruritus, bronchospasm, swelling face, eyelid oedema, erythema, contact dermatitis, chest discomfort, anaphylactic or anaphylactoid reactions have been reported (see **Contraindications**)

Metabolism and Nutrition Disorders:
Hyperkalaemia

Cardiac Disorders:
Cardiac arrest, Ventricular fibrillation, Torsade de pointes, Ventricular tachycardia, Electrocardiogram QT prolonged

Respiratory, Thoracic, and Mediastinal Disorders:
Respiratory depression

Gastrointestinal Disorders:
Pancreatitis

Musculoskeletal, Connective Tissue and Bone Disorders:
Rhabdomyolysis, Muscle rigidity

General Disorders and Administration Site Conditions:
Oedema

Laboratory Findings:
Transient elevations in glucose, liver function tests, and white blood cell count may occur as with use of other anaesthetic agents.

DOSAGE AND ADMINISTRATION:

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 is administered by inhalation. The concentration of Sevoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using a vaporizer calibrated specifically for sevoflurane.

Replacement of Desiccated CO_2 Absorbents:

CO_2 absorbents should not be allowed to dry out when inhalational anaesthetics are being delivered. When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced before administration of sevoflurane. The exothermic reaction that occurs with sevoflurane and CO_2 absorbents is increased **when the CO_2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO_2 absorbent canisters.** Extremely rare cases of extreme heat, smoke and/or spontaneous fire in the respiratory circuit of the anesthesia machine have been reported during sevoflurane use in conjunction with the use of a desiccated CO_2 absorbent. Rapid changes in the colour of some CO_2 absorbents or an unusually delayed rise in the delivered (inspired) gas concentration of sevoflurane compared with the vaporizer setting may indicate excessive heating of the CO_2 absorbent canister and chemical breakdown of sevoflurane.

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

Induction:
Dosage should be individualized 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 anesthesia in less than 2 minutes. In children inspired concentrations of up to 7% sevoflurane usually produce surgical anesthesia in less than 2 minutes.

Maintenance:
Dosage should be individualized and titrated to the desired effect according to the patient's age (with minimum alveolar concentration (MAC) of sevoflurane decreasing with increasing patient age) and clinical status. Surgical levels of anesthesia can usually be achieved with concentrations of 0.5-3% sevoflurane with or without the concomitant use of nitrous oxide.

Table 5: Effect of age on minimum alveolar concentration (MAC) of sevoflurane

MAC Values for Adults and Paediatric Patients According to Age

Age of Patient (years)	Sevoflurane in O_2	Sevoflurane in 65% N_2O/35% O_2*
<3 [#]	3.3-2.6%%	2.0%
3-<5	2.5%	Not available
5 - 12	2.4%	Not available
25	2.5%	1.4%
35	2.2%	1.2%
40	2.05%	1.1%
50	1.8%	0.98%
60	1.6%	0.87%
80	1.4%	0.70%

[#] Neonates are full-term gestational age. MAC in premature infants has not been determined
* In children, 60% N_2O/40% O_2 was used.

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

The minimum alveolar concentration (MAC) is the concentration at which 50% of the population tested does not move in response to a single stimulus of skin incision. MAC equivalents for sevoflurane for various age groups are summarized in Table 5 (above).

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

Renal or hepatic impairment:
Sevoflurane did not exacerbate pre-existing renal or hepatic impairment in clinical studies. However, caution is recommended when using sevoflurane in patients with renal insufficiency and renal function should be monitored postoperatively.

OVERDOSAGE:

Symptoms of overdose include respiratory depression and circulatory insufficiency. In the event of overdosage, or what may appear to be overdosage, the following action should be taken: discontinue administration of sevoflurane, maintain a patent airway, initiate assisted or controlled ventilation with 100% oxygen, and maintain adequate cardiovascular function.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS:

Sevoflurane, Volatile Liquid for Inhalation, is available in an aluminium bottle containing 250 mL sevoflurane.

Store below 30°C
The bottle cap should be replaced securely after each use of sevoflurane.

NAME AND ADDRESS OF THE MANUFACTURER AND SPONSOR:

Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie NSW 2146

POISON SCHEDULE OF THE MEDICINE: Schedule 4

DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG): 19 December 2005

DATE OF MOST RECENT AMENDMENT: 21 Jan 2014