PRODUCT MONOGRAPH

PrSOJOURN™ SEVOFLURANE

Sevoflurane, USP Liquid for Inhalation

Volatile Liquid
99.97% w/w sevoflurane (on anhydrous basis)

Inhalation Anesthetic

Piramal Critical Care Inc.
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Table of Contents

SOJOURN™ SEVOFLURANE

Sevoflurane, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Inhalation	Liquid/ 99.97% w/w Sevoflurane, USP (on anhydrous basis)	NONE

INDICATIONS AND CLINICAL USE

Sojourn™ Sevoflurane (sevoflurane, USP) is indicated for:

- induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

Geriatrics (> 65 years of age):
For a brief discussion, see **WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics.**

Pediatrics (< 18 years of age):
For a brief discussion, see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics.

CONTRAINDICATIONS

- Sojourn™ Sevoflurane (sevoflurane, USP) is contraindicated in patients with known sensitivity to sevoflurane or to other halogenated agents.

- Sojourn™ Sevoflurane is contraindicated in patients in whom liver dysfunction, jaundice or unexplained fever, leucocytosis, or eosinophilia has occurred after a previous halogenated anesthetic administration (see **WARNINGS AND PRECAUTIONS**).

- Sojourn™ Sevoflurane is contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia, or in patients with a known or suspected history of malignant hyperthermia.

- Sojourn™ Sevoflurane should not be used when general anesthesia is contraindicated.

WARNINGS AND PRECAUTIONS

General

SOJOURN™ 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.

The concentration of sevoflurane being delivered from a vaporizer must be known exactly. Monitoring of end-tidal sevoflurane concentration may be considered. As volatile anesthetics differ in physical properties, only vaporizers specifically calibrated for sevoflurane must be used. The administration of general anesthesia must be individualized based on the patient's response.

Fresh gas flow rates of less than 2 L/min in a circle absorber system are not recommended, as safety at lower rates has not yet been established.

Compound A is produced when sevoflurane interacts with soda lime and BARALYME® (see **ACTION AND CLINICAL PHARMACOLOGY**). Its concentration in a circle absorber system increases with increasing absorber temperature and 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®. Although Compound A is a dose-dependent nephrotoxin in rats, there have been no cases of renal toxicity reported in humans, when sevoflurane is used as recommended. During the maintenance of anesthesia, increasing the concentration of sevoflurane produces dose-dependent decreases in blood pressure. Due to sevoflurane'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.

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

Safe Use of CO_2 Absorbents

Carbon dioxide absorbents containing potassium hydroxide should not be used, as safe limits for its level of hydration have not been established.

Care should be taken to avoid using dried out (i.e., desiccated) CO_2 absorbents. 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.

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 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. See **STORAGE AND STABILITY**. 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 ($\geq$ 2 hours). Concentrations of formaldehyde observed at the anesthesia respiratory circuit (using sodium hydroxide containing absorbents) were consistent with levels known to cause respiratory irritation.

Congenital, Familial and Genetic Disorders

Cases of ventricular arrhythmia were reported in pediatric patients with Pompe's disease during anesthesia, including inhalation anesthesia. Caution should be exercised in administering general anesthesia, including sevoflurane, to patients with mitochondrial disorders.

Carcinogenesis and Mutagenesis

Studies on carcinogenesis have not been performed. No mutagenic effect was noted in the Ames test.

Cardiovascular

Caution should be exercised when administering sevoflurane to susceptible patients. sevoflurane can prolong QT intervals in adults and children. This effect is exacerbated by some of the patient's disease conditions or concomitant peri-operative medications. Isolated post-market cases of cardiac arrhythmia associated with the QT prolongation

have been reported. There are very rare reports of torsade de pointes, some of which were fatal.

Endocrine and Metabolism

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.

In clinical trials, one case of malignant hyperthermia was reported. In genetically susceptible pigs, sevoflurane induced 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 non-specific signs may also appear during light anesthesia, acute hypoxia, hypercapnia and hypovolemia.

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

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.

Hepatic/Biliary/Pancreatic

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.

Hepatitis

As with other halogenated anesthetics, sevoflurane may cause sensitivity hepatitis in patients who have been sensitized by previous exposure to halogenated anesthetics (see **CONTRAINDICATIONS and ADVERSE REACTIONS**). Therefore, appropriate alternative anesthetic agent(s) should be considered, this is especially important in

patients with pre-existing hepatic conditions.

Hepatic Impairment

In a limited number of patients with mild-to-moderate hepatic impairment (N = 16), the hepatic function was not affected by sevoflurane. The safety of sevoflurane in patients with severe hepatic impairment has not been established; therefore, sevoflurane should be used with caution in these patients.

Neurologic

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. 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.

Peri-Operative Considerations

Neurosurgery

Due to the limited number of patients who received sevoflurane during neurosurgical procedures (N = 22), safety in neurosurgery has not been fully established at this time and sevoflurane should be used with caution. In a study of 20 patients, there was no difference between sevoflurane and isoflurane with regard to recovery from anesthesia. In 2 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 in conjunction with ICP-reducing maneuvers such as hyperventilation.

Renal

Because clinical experience in administering sevoflurane in patients with renal insufficiencies (creatinine > 1.5 mg/dL) is limited (N = 35), its safety in these patients has not been established. Therefore, sevoflurane should be used with caution in patients with renal insufficiency. Limited pharmacokinetic data in these patients appear to suggest that the half-life of sevoflurane may be increased. The clinical significance is unknown at this time (see **ACTION AND CLINICAL PHARMACOLOGY**).

Special Populations

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Sevoflurane should be used during pregnancy only if clearly needed.

Cesarean Section

Due to the limited number of patients studied, safety in cesarean section has not been fully established at this time and sevoflurane should be used with caution. Sevoflurane has been used as part of general anesthesia for elective cesarean section in 29 women. There were no untoward effects in mother or neonate.

Labor and Delivery

The safety of sevoflurane in labor and delivery has not yet been demonstrated; therefore, sevoflurane should be used with caution in these patients.

Nursing Mothers

It is not known whether sevoflurane or its metabolites is excreted in human milk. Due to lack of information, women should be advised to skip breast-feeding for 48 hours after receiving sevoflurane and discard milk produced during this period.

Pediatrics (< 18 years of age)

The concentration of sevoflurane required for maintenance of general anesthesia is age-dependent (see **DOSAGE AND ADMINISTRATION**). Incidences of bradycardia (more than 20 beats/min less than normal) is lower for sevoflurane (3%) than for halothane (7%). Emergence times for sevoflurane are faster than with halothane (12 vs 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%).

Geriatrics (> 65 years of age)

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. In adults, the incidence of bradycardia is greater with sevoflurane than with isoflurane.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse events are derived from controlled clinical trials conducted in the United States, Canada and Europe. The reference drugs were isoflurane, enflurane, and propofol in adults and halothane in pediatric patients. The studies were conducted using a variety of premedications, other anesthetics, and surgical procedures of varying length. Most adverse events reported were mild and transient, and may reflect the surgical procedures, patient characteristics (including disease) and/or medications administered.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

Of the 5182 patients enrolled in the clinical trials, 2906 were exposed to sevoflurane, including 118 adults and 507 pediatric patients who underwent mask induction. Each patient was counted once for each type of adverse event. Adverse events reported in patients in clinical trials are presented within each body system in **Table 1, Table 2** and **Table 3**. One case of malignant hyperthermia was reported in pre-registration clinical trials.

Table 1: Adverse Events During Induction Period (From Onset of Anesthesia by Mask Induction to Surgical Incision) Possibly or Probably Related with Incidence >1%

Body System	Adult Patients N = 118 (%)	Pediatric Patients N = 507 (%)
Cardiovascular		
Bradycardia	5%	-
Hypotension	4%	4%
Tachycardia	2%	6%
Nervous System		
Agitation	7%	15%
Increased salivation	-	2%
Respiratory System		
Airway obstruction	8%	-
Apnea	-	2%
Breath-holding	5%	5%
Cough increased	5%	5%
Laryngospasm	8%	3%

NOTE: Similar incidence of adverse events was noted when all adverse reactions were recorded, not only possibly or probably related.

Table 2: Adverse Events For All Patients During All Anesthetic Periods with Possibly or Probably Related Incidence ≥ 1%.

Body System	Sevoflurane N = 2906 (%)
Body as a Whole	
Fever	1%
Headache	1%
Hypothermia	1%
Movement	1%
Shivering	6%
Cardiovascular	
Bradycardia	5%
Hypertension	2%
Hypotension	11%
Tachycardia	2%
Digestive System	
Nausea	25%
Vomiting	18%
Nervous System	
Agitation	9%
Dizziness	4%
Increased salivation	4%
Somnolence	9%
Respiratory System	
Breathholding	2%
Cough increased	11%
Laryngospasm	2%

Table 3: All Adverse Events For All Patients During All Anesthetic Periods with Incidence ≥ 1%

Body System	Sevoflurane N = 2906 (%)	Reference Agent N = 2276 (%)
Body as a Whole		
Fever	11%	12%
Headache	2%	3%
Hypothermia	2%	2%
Movement	1%	1%
Shivering	7%	8%
Cardiovascular		
Bradycardia	7%	8%
Hypertension	10%	9%
Hypotension	15%	16%
Tachycardia	4%	4%
Digestive System		
Nausea	37%	36%
Vomiting	25%	27%
Nervous System		
Agitation	11%	9%
Dizziness	8%	9%
Increased salivation	7%	11%
Somnolence	14%	17%
Respiratory System		
Breathholding	3%	3%
Cough increased	24%	29%
Laryngospasm	2%	3%

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse events, with incidence < 1% (reported in 3 or more patients), for all patients (N = 2906) during all anesthetic periods are listed below:

Body as a Whole	asthenia, pain
Cardiovascular	arrhythmia, atrial arrhythmia, atrial fibrillation, bigeminy, complete AV block, hemorrhage, inverted T Wave, second degree AV block, S-T depressed, supraventricular extrasystoles, syncope, ventricular extrasystoles
Hemic and Lymphatic System	leucocytosis, thrombocytopenia
Metabolism and Nutrition	acidosis, albuminuria, bilirubinemia, fluorosis, glycosuria, hyperglycemia, hypophosphatemia, increases in ALT, AST, BUN, LDH, alkaline phosphatase, creatinine,
Nervous System	confusion, crying, dry mouth, hypertonia, insomnia, nervousness
Respiratory System	apnea, bronchospasm, dyspnea, hiccup, hyperventilation, hypoventilation, hypoxia, pharyngitis, sputum increased, stridor, wheezing,
Skin and Special Senses	conjunctivitis, pruritus, rash, taste perversion
Urogenital	oliguria, urination impaired, urinary retention, urine abnormality

Abnormal Hematologic and Clinical Chemistry Findings

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

Post-Market Adverse Drug Reactions

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 reliably the true incidence of adverse events or establish a causal relationship to sevoflurane exposure.

QT Prolongation

There are literature and postmarket reports that link Sevoflurane with QT prolongation. Very rare cases of torsade de pointes, some resulting in deaths, have been reported.
See **WARNINGS AND PRECAUTIONS, Cardiovascular**.

Cardiac Arrest

There have been very rare post-marketing reports of cardiac arrest in the setting of sevoflurane use.

Malignant Hyperthermia

There have been post-marketing reports of rare events of malignant hyperthermia. See **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS.**

Anaphylactic and Anaphylactoid Reactions

Rare events of allergic reactions, such as rash, uticaria, pruritus, bronchospasm, anaphylactic or anaphylactoid reactions have also been reported. See **CONTRAINDICATIONS.**

Hypersensitivity

Rare reports of hypersensitivity (including dermatitis contact, rash, dyspnoea, wheezing, chest discomfort, swelling face, or anaphylactic reaction) have been received, particularly in association with long-term occupational exposure to inhaled anesthetic agents, including sevoflurane.

Seizure-like Activity

Cases of dystonic movement with spontaneous resolution have been reported in children receiving sevoflurane for induction of anesthesia. Seizure-like activity may occur on extremely rare occasions following sevoflurane administration. Reported events were or short duration and there was no evidence of any abnormality during emergence from anesthesia or in the post-operative period.

Post-operative Hepatitis

There have also been reports of post-operative hepatitis. 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. Due to the uncontrolled nature of these spontaneous reports, a causal relationship to sevoflurane has not been established.

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

Table 4. Established or Potential Drug-Drug Interactions

Drug	Effect	Clinical comment
Intravenous anesthetics	↓ MAC of sevoflurane	Sevoflurane administration is compatible with barbiturates and non-barbiturates (such as propofol).
Benzodiazepines	↓ MAC of sevoflurane	Benzodiazepines would be expected to decrease the MAC of sevoflurane in the same manner as with other inhalational anesthetics. Sevoflurane administration is compatible with benzodiazepines as commonly used in surgical practice.
Neuromuscular Blocking Agents	↑ neuromuscular effect	As is the case with other volatile anesthetics, sevoflurane increases both the intensity and duration of neuromuscular blockade induced by non-depolarizing muscle relaxants. The effect of sevoflurane on succinylcholine and the duration of depolarizing neuromuscular blockade has not been studied.
Nitrous Oxide	↓ MAC of sevoflurane	As with other halogenated volatile anesthetics, the anesthetic 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 pediatric patients. See **DOSAGE AND ADMINISTRATION**.
Opioids	↓ MAC of sevoflurane	Opioids would be expected to decrease the MAC of sevoflurane in the same manner as with other inhalational anesthetics. Sevoflurane administration is compatible with opioids as commonly used in surgical practice.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

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, Neurologic**).

DOSAGE AND ADMINISTRATION

Dosing Considerations

Fresh gas flow rates of less than 2 L/min in a circle absorber system are not recommended, as safety at lower rates has not yet been established.

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. The administration of general anesthesia must be individualized based on the patient's response.

Pre-anesthetic medication: No specific premedication is either indicated or contraindicated with sevoflurane. The decision as to whether or not to premedicate and the choice of premedication is left to the discretion of the anesthesiologist.

Induction: Sevoflurane has a non-pungent odour and does not cause respiratory irritability; therefore, it is suitable for mask induction in pediatrics and adults.

Maintenance: Surgical levels of anesthesia can usually be achieved with concentrations of 0.5 to 3% sevoflurane with or without the concomitant use of nitrous oxide. Sevoflurane can be administered with any type of anesthesia circuit.

Recommended Dose and Dosage Adjustment

MAC values according to age are presented in **Table 5**.

Table 5 MAC Values According to Age			
Age of Patient	**Number of Patients**	**MAC in Oxygen**	**MAC in 65% N_2O / 35% O_2**
Infants			
1 - < 6 months	26	3.0%	---
6 - < 12 months		2.8%	---
Children			
1 - < 3 years	39	2.6%	2.0%
3 - 12 years		2.5%	---
Adults			
25 years		2.5%	1.4%
40 years	41	2.1%	1.1%
60 years		1.6%	0.9%
80 years		1.4%	0.7%
Note 1: In 12 neonates of full-term gestational age, MAC was determined to be 3.3%. Note 2: In 1 - < 3 yrs old pediatric patients, 60% N_2O / 40% O_2 was used.			

Administration

SOJOURN™ Sevoflurane should be administered only by persons trained in the administration of general anesthesia (see **WARNINGS AND PRECAUTIONS**).

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

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 oxygen and maintain adequate cardiovascular function.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

SOJOURN™ Sevoflurane is an inhalational anesthetic agent for use in induction and maintenance of general anesthesia. Sevoflurane has a non-pungent odour and does not cause respiratory irritability. Sevoflurane is suitable for mask induction in adults and pediatric. Minimum alveolar concentration (MAC) of sevoflurane in oxygen for a 40 year old adult is 2.1%. The MAC of sevoflurane decreases with age. (See **DOSAGE AND ADMINISTRATION** for details).

Emergence times in pediatric patients are faster for sevoflurane (12 minutes) than for halothane (19 minutes). Time to first analgesia in pediatric patients is earlier in sevoflurane (approx. 52 minutes) than with halothane (approx. 68 minutes). The facts should be taken into account in cases where post-anesthesia pain is anticipated.

Pharmacokinetics

Solubility

Because of the low solubility of sevoflurane in blood (blood/gas partition coefficient at 37°C = 0.63 to 0.69), a minimal amount of sevoflurane is required to be dissolved in the blood before the alveolar partial pressure is in equilibrium with the arterial partial pressure. Therefore there is a rapid rate of increase in the alveolar (end-tidal) concentration (F_A) toward the inspired concentration (F_I) during induction and rapid elimination via the lungs when it is discontinued.

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

Sevoflurane is metabolized by cytochrome P450 2E1, to hexafluoroisopropanol (HFIP) with the release of inorganic fluoride and CO_2. Once formed, HFIP is rapidly conjugated with glucuronic acid and eliminated as a urinary metabolite. No other metabolite pathways for sevoflurane have been identified. *In vivo*metabolism studies suggest that approximately 5% of the sevoflurane dose may be metabolized.

Cytochrome P450 2E1 is the principal isoform identified for sevoflurane metabolism and this may be induced by chronic exposure to isoniazide and ethanol. This is similar to the metabolism of isoflurane and enflurane and is distinct from that of methoxyflurane which is metabolized via a variety of cytochrome P450 isoforms. The metabolism of sevoflurane is not inducible by barbiturates. Inorganic fluoride concentrations peak within 2 hours of the end of sevoflurane anesthesia and return to baseline concentrations within 48 hours post-anesthesia in the majority of cases (67%). The rapid and extensive pulmonary elimination of sevoflurane minimizes the amount of anesthetic available for metabolism.

In 12 clinical trials with sevoflurane, approximately 7% (55 out of 886) of adults evaluated for inorganic fluoride had serum concentrations greater than 50 µM; there were no reports of toxicity associated with elevated fluoride ion levels.

Excretion

Up to 3.5% of the sevoflurane dose appears in the urine as inorganic fluoride. Studies on fluoride indicate that up to 50% of fluoride clearance is non-renal (via fluoride being taken up into bone).

Compound A Production in Anesthesia Circuit

The only known degradation reaction in the clinical setting is through direct contact with CO_2 absorbents (soda lime and BARALYME®) producing Compound A (pentafluoroisopropenyl fluoromethyl ether).

The concentrations of Compound A measured in the anesthesia circuit when sevoflurane is used as indicated are not known to be deleterious to humans. Fresh gas flow rates below 2 L/min in a circle absorber system are not recommended, as safety at lower rates has not yet been established.

Special Populations and Conditions

Pediatrics

Sevoflurane pharmacokinetics have not been investigated in pediatric population.

Geriatrics

Sevoflurane pharmacokinetics have not been investigated in geriatric population.

Gender

No gender related pharmacokinetic differences have been observed in adult patients studied.

Race

Pharmacokinetic differences due to race have not been identified.

Hepatic Insufficiency

Limited pharmacokinetic data in these patients appear to suggest that the half-life of sevoflurane may be increased. The clinical significance is unknown at this time.

Renal Insufficiency

Limited pharmacokinetic data in these patients appear to suggest that the half-life of sevoflurane may be increased. The clinical significance is unknown at this time.

STORAGE AND STABILITY

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 those containing potassium hydroxide), 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 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 its degradants, Compounds B, C, and D may occur.

The interaction with CO_2 absorbents is not unique to sevoflurane. 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.

Storage Conditions

Sevoflurane should be stored between 15 and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition

SOJOURN™ Sevoflurane is a clear, colorless, liquid. The finished product is comprised only of the active drug substance, sevoflurane (about 99.97% w/w on anhydrous basis).

Availability of Dosage Forms

SOJOURN™ Sevoflurane is available in 250 mL amber colored glass bottles.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

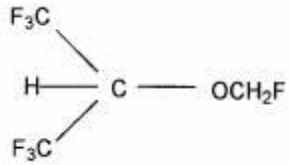
Drug Substance

Proper name: Sevoflurane

Chemical name: Fluoromethyl 2,2,2-trifluoro-l-(trifluoromethyl)ethyl ether

Molecular formula and molecular mass: $C_4H_3F_7O$ 200.05

Structural formula:



Physicochemical properties: Sevoflurane, a nonflammable and nonexplosive liquid administered by vaporization, is a halogenated general inhalation anesthetic drug. The boiling point is 58.6°C at 760 mm Hg, and the vapor pressure (in mm Hg) is 157 mm Hg at 20°C, 197 mm Hg at 25°C and 317 mm Hg at 36°C. Sevoflurane is nonpungent. It is miscible with ethanol, ether, chloroform and petroleum benzene, and it is slightly soluble in water.

Vapor pressure (mm Hg) can be calculated using the equation:

$Log_{10}P_{vap} = A+B/T$

A = 8.086
B = -1726.68
T = °C + 273.16°K (Kelvin)

The specific gravity is 1.520 - 1.525 at 20°C

Distribution Partition Coefficients at 37°C:

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

Mean Component/Gas Partition Coefficients at 25°C for polymers used commonly in medical applications:

Conductive rubber	14.0
Butyl rubber	7.7
Polyvinyl chloride	17.4
Polyethylene	1.3

CLINICAL TRIALS

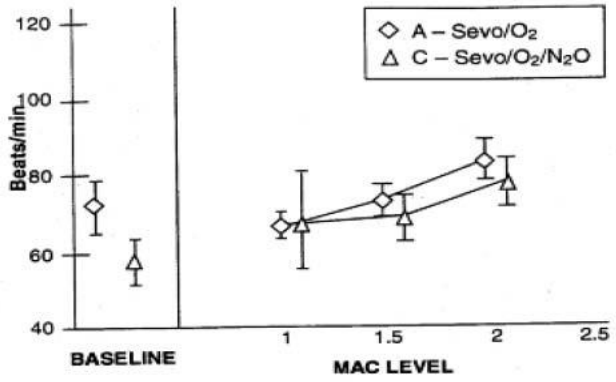
Study Results

Cardiovascular Effects

Sevoflurane was studied in 14 healthy volunteers (18-35 years old) comparing sevoflurane-O2 (Sevo/O2) to sevoflurane-O2/N2O (Sevo/O2/N2O) during 7 hours of anesthesia. During controlled ventilation, hemodynamic parameters measured are shown in Figures 1 to 4. .

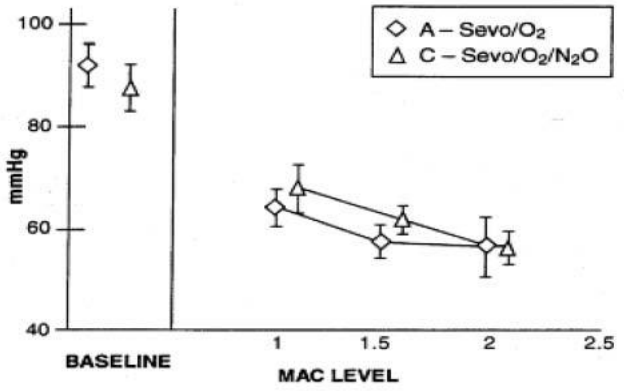
Figures 1 to 4

Figure 1



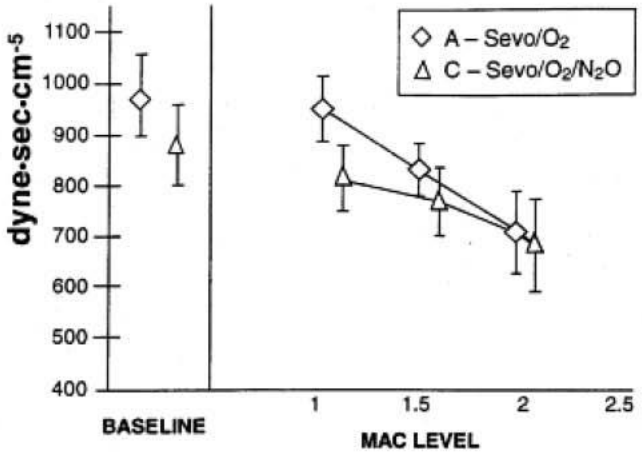
Heart Rate - Sevoflurane does not produce an increase in heart rate with or without nitrous oxide at doses less than 2 MAC.

Figure 2



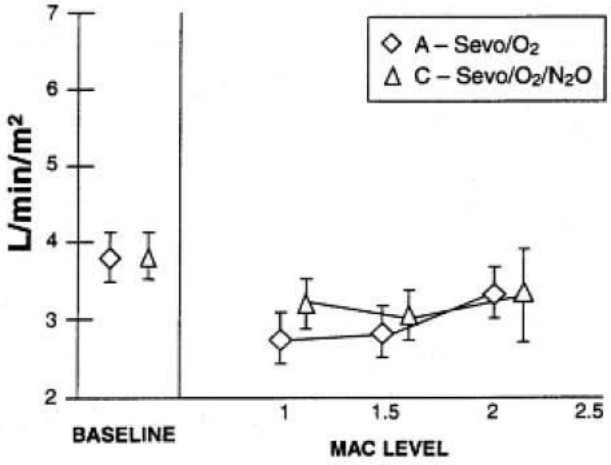
Mean Arterial Pressure - The decrease in mean arterial pressure seen with sevoflurane with or without nitrous oxide is dose dependent at all MAC values.

Figure 3



Systemic Vascular Resistance - The decrease in systemic vascular resistance seen with sevoflurane with or without nitrous oxide is dose dependent at all MAC values.

Figure 4



Cardiac Index - Sevoflurane has a dose-related cardiac depressant effect with or without nitrous oxide.

A study investigating the epinephrine-induced arrhythmogenic effect of sevoflurane versus isoflurane in adult patients undergoing transsphenoidal hypophysectomy (N = 40) demonstrated that the threshold dose of epinephrine (i.e., the dose at which the first sign of arrhythmia was observed) producing multiple ventricular arrhythmias was 5 mcg/kg in both groups.

Cardiovascular Surgery / Coronary Artery Bypass Graft (CABG) Surgery

Sevoflurane was compared to isoflurane as an adjunct with opioids in a multicentre study of 273 patients undergoing CABG surgery. The average 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 approx. 18 minutes, isoflurane approx. 17 minutes) of ischemic events, number of patients with diagnosis of myocardial infarction (sevoflurane 8%, isoflurane 10%), time to hemodynamic stability (sevoflurane approx. 5 hrs, isoflurane approx. 6 hrs), or use of cardioactive drugs (sevoflurane 53%, isoflurane 47%).

Non-Cardiac Surgery Patients at Risk for Myocardial Ischemia

Sevoflurane-N_2O was compared to isoflurane-N_2O for maintenance of anesthesia in a multicentre study of 214 patients who were at mild-to-moderate risk for myocardial ischemia who underwent elective non-cardiac 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 hemodynamic variation (tachycardia, bradycardia, hypertension, hypotension, and ischemia without hemodynamic abnormality). No statistical differences were observed between the two regimens with respect to intra-operative incidence of myocardial ischemia (sevoflurane 6%, isoflurane 3%) or post-operative incidence of ischemic events (sevoflurane 10%, isoflurane 16%). No statistical differences were observed between the treatment groups for the incidences of study drug-related adverse experience by body system or by COSTART term (sevoflurane 60%, isoflurane 61%). There was one death in sevoflurane group while four deaths occurred in the isoflurane group. None of these deaths were considered by the investigator to be drug-related.

Pediatric Anesthesia

The concentration of sevoflurane required for maintenance of general anesthesia is age-dependent (see **DOSAGE AND ADMINISTRATION**). Incidences of bradycardia (more than 20 beats/min less than normal) is lower for sevoflurane (3%) than for halothane (7%). Emergence times for sevoflurane are faster than with halothane (12 vs 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%).

DETAILED PHARMACOLOGY

Methyl ethers have proven to be a successful series of anesthetics because of several characteristics: molecular stability, non-flammability, lack of arrhythmogenicity, lack of neuronal excitation, relative cardiovascular stability, large lethal to anesthetic concentration ratio, minimal effect on cerebral blood flow at low concentrations and minimal end-organ effects. In addition to these characteristics, sevoflurane exhibits a low blood solubility with a blood gas partition coefficient of 0.63 to 0.69 at 37°C and has a pleasant, non-irritating odor. These qualities provide a rapid and smooth inhalational induction of, and rapid recovery from, anesthesia.

Equipotent doses of sevoflurane and isoflurane produce similar effects on cerebral blood flow (CBF), cerebral metabolic rate for oxygen ($CMRO_2$), intracranial pressure (ICP) and electroencephalogram patterns (EEG). In contrast, after short-term exposure, sevoflurane administration (1 MAC) produces a smaller increase in ICP than does an equipotent concentration of halothane.

Anesthesia with sevoflurane is both time- and concentration-dependent and involves suppression of cerebral cortex activity (loss of awareness and motor reflexes), suppression of the cerebellum and mesencephalon (loss of righting reflex, corneal reflex), suppression of the spinal cord (loss of the tail pinch response), and suppression of the medulla oblongata (depression of respiration).

Sevoflurane suppresses heart rate and arterial blood pressure in a dose-dependent fashion. In general, the hemodynamic/cardiovascular effects of sevoflurane are comparable to those of isoflurane. However, a more pronounced tachycardia was observed in dogs exposed to 1.2 MAC sevoflurane than those animals exposed to 1.2 MAC isoflurane. The magnitude of myocardial contractile depression observed in dogs during sevoflurane anesthesia was similar to those previously reported for isoflurane and desflurane; however, sevoflurane appears to cause less depression of the inotropic state than that reported for halothane.

Sevoflurane does not appear to have any remarkable coronary vasodilatory effects, does not negatively affect the blood flow distribution in areas of local myocardial ischemia, and, therefore, does not appear to exacerbate myocardial ischemia. Sevoflurane does not reduce collaterally-derived myocardial perfusion or cause coronary steal.

At clinical concentrations in the absence of pacing, sevoflurane does not affect atrioventricular (A-V) conduction. Sevoflurane appears to have a lower risk for the potentiation of epinephrineinduced arrhythmias, or other pressoramine-induced arrhythmias, than either halothane or enflurane.

The administration of epinephrine during sevoflurane anesthesia does not appear to be associated with the production of ventricular arrhythmia. In a dog model, halothane was

more sensitizing to the myocardium in the presence of pressoramines than was sevoflurane. Also, in the same dog model, ventricular fibrillation was observed with epinephrine and norepinephrine under halothane, no ventricular fibrillation was produced under sevoflurane anesthesia in this study.

Mean MAC for sevoflurane has been determined as 2.2% in rats, 2.3% in mice, 3.61 to 3.7% in rabbits, 2.36% in dogs, 2.58% in cats, and 2.12% in newborn swine.

Sevoflurane will trigger malignant hyperthermia (MH) in susceptible pigs; however, it is a weak trigger. The onset of MH is slow and easily reversible. In contrast, halothane triggers MH in susceptible pigs much sooner and more strongly than does sevoflurane.

TOXICOLOGY

Acute Toxicity

Five laboratory animal species (rat, mouse, rabbit, dog, monkey) have been studied to determine the acute toxic effects and median lethal concentration of sevoflurane via the inhalation route and, in rodents, by oral, and parenteral routes. Calculated median lethal concentrations for 1hour inhalation exposure ranged from 5.8% in the rat to 10.6% in rabbits. Prolongation of exposure lowered the LC_{50} within each species (See **Table 6**).

Table 6
Summary of Calculated Median Lethal Concentrations

Species	Inhalation LC_{50} (%)	
	1 hour	3 hour
Mouse	8.3	2.9
Rat	5.8	2.9
Rabbit	10.6	
Dog	7.3	
Monkey	--	6.8

Sevoflurane was virtually non-toxic orally (LD_{50} 10.8 - 24.3 mL/kg) and parenterally (LD_{50} 6.3 - 11.7 mL/kg). No significant differences in response to sevoflurane were detected between males and females. Neonatal rodents were shown to be more tolerant to acute exposures than adults.

Dyspnea and cyanosis appeared to be the primary cause of death following acute inhalation exposure in all species studied. There was no clear organ pathology associated with acute sevoflurane exposure in these studies even at lethal concentrations.

Subchronic Toxicity

Repeated exposure studies have confirmed the absence of any specific organ toxicity associated with non-lethal concentrations of sevoflurane. Rats and monkeys have been exposed for up to 3 hours/day, 3 days/week, for 8 weeks at concentrations ranging from 0.1 to 1.0 MAC (0.22 to 2.2%) and 1.0 to 2.5 MAC (2 to 5%), respectively. Dogs have been repeatedly anesthetized (3 hours/day, 5 days/week for 2 weeks) at concentrations of up to 5%. Dogs and monkeys in these studies revealed no evidence of autonomic or central nervous system stimulation, cardiac arrhythmia or unexpected cardiorespiratory depression. Bradycardia was rarely reported in dogs, and was never observed in monkeys. Clinical observations, hematology and pathology were unremarkable, indicating no adverse effects.

Reproduction and Teratology

There were no significant effects on male and female reproductive capabilities at exposure concentrations of up to 1.0 MAC (2.2%) in a classic Segment I reproduction study. Systemic toxicity, as manifested by reductions in body weight gain, was observed in the males at exposures > 0.5 MAC (1.1%) and at exposures > 0.3 MAC (0.66%) in females.

Fetal body weights were slightly reduced at these maternally toxic exposure levels (> 0.3 MAC), and an increase in skeletal variations at the highest exposure level, a common occurrence in this species, was also observed.

Developmental toxicity (Segment II and III) studies in rats indicate that sevoflurane is not a selective developmental toxicant. Similar to what was observed in the rat reproduction study, reductions in fetal and neonatal body weights and increased skeletal variations were observed only at maternally toxic concentrations of 1.0 MAC (2.2%). No effects on offspring viability, behaviour or reproductive capability was observed.

In rabbits, no developmental toxicity was observed at maternally toxic concentrations of up to 1.0 MAC (1.8%). Mutagenicity studies indicate that sevoflurane is not mutagenic when tested both *in vitro* and *in vivo.*

Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

Special Toxicity Studies

Compound A

In Wistar rats the LC_{50} of Compound A was 1050 to 1090 ppm in animals exposed for 1 hour and 400 to 420 ppm in animals exposed for 3 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 eight week chronic toxicity study (24 exposures, 3 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 alone or in combination with 2.2% sevoflurane. Control groups were exposed to air. The threshold, at which reversible alterations in urinary and clinical parameters indicative of renal changes (concentrationdependent increases in BUN, creatinine, glucose, protein/creatinine ratios and N-acetyl-glucosamidase/ creatinine ratios) were observed, was 114 ppm Compound A. Histological lesions were reversible as indicated by histological examinations and by urinalysis surrogate markers (ketones, occult blood, glucose, NAG/creatinine, protein/creatinine).

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 (β-lyase) involved in haloalkene nephrotoxicity is tenfold greater in the rat than it is in humans.

In the clinical situation, the highest concentration of Compound A in the anesthesia circuit with soda lime as the CO_2 absorbant 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 absorbant with no evidence of renal dysfunction.

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 3 hours resulted in no adverse effects on renal parameters or tissue histology in Wistar rats.

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PART III: CONSUMER INFORMATION

Pr Sojourn™ Sevoflurane

This leaflet is PART III of a three-part "Product Monograph" published when Sojourn™ Sevoflurane was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Sojourn™ Sevoflurane. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

SOJOURN™ Sevoflurane is a general anesthetic used during surgery.

What it does:

SOJOURN™ Sevoflurane causes unconsciousness, muscle relaxation, and loss of sensation over the entire body so that surgery can be performed.

When it should not be used:

SOJOURN™ Sevoflurane should not be used in patients who:

- are allergic to sevoflurane or other halogenated agents
- have experienced liver problems, jaundice, unexplained fever, or certain types of inflammation reactions after a previous halogenated anesthetic administration
- are susceptible to malignant hyperthermia

What the medicinal ingredient is:

Sevoflurane, USP

What the important non-medicinal ingredients are:

The finished product is composed solely of the active ingredient, sevoflurane

What dosage forms it comes in:

SOJOURN™ Sevoflurane is available as a volatile liquid that is 99.97% pure.

WARNINGS AND PRECAUTIONS

Recovery of consciousness following SOJOURN™ Sevoflurane administration generally occurs within minutes. As with other anesthetics, small changes in mood may persist for several days following administration.

Performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anesthesia.

INTERACTIONS WITH THIS MEDICATION

Many drugs may interact with SOJOURN™ Sevoflurane. Tell your doctor if you had a history of drug interactions. Your doctor will manage according to your condition.

PROPER USE OF THIS MEDICATION

Usual dose:

The proper dose is determined by a doctor trained in the administration of general anesthesia.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Known side effects when you wake up include: feeling agitated, increased cough, nausea, and vomiting.

You should talk to your anesthesia professional prior to surgery if you are aware of any of the following conditions:

- You have difficulty with intubations
- You are susceptible to malignant hyperthermia
- You are taking medications, nonprescription medications, or herbal medicines
- You have kidney or liver problems
- You have Pompe's disease or a mitochondrial disorder
- You are pregnant or nursing

SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

After your surgery you should tell your doctor if you have any of the following reactions:

- Chills
- Difficulty breathing/choking
- Dizziness
- Elevated rise in blood glucose, if measured
- High blood pressure
- Hives
- Jaundice/yellowing of the eyeballs
- Low blood pressure, if measured
- Mild to severe allergic reactions
- Rapid heartbeat
- Rash
- Seizures/seizure-like activity
- Severe itching
- Slow heartbeat
- Sudden fever with stiffness, pain and weakness in your muscles
- Wheezing.

This is not a complete list of side effects. For any unexpected effects while taking Sojourn™ (Sevoflurane, USP), contact your doctor or pharmacist.

HOW TO STORE IT

SOJOURN™ Sevoflurane should be stored between 15 and 30 °C.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report on line at:**
  www.healthcanada.gc.ca/medeffect
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Website at
http://www.healthcanada.gc.ca/medeffect

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found in the Health Canada Drug Product Database or by contacting the sponsor,

PIRAMAL CRITICAL CARE INC. at
1-888-822-8431

This leaflet was prepared by PIRAMAL CRITICAL CARE, INC.

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