SEVORANE®

(Sevoflurane)

DESCRIPTION

Sevoflurane is a nonflammable liquid anesthetic agent administered by vapori-zation. It is a fluorinated derivative of methyl isopropyl ether. Sevoflurane is identified chemically as fluoromethyl 2, 2, 2-trifluoro-1-(trifluoromethyl) ethyl ether and has a molecular weight of 200.05.
Its structural formula is as follows:

Sevoflurane has the following physical and chemical properties:

Table 1. Physical and Chemical Properties of Sevoflurane

Physical/Chemical Property	Value
Boiling Point at 760 mm Hg	58.6°C
Specific Gravity at 20°C	1.520-1.525
Vapor pressure (calculated) 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 Water/Gas Olive Oil/Gas Brain/Gas	 0.63-0.69 0.36 47.2-53.9 1.15

* Equation for vapor pressure (calculated), mm Hg: Log10Pvap=A+B/T, where: A = 8.086; B = -1726.68; T = °C + 273.16°K (Kelvin)

Table 2. Mean Component/Gas Partition Coefficients at 25°C for Polymers Used Commonly in Medical Applications

Polymer	Mean Component/Gas Partition Coefficients at 25°C
Conductive rubber	14.0
Butyl rubber	7.7
Polyvinyl chloride	17.4
Polyethylene	1.3

Sevoflurane is nonflammable and non-explosive as defined by the requirements of International Electrotechnical Commission 601-2-13.
Sevoflurane is a clear, colorless, liquid. Sevoflurane is nonpungent. It is miscible with ethanol, ether, chloroform and petroleum benzene, and it is slightly soluble in water.

Sevoflurane Degradation

Sevoflurane is stable when stored under normal room lighting conditions. No discernible degradation of sevoflurane occurs in the presence of strong acids or heat. Sevoflurane is not corrosive to stainless steel, brass, aluminum, nickel-plated brass, chrome plated brass, or copper beryllium alloy.
Chemical degradation can occur upon exposure of inhaled anesthetics to CO_2 absorbent within the anesthesia machine. When used as directed with fresh absorbents, degradation of sevoflurane is minimal, and degradants are undetectable or non-toxic. Sevoflurane degradation and subsequent degradant formation are enhanced by increasing absorbent temperature, desiccated CO_2 absorbent (especially potassium hydroxide-containing), increased sevoflurane concentration and decreased fresh gas flow. Sevoflurane can undergo alkaline degradation by two pathways. The first results from the loss of hydrogen fluoride with the formation of pentafluoroisopropanyl fluoromethyl ether (PIFE or more commonly known as Compound A). The second pathway for degradation of sevoflurane occurs only in the presence of desiccated CO_2 absorbents and leads to the dissociation of sevoflurane into hexafluoroisopropanol (HFIP) and formaldehyde. HFIP is inactive, non-genotoxic, rapidly glucoronidated, cleared, and has toxicity comparable to sevoflurane. Formaldehyde is present during normal metabolic processes. Upon exposure to a highly desiccated absorbent, formaldehyde can further degrade into methanol and formate. Formate can contribute to the formation of carbon monoxide, in the presence of high temperature. Methanol can react with Compound A to form the methoxy addition product Compound B. Compound B can undergo further HF elimination to form Compounds C, D, and E. With highly desiccated absorbents, especially those containing potassium hydroxide, the formation of formaldehyde, methanol, carbon monoxide, Compound A and perhaps some of it's degradants, Compounds B, C, and D may occur.

Lewis Acid Degradation

At least 300 ppm of water is added as a Lewis Acid inhibitor. No other additives or chemical stabilizers are utilized.

INDICATIONS

Sevoflurane may be used for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

DOSAGE AND ADMINISTRATION

Premedication

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 being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using a vaporizer calibrated specifically for sevoflurane.

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

Maintenance

Surgical levels of anesthesia may be sustained with concentrations of 0.5 - 3% sevoflurane with or without the concomitant use of nitrous oxide (see DRUG INTERCTIONS, *Nitrous Oxide*).

Table 3: MAC Values for Adults and Pediatric 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 1 - < 3 year old pediatric patients, 60% $N_20/40\%0_2$ was used.

Emergence

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

Elderly

MAC (Minimum Alveolar Concentration) 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.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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 anesthesia. Facilities for maintenance of a patent airway, artificial ventilation and oxygen enrichment, and circulatory resuscitation must be immediately available.
The concentration of sevoflurane being delivered from a vaporizer must be known exactly. As volatile anaesthetics differ in their physical properties, only vaporizers specifically calibrated for sevoflurane must be used. The administration of general anaesthesia must be individualized based on the patient's response. Hypotension and respiratory depression increase as anesthesia 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.
Isolated cases of ventricular arrhythmia were reported in pediatric patients with Pompe's disease.
Caution should be exercised in administering general anesthesia, including sevoflurane, to patients with mitochondrial disorders.

Hepatic

Very rare cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice have been reported from postmarketing experiences. Clinical judgment should be exercised when sevoflurane is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction (see ADVERSE REACTIONS).
It has been reported that previous exposure to halogenated hydrocarbon anesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury.

Malignant Hyperthermia

In susceptible individuals, potent inhalation anesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. 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 trials, one case of malignant hyperthermia was reported. In addition, there have been postmarketing reports of malignant hyperthermia. Some of these reports have been fatal.
Treatment 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.

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

General

During maintenance of anesthesia, increasing the concentration of sevoflurane produces dose-dependent decreases in blood pressure. Excessive decrease in blood pressure may be related to depth of anesthesia and in such instances may be corrected by decreasing the inspired concentration of sevoflurane. As with all anesthetics, maintenance of hemodynamic stability is important to the avoidance of myocardial ischemia in patients with coronary artery disease. The recovery from general anesthesia should be assessed carefully before patients are discharged from the post-anesthesia care unit.
Although recovery of consciousness following sevoflurane administration generally occurs within minutes, the impact on intellectual function for two or three days following anesthesia has not been studied. As with other anesthetics, small changes in moods may persist for several days following administration. (see EFFECTS ON ABILITY TO DRIVE AND USE MACHINES).

Replacement of Desiccated CO_2 Absorbents:

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, specifically those containing potassium hydroxide. 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 DESCRIPTION) 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 anesthesia machine using desiccated CO_2 absorbents and maximum sevoflurane concentrations (8%) for extended periods of time (>2 hours). Concentrations of formaldehyde observed at the anesthesia 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 color indicator of most CO_2 absorbents does not necessarily change as a result of 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.

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 yet been fully established. Therefore, sevoflurane should be used with caution in patients with renal insufficiency.

Neurosurgery

In patients at risk for elevations of ICP, sevoflurane should be administered cautiously in conjunction with ICP-reducing maneuvers such as hyperventilation.

Seizures

Rare cases of seizures have been reported in association with sevoflurane use (see WARNINGS AND PRECAUTIONS – Pediatric Use and ADVERSE REACTIONS).

Pediatric Use

The use of sevoflurane has been associated with seizures. Many of these have occurred in children and young adults starting from 2 months of age, most of whom had no predisposing risk factors. Clinical judgment should be exercised when using sevoflurane in patients who may be at risk for seizures. (see ADVERSE REACTIONS).

DRUG INTERACTIONS

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 anesthetics due to the risk of additive negative inotropic effect.
Concomitant use of succinylcholine with inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the post-operative period.

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

Barbiturates

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

Benzodiazepines and Opioids

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

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 PHARMACOLOGIC PROPERTIES, Pharmacokinetics, Metabolism and Fluoride Ion).

Nitrous Oxide

As with other halogenated volatile anesthetics, 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 pediatric patients. (see DOSAGE AND ADMINISTRATION, Maintenance)

Neuromuscular Blocking Agents

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

PREGNANCY & LACTATION

Pregnancy Category B

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

Labor and Delivery

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

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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 anesthesia.

Nursing Mothers

It is not known whether sevoflurane or its metabolites is 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anesthesia (see WARNINGS AND PRECAUTIONS).

ADVERSE REACTIONS

As with all potent inhaled anesthetics, sevoflurane may cause dose-dependent cardiorespiratory 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 anesthesia, which may be due to inhalational anesthetic, other agents administered intraoperatively or post-operatively, and to the patient's response to the surgical procedure.

Adverse Reaction Data Derived From Clinical Trials

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

The most commonly reported adverse reactions were as follows:

In adult patients: hypotension, nausea and vomiting;

In elderly patients: bradycardia, hypotension and nausea; and

In paediatric patients: agitation, cough, vomiting and nausea.

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.

Table 4: Summary of Most Frequent Adverse Drug Reactions in Sevoflurane Clinical Trials

System Organ Class	Frequency	Adverse Reactions
Psychiatric disorders	Very Common	Agitation
Nervous system disorders	Common	Somnolence, Dizziness, Headache
Cardiac disorders	Very Common Common Uncommon Unknown	Bradycardia Tachycardia Atrioventricular block complete QT prolongation associated with Torsade
Vascular disorders	Very Common Common	Hypotension Hypertension
Respiratory, thoracic and mediastinal disorders	Very Common Common	Cough Respiratory disorder Laryngospasm
Gastrointestinal disorders	Very Common Common	Nausea, Vomiting Salivary hypersecretion
General disorders and administration site conditions	Common	Chills Pyrexia
Investigations	Common	Blood glucose abnormal Liver function test abnormal* White blood cell count abnormal Fluoride increased**
Injury, poisoning and procedural complications	Common	Hypothermia

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

** 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 concen-trations were not associated with impairment of renal function.

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.

Table 5: 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 anesthetic agents

\# There have been very rare postmarketing reports of cardiac arrest in the setting of sevoflurane use.

DRUG ABUSE AND DEPENDENCE

None known.

OVERDOSAGE

In the event of apparent 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

In a variety of animal species including man, sevoflurane has been demonstrat-ed to be a fast acting, non-irritating agent. Administration has been associated with a smooth, rapid loss of consciousness during inhalational induction and a rapid recovery following discontinuation of anesthesia.

Induction is accomplished, with a minimum of excitement or signs of upper respiratory irritation, no evidence of excessive secretions within the tracheobronchial tree and no central nervous system stimulation. In pediatric studies in which mask induction was performed, the incidence of coughing was statistically significantly lower with sevoflurane than with halothane.

Like other potent inhalational anesthetics, sevoflurane depresses respiratory function and blood pressure in a dose-related manner.

In both dogs and humans, the epinephrine-induced arrhythmogenic threshold for sevoflurane was comparable to that of isoflurane and higher than that of halothane.

Studies in dogs have demonstrated sevoflurane does not reduce collateral myocardial perfusion. In clinical studies, the incidence of myocardial ischemia and myocardial infarction in patients at risk for myocardial ischemia was comparable between sevoflurane and isoflurane.

Animal studies have shown 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 sevoflu-rane and isoflurane. Sevoflurane has minimal effect on ICP (intracranial pressure) and preserves CO_2 responsiveness.

Sevoflurane does not affect renal concentrating ability, even after prolonged anesthetic exposure, up to approximately nine hours.

Minimum Alveolar Concentration

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. For MAC equivalents for sevoflurane for various age groups, see Dosage And Administration section.

The MAC of sevoflurane in oxygen was determined to be 2.05% for a 40 year old adult. As with other halogenated agents, MAC decreases with age and with the addition of nitrous oxide.

Pharmacokinetics

Solubility

The low solubility of sevoflurane in blood would suggest 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 (washin) value at 30 minutes for sevoflurane was 0.85. The FA/FAO (washout) value at five minutes was 0.15.

Distribution

The effects of sevoflurane on the displacement of drugs from serum and tissue proteins have not been investigated. Other fluorinated volatile anesthetics have been shown to displace drugs 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 drugs that are highly bound and have a small volume of distribution (e.g., phenytoin).

Metabolism

The rapid pulmonary elimination of sevoflurane minimizes the amount of anesthetic available for metabolism. In humans <5% sevoflurane absorbed is metabolized via cytochrome P450 2E1 isoform to hexafluorisopropanol (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 as a urinary metabolite. No other metabolic pathways for sevoflurane have been identified. It is the only fluorinated volatile anesthetic which is not metabolized to trifluoroacetic acid.

Fluoride Ion

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

The defluorination of sevoflurane is not inducible by barbiturates.

Approximately 7% of adults evaluated for inorganic fluoride concentrations in the Abbott Clinical Program experienced concentrations greater than 50 µM; no clinically significant effect on renal function was observed in any of these individuals(see DRUG INTERACTIONS, Inducers of CYP2E1).

PRE-CLINICAL SAFETY DATA

Sevoflurane has a low order of acute toxicity in rats, mice, rabbits, dogs and monkeys. Anesthesia induction was smooth and rapid, with no struggling, signs of gasping or other undesirable reactions. Deaths from exposure to lethal concentrations were due to respiratory arrest. Exposure was not associated with any specific organ toxicity or developmental toxicity in laboratory animals.

Fischer 344 rats were anesthetized within two to three minutes after start of exposure to sevoflurane (1.4%) for up to ten hours. There were no functional or morphologic defects following administration of sevoflurane.

In a Segment I reproduction study, sevoflurane had no significant effects on male or female reproductive capabilities at exposure concentrations of up to 1.0 MAC (2.2%). Segment II and III studies in rats indicate sevoflurane is not a selective developmental toxicant.

Compound A

In Wistar rats the LC50 of Compound A was 1050 to1090 ppm in animals exposed for one hour and 400 to 420 ppm in animals exposed for three hours (median lethal concentrations were approximately 1070 and 330 to 490 ppm, respectively). In rats exposed to 30, 60, or 120 ppm of Compound A in an 8-week chronic toxicity study (24 exposures, three hours/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 to 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 drug, 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 (ß-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 flow rates. 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 anesthesia circuit with soda lime as the CO_2 absorbent was 15 ppm in pediatrics 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 anesthesia circuit did not exceed 1.5 ppm. Inhalation exposure to Compound B at concentrations of up to 2400 ppm (0.24%) for three hours resulted in no adverse effects on renal parameters or tissue histology in Wistar rats.

Carcinogenesis

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.

DESCRIPTION OF CLINICAL STUDIES

Efficacy

Numerous clinical studies have been conducted with sevoflurane as the anesthetic agent for pediatric and adult patients. The results have shown sevoflurane provides smooth, rapid induction of, as well as rapid emergence from, anesthesia.

Sevoflurane was associated with faster times to induction and to such recovery events as emergence, response to command, and orientation compared to reference drugs.

Adult Anesthesia

Mask Induction

In adult studies in which mask induction was performed, sevoflurane was demonstrated to provide smooth and rapid induction of anesthesia.

Maintenance

In 3 outpatient and 25 inpatient studies involving 3591 adult patients (2022 sevoflurane, 1196 isoflurane, 111 enflurane, 262 propofol) sevoflurane was demonstrated to be an effective agent for the maintenance of anesthesia.

Sevoflurane was demonstrated to be an appropriate agent for use in neurosurgery, Cesarean section, patients undergoing coronar y arter y bypass surger y (CABG), and non-cardiac patients at risk for myocardial ischemia.

Pediatric Anesthesia

In two outpatient and three inpatient studies involving 1498 pediatric patients (837 sevoflurane, 661 halothane), sevoflurane was demonstrated to be an effective agent for the induction and maintenance of anesthesia.

Mask Induction

In pediatric studies in which mask induction was performed, the induction time was statistically significantly shorter and the incidence of coughing was statistically significantly lower with sevoflurane than with halothane.

Safety

Clinical studies were conducted in a wide variety of patient populations (children, adults, elderly, renally impaired, hepatically impaired, obese, patients undergoing cardiac bypass surger y, patients treated with aminoglycosides or metabolic inducers, patients exposed to repeat surgeries, patients undergoing surgeries > 6 hours in duration). The results of evaluations of laboratory parameters (e.g., SGPT, SGOT, alkaline phosphatase, total bilirubin, serum creatinine, BUN) as well as investigator-reported incidence of adverse events relating to hepatic and renal function, demonstrated sevoflurane did not have a clinically significant effect on liver or kidney function, nor did it exacerbate pre-existing renal or hepatic impairment within these study populations (see WARNINGS AND PRECAUTIONS – Hepatic and ADVERSE REACTIONS). These studies also demonstrated there were no statistically significant differences between sevoflurane and reference agents in the proportions of patients showing changes in any clinical chemistry parameter.

The impact on renal function was comparable among sevoflurane and the reference drugs, between types of anesthesia circuits, among flow rates, and between patients with or without inorganic fluoride concentrations >50 µm.

The incidence of renal dysfunction was < 1% for both sevoflurane (0.17%) and reference drugs (0.22%; isoflurane, halothane, enflurane, propofol) in comparative studies. This overall incidence is consistent with that of a general surgical population. In all cases, an alternate cause or reasonable explanation existed for the renal dysfunction.

Hepatically Impaired

During clinical development, sevoflurane was effective and well-tolerated when used as the primary agent for the maintenance of anesthesia in patients with impaired hepatic function, Child-Pugh Class A and B, and sevoflurane did not exacerbate pre-existing hepatic impairment.

For hepatic adverse events seen in postmarketing experience, see WARNINGS AND PRECAUTIONS - Hepatic and ADVERSE REACTIONS).

Renally Impaired

Sevoflurane was evaluated in renally impaired patients with baseline serum creatinine >1.5 mg/dL (130 µmole/L). Based on the incidence and magnitude of changes in serum creatinine concentrations, sevoflurane did not further deteriorate renal function.

STORAGE

Store below 25˚C.

HOW SUPPLIED

Sevoflurane, is packaged in amber colored bottles containing 250 mL sevoflurane. (List No. 4456)

Manufactured by:

Aesica Queenborough Ltd.,
Queenborough, Kent, ME11 5EL, UK

Marketed by:

Getz Pharma (Pvt.) Limited
Karachi, Pakistan.

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