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(91)07190056 15

Baxter

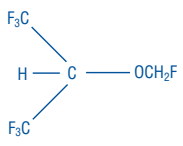
Sevoflurane Inhalation Anesthetic Liquid 100%

PACKAGE INSERT

DESCRIPTION

Sevoflurane, USP, volatile liquid for inhalation, a nonflammable and nonexplosive liquid administered by vaporization, is a halogenated general inhalation anesthetic drug.

Sevoflurane, USP is fluoromethyl 2,2,2,-trifluoro-1-(trifluoromethyl) ethyl ether and its structural formula is:



Sevoflurane, USP, 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
Vapor pressure in mm Hg	157 mm Hg at 20°C
	197 mm Hg at 25°C
	317 mm Hg at 36°C

FPO

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

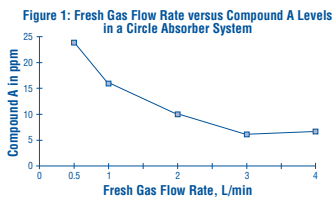
Sevoflurane, USP is nonflammable and nonexplosive as defined by the requirements of International Electrotechnical Commission 601-2-13.

Sevoflurane, USP is a clear, colorless, liquid containing no additives. Sevoflurane, USP is not corrosive to stainless steel, brass, aluminum, nickel-plated brass, chrome-plated brass or copper beryllium. Sevoflurane, USP is nonpungent. It is miscible with ethanol, ether, chloroform, and benzene, and it is slightly soluble in water. Sevoflurane, USP is stable when stored under normal room lighting conditions according to instructions. No discernible degradation of sevoflurane, USP occurs in the presence of strong acids or heat. When in contact with alkaline CO_2 absorbents (e.g. Baralyme® and to a lesser extent soda lime) within the anesthesia machine, Sevoflurane, USP can undergo degradation under certain conditions. Degradation of sevoflurane, USP is minimal, and degradants are either undetectable or present in non-toxic amounts when used as directed with fresh absorbents. Sevoflurane, USP degradation and subsequent degradant formation are enhanced by increasing absorbent temperature increased sevoflurane, USP concentration, decreased fresh gas flow and desiccated CO_2 absorbents (especially with potassium hydroxide containing absorbents e.g. Baralyme).

Sevoflurane, USP alkaline degradation occurs by two pathways. The first results from the loss of hydrogen fluoride with the formation of 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 second pathway for degradation of sevoflurane, USP, which occurs primarily in the presence of desiccated CO_2 absorbents, is discussed later.

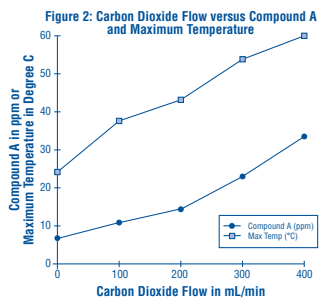
In the first pathway, the defluorination pathway, the production of degradants in the anesthesia circuit results from the extraction of the acidic proton in the presence of a strong base (KOH and/or NaOH) forming an alkene (Compound A) from sevoflurane, USP similar to formation of 2-bromo-2-chloro-1,1-difluoro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

Figure 1: Fresh Gas Flow Rate versus Compound A Levels in a Circle Absorber System



Since the reaction of carbon dioxide with absorbents is exothermic, the 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.

Figure 2: Carbon Dioxide Flow versus Compound A and Maximum Temperature



Compound A concentration in a circle absorber system increases as a function of increasing CO_2 absorbent temperature and composition (Baralyme producing higher levels than soda lime), increased body temperature, and increased minute ventilation, and decreasing fresh gas flow rates. It has been reported that the concentration of Compound A increases significantly with prolonged dehydration of Baralyme.

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 pediatric 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 levels of Compound A at which toxicity occurs in humans is not known.

The second pathway for degradation of sevoflurane, USP occurs primarily in the presence of desiccated CO_2 absorbents and leads to the dissociation of sevoflurane, USP into hexafluoroisopropanol (HFIP) and formaldehyde. HFIP is inactive, non-genotoxic, rapidly glucuronidated and cleared by the liver. 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 that can be associated with desiccated Baralyme. 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.

Sevoflurane, USP degradants were observed in the respiratory circuit of an experimental anesthesia machine using desiccated CO_2 absorbents and maximum sevoflurane, USP concentrations (8%) for extended periods of time (>2 hours). Concentrations of formaldehyde observed with desiccated soda lime in this experimental anesthesia respiratory circuit were consistent with levels that could potentially result in respiratory irritation. Although KOH containing CO_2 absorbents are no longer commercially available, in the laboratory experiments, exposure of sevoflurane, USP to the desiccated KOH containing CO_2 absorbent, Baralyme, resulted in the detection of substantially greater degradant levels.

CLINICAL PHARMACOLOGY

Sevoflurane, USP is an inhalational anesthetic agent for use in induction and maintenance of general anesthesia. Minimum alveolar concentration (MAC) of sevoflurane, USP in oxygen for a 40-year-old adult is 2.1%. The MAC of sevoflurane, USP decreases with age (see DOSAGE AND ADMINISTRATION for details).

Pharmacokinetics

Sevoflurane, USP is weakly soluble in blood and tissue, resulting in the rapid achievement of a sufficient alveolar concentration to produce anesthesia and a subsequent rapid elimination until cessation of anesthesia.

In humans, < 5% of sevoflurane, USP absorbed is metabolised in the liver to hexafluoroisopropanol (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 in the urine.

The rapid and extensive pulmonary elimination of sevoflurane, USP minimises the quantity available for metabolism. The metabolism of sevoflurane, USP is not induced by barbiturates.

Pharmacodynamics

Pharmacotherapeutic group: anesthetics, general; halogenated hydrocarbons.

ATC code: N01AB08

Sevoflurane, USP is a halogenated methyl isopropyl ether inhalational anesthetic which produces a rapid induction and recovery phase. MAC (minimum alveolar concentration) is age specific (see DOSAGE AND ADMINISTRATION).

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

Cardiovascular effects: Sevoflurane, USP may produce concentration-related decrease of blood pressure. Sevoflurane, USP produces a sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered epinephrine. This sensitisation is similar to that produced by isoflurane.

INDICATIONS AND USAGE

Sevoflurane, USP is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

Sevoflurane, USP 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 level of anesthesia may be altered rapidly, only vaporizers producing predictable concentrations of sevoflurane, USP should be used.

CONTRAINDICATIONS

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

WARNINGS

Risk of Renal Injury

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. Animal and human studies demonstrate that sevoflurane, USP 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, USP. During sevoflurane, USP 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, USP 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.

Because clinical experience in administering sevoflurane, USP to patients with renal insufficiency (creatinine >1.5 mg/dL) is limited, its safety in these patients has not been established.

Sevoflurane, USP may present an increased risk in patients with known sensitivity to volatile halogenated anesthetic agents. KOH containing CO_2 absorbents are not recommended for use with sevoflurane, USP.

Risk of Respiratory Depression

Sevoflurane, USP may cause respiratory depression, which may be augmented by opioid premedication or other agents causing respiratory depression. Monitor respiration and, if necessary, assist with ventilation (see PRECAUTIONS).

Risk of QT Prolongation

Reports of QT prolongation, associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering sevoflurane, USP to susceptible patients (e.g. patients with congenital Long QT Syndrome or patients taking drugs that can prolong the QT interval.

Malignant Hyperthermia

In susceptible individuals, potent inhalation anesthetic agents, including sevoflurane, USP, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. Sevoflurane, USP can induce malignant hyperthermia in genetically susceptible individuals, such as those with certain inherited ryanodine receptor mutations. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anesthesia, acute hypoxia, hypercapnia, and hypovolemia.

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

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

Perioperative Hyperkalemia

Use of inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during 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 hyperkalemia and resistant arrythmias is recommended as is subsequent evaluation for latent neuromuscular disease.

Risk of Driving and Operating Machinery

Performance of activities requiring mental alertness, such as driving or operating machinery, may be impaired after sevoflurane, USP anesthesia.

PRECAUTIONS

During the maintenance of anesthesia, increasing the concentration of sevoflurane, USP produces dose-dependent decreases in blood pressure. Due to sevoflurane, USP's insolubility in blood, these hemodynamic changes may occur more rapidly than with other volatile anesthetics. 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, USP.

Rare cases of seizures have been reported in association with sevoflurane, USP use (see ADVERSE REACTIONS).

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

DRUG INTERACTIONS

Sevoflurane, USP 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.

Nitrous oxide

As with other halogenated volatile anesthetics, the MAC of sevoflurane, USP is decreased when administered in combination with nitrous oxide. The MAC equivalent is reduced approximately 50% in adult and approximately 25% in pediatric patients.

Neuromuscular blocking agents

As with other inhalational anesthetic agents, sevoflurane, USP affects both the intensity and duration of neuromuscular blockade by non-depolarizing muscle relaxants. When used to supplement alfentanil-N_2O anesthesia, sevoflurane and isoflurane, USP potentiates neuromuscular block induced with pancuronium, vecuronium or atracurium. The dosage adjustments for these muscle relaxants when administered with sevoflurane, USP are similar to those required with isoflurane. The effect of sevoflurane, USP on succinylcholine and the duration of depolarizing neuromuscular blockade has not been studied.

The potentiation of the muscle relaxant effects produced by sevoflurane, USP requires equilibriation of muscle with delivered partial pressure of sevoflurane, USP.

Dosage reduction of neuromuscular blocking agents during induction of anesthesia 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, USP administration.

Among non-depolarizing 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-depolarizing muscle relaxants; and, (2) during maintenance of anesthesia, the dose of non-depolarizing muscle relaxants is likely to be reduced compared to that during N_2O/opioid anesthesia. Administration of supplemental doses of muscle relaxants should be guided by the response to nerve stimulation.

Benzodiazepines and opioids

Benzodiazepines and opiates are expected to decrease the MAC of sevoflurane, USP to the same manner as other inhaled anesthetics. Sevoflurane, USP administration is compatible with benzodiazepines and opioids as commonly used in surgical practice.

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

Beta blockers

Sevoflurane, USP may increase the negative ionotropic, chronotropic and dromotropic effects of beta blockers through blockade of cardiovascular compensation mechanisms.

Epinephrine/adrenaline

Sevoflurane, USP 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.

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, USP and lead to significant increases in plasma fluoride concentrations. Concomitant use of sevoflurane, USP and isoniazid can potentiate the hepatotoxic effects of isoniazid.

Indirect-acting sympathomimetics

There is a risk of acute hypertensive episode with the concomitant use of sevoflurane, USP and indirect sympathomimetic medicinal products (amphetamines, ephedrine).

Verapamil

Atrioventricular impairment of conduction was observed when verapamil and sevoflurane, USP were administered at the same time.

St John's Wort

Severe hypotension and delayed emergence from anesthesia with halogenated inhalational anesthetics have been reported in patients treated long-term with St John's Wort.

Barbiturates

Sevoflurane, USP administration is compatible with barbiturates, propofol and other commonly used intravenous anesthetics. Lower concentrations of sevoflurane, USP may be required following use of an intravenous anesthetic.

Desiccated CO_2 Absorbents

An exothermic reaction occurs when sevoflurane, USP is exposed to CO_2 absorbents. This reaction 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 breathing circuit have been reported during sevoflurane, USP use in conjunction with the use of desiccated CO_2 absorbent, specifically those containing potassium hydroxide (e.g. Baralyme). KOH containing CO_2 absorbents are not recommended for use with sevoflurane, USP. An unusually delayed rise or unexpected decline of inspired sevoflurane, USP concentration compared to the vaporizer setting may be associated with excessive heating of the CO_2 absorbent and chemical breakdown of sevoflurane, USP.

As with other inhalational anesthetics, degradation and production of degradation products can occur when sevoflurane, USP is exposed to desiccated absorbents. When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced. The color indicator of most CO_2 absorbents may not change upon desiccation. Therefore, the lack of significant color change should not be taken as an assurance of adequate hydration. CO_2 absorbents should be replaced routinely regardless of the state of the color indicator.

Pregnancy Category B: Reproduction studies have been performed in rats and rabbits at doses up to 1 MAC (minimum alveolar concentration) without CO_2 absorbent and have revealed no evidence of impaired fertility or harm to the fetus due to sevoflurane, USP at 0.3 MAC, the highest nontoxic dose. Developmental and reproductive toxicity studies of sevoflurane, USP in animals in the presence of strong alkalies (i.e., degradation of sevoflurane, USP and production of Compound A) have not been conducted. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, sevoflurane, USP should be used during pregnancy only if clearly needed.

Labor and Delivery: Sevoflurane, USP has been used as part of general anesthesia for elective cesarean section in 29 women. There were no untoward effects in mother or neonate. The safety of sevoflurane, USP in labor and delivery has not been demonstrated.

Nursing Mothers: The concentrations of sevoflurane, USP in milk are probably of no clinical importance 24 hours after anesthesia. Because of rapid washout, sevoflurane, USP concentrations in milk are predicted to be below those found with many other volatile anesthetics.

Geriatric Use

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

Pediatric Use

Induction and maintenance of general anesthesia with sevoflurane, USP have been established in pediatric patients aged 1 to 18 years (see ADVERSE REACTIONS). Sevoflurane, USP has a nonpungent odor and is suitable for mask induction in pediatric patients.

The concentration of sevoflurane, USP required for maintenance of general anesthesia is age dependent. When used in combination with nitrous oxide, the MAC equivalent dose of sevoflurane, USP should be reduced in pediatric patients. MAC in premature infants has not been determined. (See DOSAGE AND ADMINISTRATION for recommendations in pediatric patients 1 day of age and older.)

The use of sevoflurane, USP has been associated with seizures (see PRECAUTIONS and ADVERSE REACTIONS). 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. Clinical judgement should be exercised when using sevoflurane, USP in patients who may be at risk for seizures. Dystonic movements in children have been observed (see ADVERSE REACTIONS).

ADVERSE REACTIONS

Summary of the safety profile

As with all potent inhalational anesthetics, sevoflurane can produce dose dependent cardiac respiratory depression. Most of the adverse reactions are mild to moderate in severity and transient in duration. Nausea, vomiting and delirium have been reported in the post-operative period – common symptoms following surgery and general anesthesia – which may be due to the inhalational anesthetic, other agents administered intra-operatively or post-operatively, or the patient's reaction 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 pediatric patients: agitation, cough, vomiting and nausea.

Tabulated summary of adverse reactions

All reactions at least possibly related to sevoflurane from compiled reports 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.

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".

Summary of Most Frequent Adverse Drug Reactions

System Organ Class	Frequency	Adverse Reactions
Immune system disorders	Unknown	Anaphylactic reaction [1] Anaphylactoid reaction Hypersensitivity [1]
Blood and lymphatic system disorders	Uncommon	Leukocytosis
Psychiatric disorders	Common Uncommon	Agitation Confusion Delirium
Nervous system disorders	Common Unknown	Somnolence Dizziness Headache Convulsion [2, 3] Dystonia Increased intracranial pressure Seizures Dystonic movements
Cardiac disorders	Very Common Common Uncommon Unknown	Bradycardia Tachycardia Atrioventricular block complete, Cardiac arrhythmias (including ventricular arrhythmias), atrial fibrillation, 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 Laryngospasm Airway obstruction Apnoea Asthma Hypoxia Bronchospasm Dyspnoea [1] Wheezing [1] Breath holding Respiratory depression
Gastrointestinal disorders	Very Common Common Unknown	Nausea Vomiting Salivary hypersecretion Pancreatitis
Metabolism And Nutrition Disorders	Common Unknown	Blood glucose abnormal Hyperkalemia
Musculoskeletal connective tissue and bone disorders	Unknown	Muscle rigidity Rhabdomyolysis
Hepato-biliary disorders	Unknown	Hepatitis [1,2] Hepatic failure [1,2] Hepatic necrosis [1,2] Jaundice
Renal and Urinary Disorders	Uncommon	Urinary retention Glycosuria Renal failure acute
Skin and subcutaneous tissue disorders	Unknown	Dermatitis contact [1] Pruritus Rash [1] Swelling face [1] Urticaria
General disorders and administration site conditions	Common Unknown	Chills Pyrexia Hypothermia Chest discomfort [1] Hyperthermia malignant [1,2] Edema
Investigations	Common Uncommon	Blood glucose abnormal Liver function test abnormal [5] White blood cell count abnormal Aspartate aminotransferase increased Blood fluoride increased[6] Alanine aminotransferase increased Blood creatinine increased Blood lactate dehydrogenase increased
Injury, poisoning and procedural complications	Common	Hypothermia

[1] See section ADVERSE REACTIONS – Description of selected adverse reactions.

[2] See section WARNINGS and PRECAUTIONS

[3] See section ADVERSE REACTIONS – Pediatric population.

[4] There have been very rare postmarketing reports of cardiac arrest in the setting of sevoflurane use.

[5] Occasional cases of transient changes in hepatic function tests were reported with sevoflurane and reference agents.

[6] Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anaesthesia. See Description of selected adverse reactions below.

Description of selected adverse reactions

Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anesthesia. Concentrations of inorganic fluoride generally peak within two hours of the end of sevoflurane anesthesia 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 anesthetic agents, including sevoflurane. However, the actual incidence and relationship of sevoflurane to these events cannot be established with certainty.

Rare reports of hypersensitivity (including contact dermatitis, rash, dyspnoea, wheezing, chest discomfort, swelling face, eyelid edema, erythema, urticaria, pruritis bronchospasm, anaphylactic or anaphylactoid reactions have been reported particularly in association with long-term occupational exposure to inhaled anesthetic agents, including sevoflurane.

In susceptible individuals, potent inhalation anesthetic agents may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia (see WARNINGS).

Pediatric population

The use of sevoflurane, USP 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, USP induction, during emergence, and during post-operative recovery up to a day following anesthesia. Clinical judgment should be exercised when using sevoflurane, USP in patients who may be at risk for seizures (see WARNINGS and PRECAUTIONS).

General disorders and administration site conditions:

Edema overdose.

Symptoms of overdose include respiratory depression and circulatory insufficiency. In the event of apparent overdosage, see OVERDOSAGE.

Laboratory Findings

Transient elevations in glucose, liver functions tests and white blood cell count may occur as with use of other anesthetic agents.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken: discontinue administration of sevoflurane, USP, maintain a patent airway, initiate assisted or controlled ventilation with oxygen, and maintain adequate cardiovascular function.

DOSAGE AND ADMINISTRATION

Pre-anesthetic Medication

The need and choice of premedication should be selected according to the need of the individual patient, and at the discretion of the anesthesiologist.

Surgical Anesthesia

The concentration of sevoflurane, USP delivered via a vaporizer during anesthesia should be known. This may be accomplished by using a vaporizer calibrated specifically for sevoflurane, USP.

Anesthesia 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, USP. Induction with sevoflurane, USP may be achieved in oxygen (O_2) with or without nitrous oxide (N_2O). For induction, inspired concentrations of up to 8% sevoflurane, USP may be used to achieve surgical anesthesia in less than two minutes in both adults and children.

Maintenance of anesthesia

Surgical levels of anesthesia may be maintained by inhalation of 0.5-3% sevoflurane, USP in O_2 with or without concomitant use of N_2O.

Table 1: MAC Values for Adults and Pediatric Patients According to Age

Age of Patient (years)	Sevoflurane in Oxygen	Sevoflurane in 65% N_2O/35% O_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 1 - <3 year old pediatric patients, 60% N_2O/40% O_2 was used.

Emergence

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

Elderly

The Minimum Alveolar Concentration (MAC) decreases with increasing age. The average concentration of sevoflurane, USP to achieve MAC in an 80-year-old is approximately 50% of that required in a 20-year-old.

Directions for Filling Vaporizers

Utilize an adapter, as appropriate, when filling the vaporizer with sevoflurane, USP.

How supplied

Sevoflurane, USP, Volatile Liquid for Inhalation, is available as: Aluminum bottle containing 250 mL sevoflurane, USP.

Safety and handling

CO_2 absorbents should not be allowed to dry out when inhalation anesthetics are being administered.

OCCUPATIONAL CAUTION

There is no specific work exposure limit established for sevoflurane, USP. However, the National Institute for Occupational Safety and Health has recommended an 8 hour time-weighted average limit of 2 ppm for halogenated anesthetic agents in general (0.5 ppm when coupled with exposure to N_2O). (see ADVERSE REACTIONS).

Storage

Store below 30ºC.

The bottle cap should be replaced securely after each use of sevoflurane, USP.

FPO

Baxter

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Guayama, Puerto Rico 00784 USA

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