

# PRODUCT MONOGRAPH

**Pr SEVORANE<sup>®</sup> AF**

Sevoflurane

volatile liquid (99.9875% v/v sevoflurane on anhydrous basis)

Inhalation Anesthetic

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# SEVORANE® AF

sevoflurane

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	Non-medicinal Ingredients
inhalation	volatile liquid / 99.9875% v/v sevoflurane (on anhydrous basis)	none

### INDICATIONS AND CLINICAL USE

SEVORANE® AF (sevoflurane) 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 (> 65 years of age)**.

#### Pediatrics (< 18 years of age)

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

### CONTRAINDICATIONS

- SEVORANE® AF (sevoflurane) is contraindicated in patients with known sensitivity to sevoflurane or to other halogenated inhalation anesthetics.
- SEVORANE® AF 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, Hepatic/Biliary/Pancreatic**.

- SEVORANE<sup>®</sup> AF 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.
- SEVORANE<sup>®</sup> AF should not be used when general anesthesia is contraindicated.

## WARNINGS AND PRECAUTIONS

### Serious Warnings and Precautions

- SEVORANE<sup>®</sup> AF (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.
- Desiccated carbon dioxide absorbents, or those containing potassium hydroxide should not be used. See **WARNINGS AND PRECAUTIONS, General, Safe Use of CO<sub>2</sub> Absorbents.**

### General

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 their 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.**

During the maintenance of anesthesia, increasing the concentration of SEVORANE<sup>®</sup> AF produces dose-dependent decreases in blood pressure. Due to SEVORANE<sup>®</sup> AF'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 SEVORANE<sup>®</sup> AF.

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

### **Safe Use of CO<sub>2</sub> 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<sub>2</sub> absorbents. The color indicator of most CO<sub>2</sub> 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<sub>2</sub> absorbents should be replaced routinely regardless of the state of the color indicator.

Compound A is produced when SEVORANE<sup>®</sup> AF interacts with soda lime and Baralyme<sup>®</sup>. See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Compound A Production in Anesthesia Circuit**. Its concentration in a circle absorber system increases with increasing absorber temperature and increasing SEVORANE<sup>®</sup> AF 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<sup>®</sup>. Although Compound A is a dose-dependent nephrotoxin in rats, there have been no cases of renal toxicity reported in humans, when SEVORANE<sup>®</sup> AF is used as recommended.

Rare cases of extreme heat, smoke, and/or spontaneous fire in the anesthesia machine have been reported during SEVORANE<sup>®</sup> AF use in conjunction with the use of desiccated CO<sub>2</sub> absorbent, specifically those containing potassium hydroxide. An unusually delayed rise or unexpected decline of inspired SEVORANE<sup>®</sup> AF concentration compared to the vaporizer setting may be associated with excessive heating of the CO<sub>2</sub> absorbent canister.

An exothermic reaction, enhanced sevoflurane degradation, and production of degradation products can occur when the CO<sub>2</sub> absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO<sub>2</sub> absorbent canisters. See **STORAGE AND STABILITY, 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<sub>2</sub> absorbents and maximum SEVORANE<sup>®</sup> AF 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 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 SEVORANE<sup>®</sup> AF, 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 SEVORANE<sup>®</sup> AF to susceptible patients. SEVORANE<sup>®</sup> AF can prolong the QT interval 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 SEVORANE<sup>®</sup> AF, 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 non-specific 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.

## **Mitochondrial Disorders**

Caution should be exercised in administering general anesthesia, including sevoflurane, to patients with mitochondrial disorders.

## **Hepatic/Biliary/Pancreatic**

### **Hepatitis**

Cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice have been reported in association with SEVORANE<sup>®</sup> AF from post-marketing experiences.

As with other halogenated anesthetics, SEVORANE<sup>®</sup> AF may cause sensitivity hepatitis in patients who have been sensitized by previous exposure to halogenated anesthetics (especially when the exposure interval is less than 3 months). Clinical judgement and appropriate alternative anesthetic agents should be considered when SEVORANE<sup>®</sup> AF is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction. See **CONTRAINDICATIONS** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions, Post-operative Hepatitis.**

Although the mechanism by which this occurs is still unclear, data from studies on halothane suggests that metabolism by cytochrome P450 2E1 (CYP2E1) catalyzes formation of trifluoroacetylated haptens, which may be implicated as target antigens in the mechanism of halothane-induced hepatitis. Although other halogenated anesthetics are believed to be metabolized to a much lesser degree by the CYP2E1 system (halothane by 20%, compared to sevoflurane by 3%, isoflurane by 0.2%, and desflurane by 0.01%), the reported hepatic injuries share similarities with that associated with halothane.

### **Hepatic Impairment**

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

## **Neurologic**

### **Seizures**

Cases of seizures have been reported in association with SEVORANE<sup>®</sup> AF. See **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (< 18 years of age)** and **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions, Seizures.**

## **Psychiatric**

SEVORANE<sup>®</sup> AF, as well as other general anesthetics, may cause a slight decrease in cognitive function for two to four days following anesthesia. 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 SEVORANE<sup>®</sup> AF during neurosurgical procedures (N = 22), safety in neurosurgery has not been fully established at this time and SEVORANE<sup>®</sup> AF should be used with caution. In a study of 20 patients, there was no difference between SEVORANE<sup>®</sup> AF and isoflurane with regard to recovery from anesthesia. In 2 studies, a total of 22 patients with intracranial pressure (ICP) monitors received either SEVORANE<sup>®</sup> AF or isoflurane. There was no difference between SEVORANE<sup>®</sup> AF and isoflurane with regard to ICP response to inhalation of 0.5, 1.0, and 1.5 minimum alveolar concentration (MAC) inspired concentrations of volatile agent during N<sub>2</sub>O-O<sub>2</sub>-fentanyl anesthesia. During progressive hyperventilation from PaCO<sub>2</sub> = 40 to PaCO<sub>2</sub> = 30, ICP response to hypocarbia was preserved with SEVORANE<sup>®</sup> AF at both 0.5 and 1.0 MAC concentrations. In patients at risk for elevations of ICP, SEVORANE<sup>®</sup> AF should be administered cautiously in conjunction with ICP-reducing maneuvers such as hyperventilation.

### **Renal**

Because clinical experience in administering SEVORANE<sup>®</sup> AF in patients with renal insufficiencies (creatinine > 1.5 mg/dL) is limited (N = 35), its safety in these patients has not been established. Therefore, SEVORANE<sup>®</sup> AF 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 and Conditions, Renal Insufficiency.**

### **Respiratory**

Sevoflurane inhibits spontaneous respiration, which is enhanced with concurrent use of other inhalational and intravenous anesthetics. Respiration must be closely monitored and supported by assisted or controlled ventilation when necessary. Excessive respiratory depression may be related to depth of anesthesia and responds to decreasing the inspired concentration of sevoflurane.



## **Special Populations**

### **Pregnant Women**

There are no adequate and well-controlled studies in pregnant women. SEVORANE<sup>®</sup> AF should be used during pregnancy only if the benefit outweighs the risk.

### **Labour and Delivery**

The safety of SEVORANE<sup>®</sup> AF in labour and delivery has not yet been demonstrated. SEVORANE<sup>®</sup> AF, like other inhalational agents, has relaxant effects on the uterus with the potential risk for uterine bleeding. Clinical judgment should be observed when using SEVORANE<sup>®</sup> AF during obstetric anesthesia.

### **Cesarean Section**

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

### **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 SEVORANE<sup>®</sup> AF and discard milk produced during this period.

### **Pediatrics (< 18 years of age)**

The concentration of SEVORANE<sup>®</sup> AF required for maintenance of general anesthesia is age-dependent. See **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**. Incidences of bradycardia (more than 20 beats/min less than normal) is lower for SEVORANE<sup>®</sup> AF (3%) than for halothane (7%). Emergence times for SEVORANE<sup>®</sup> AF are faster than with halothane (12 vs 19 minutes, respectively). A higher incidence of agitation occurs with SEVORANE<sup>®</sup> AF (208/837 patients or 25%) when compared with halothane (114/661 patients or 17%).

The use of SEVORANE<sup>®</sup> AF has been associated with seizures. The majority of post-marketing cases reported have occurred in children as young as 5 days of age and young adults, most of whom had no predisposing risk factors. Seizures have been reported during all phases of anesthesia (induction, maintenance, emergence) as well as in the post-operative period. Clinical judgment should be exercised when using SEVORANE<sup>®</sup> AF in patients who may be at risk for seizures. See **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions, Seizures**.

## Geriatrics (> 65 years of age)

MAC decreases with increasing age. The average concentration of SEVORANE<sup>®</sup> AF 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 SEVORANE<sup>®</sup> AF 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.

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 intra-operatively or post-operatively, and to the patient's response to the surgical procedure.

### 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 SEVORANE<sup>®</sup> AF (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%**

<b>Body System</b>	<b>Adult Patients N = 118 (%)</b>	<b>Pediatric Patients N = 507 (%)</b>
<b>Cardiovascular</b>		
Bradycardia	5%	-
Hypotension	4%	4%
Tachycardia	2%	6%
<b>Nervous System</b>		
Agitation	7%	15%
Increased salivation	-	2%
<b>Respiratory System</b>		
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  $\geq$  1%.**

<b>Body System</b>	<b>SEVORANE® AF N = 2906 (%)</b>
<b>Body as a Whole</b>	
Fever	1%
Headache	1%
Hypothermia	1%
Movement	1%
Shivering	6%
<b>Cardiovascular</b>	
Bradycardia	5%
Hypertension	2%
Hypotension	11%
Tachycardia	2%
<b>Digestive System</b>	
Nausea	25%
Vomiting	18%
<b>Nervous System</b>	
Agitation	9%
Dizziness	4%
Increased salivation	4%
Somnolence	9%
<b>Respiratory System</b>	
Breath-holding	2%
Cough increased	11%
Laryngospasm	2%

**Table 3. All Adverse Events For All Patients During All Anesthetic Periods with Incidence  $\geq$  1%**

<b>Body System</b>	<b>SEVORANE® AF N = 2906 (%)</b>	<b>Reference Agent N = 2276 (%)</b>
<b>Body as a Whole</b>		
Fever	11%	12%
Headache	2%	3%
Hypothermia	2%	2%
Movement	1%	1%
Shivering	7%	8%
<b>Cardiovascular</b>		
Bradycardia	7%	8%
Hypertension	10%	9%
Hypotension	15%	16%
Tachycardia	4%	4%
<b>Digestive System</b>		
Nausea	37%	36%
Vomiting	25%	27%
<b>Nervous System</b>		
Agitation	11%	9%
Dizziness	8%	9%
Increased salivation	7%	11%
Somnolence	14%	17%
<b>Respiratory System</b>		
Breath-holding	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 period 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 SEVORANE<sup>®</sup> AF. 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 SEVORANE<sup>®</sup> AF exposure.

### **QT Prolongation**

There are literature and postmarket reports that link SEVORANE<sup>®</sup> AF 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 SEVORANE<sup>®</sup> AF use.

## **Malignant Hyperthermia**

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

## **Anaphylactic and Anaphylactoid Reactions**

Rare events of allergic reactions, such as rash, urticaria, 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.

## **Seizures**

Cases of seizures and dystonic movement have been associated with the use of SEVORANE<sup>®</sup> AF. The majority of cases were in children and young adults, most of whom had no predisposing risk factors. Several cases reported no concomitant medications, and at least one case was confirmed by EEG. Although many cases resolved spontaneously or after treatment, cases of multiple seizures have also been reported. Seizures have occurred during or soon after SEVORANE<sup>®</sup> AF induction, during emergence, and during post-operative recovery up to a day following anesthesia.

## **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 SEVORANE<sup>®</sup> AF. Due to the uncontrolled nature of these spontaneous reports, a causal relationship to SEVORANE<sup>®</sup> AF has not been established.

## **Bradycardia**

There have been reports of bradycardia in pediatric patients with Down syndrome following exposure to sevoflurane. See **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics (< 18 years of age)**.

## **DRUG INTERACTIONS**

### **Overview**

SEVORANE<sup>®</sup> AF (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**

<b>Drug</b>	<b>Effect</b>	<b>Clinical comment</b>
Intravenous anesthetics	↓ MAC of SEVORANE® AF	SEVORANE® AF administration is compatible with barbiturates and non-barbiturates (such as propofol).
Benzodiazepines	↓ MAC of SEVORANE® AF	Benzodiazepines would be expected to decrease the MAC of SEVORANE® AF in the same manner as with other inhalational anesthetics. SEVORANE® AF administration is compatible with benzodiazepines as commonly used in surgical practice.
Calcium antagonists		SEVORANE® AF may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivatives. Caution should be exercised when calcium antagonists are used concomitantly with inhalation anesthetics due to the risk of additive negative inotropic effect.
Inducers of CYP2E1	↑ metabolism of SEVORANE® AF ↑ plasma fluoride concentrations	Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of SEVORANE® AF and lead to significant increases in plasma fluoride concentrations. Moreover, CYP2E1 metabolic pathways may be involved in the rare hepatotoxic effects observed with halogenated anesthetics, therefore, a concomitant use of CYP2E1 inducers may potentiate this risk in susceptible patients.
Neuromuscular Blocking Agents	↑ neuromuscular effect	As is the case with other volatile anesthetics, SEVORANE® AF increases both the intensity and duration of neuromuscular blockade induced by non-depolarizing muscle relaxants. The effect of SEVORANE® AF on succinylcholine and the duration of depolarizing neuromuscular blockade has not been studied.
Nitrous Oxide	↓ MAC of SEVORANE® AF	As with other halogenated volatile anesthetics, the anesthetic requirement for SEVORANE® AF is decreased when administered in combination with nitrous oxide. Using 50% N <sub>2</sub> O, the MAC equivalent dose requirement is reduced approximately 50% in adults, and approximately 25% in pediatric patients. See <b>DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment.</b>
Non-selective MAO-inhibitors		Risk of crisis during the operation. It is generally recommended that treatment should be stopped 2 weeks prior to surgery.

Opioids	↓ MAC of SEVORANE® AF	Opioids would be expected to decrease the MAC of SEVORANE® AF in the same manner as with other inhalational anesthetics. SEVORANE® AF administration is compatible with opioids as commonly used in surgical practice.
Succinylcholine		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. See <b>(WARNINGS AND PRECAUTIONS)</b> .
Sympathomimetic Agents		Beta-sympathomimetic agents like isoprenaline and alpha- and beta- sympathomimetic agents like adrenaline and noradrenaline should be used with caution during SEVORANE® AF narcosis, due to a potential risk of ventricular arrhythmia.

### **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 SEVORANE® AF (sevoflurane) being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using a vaporizer calibrated specifically for SEVORANE® AF. 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 SEVORANE<sup>®</sup> AF. The decision as to whether or not to premedicate and the choice of premedication is left to the discretion of the anesthesiologist.

## Induction

SEVORANE<sup>®</sup> AF 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% SEVORANE<sup>®</sup> AF with or without the concomitant use of nitrous oxide. See **DRUG INTERACTIONS, Drug-Drug Interactions, Table 4**. SEVORANE<sup>®</sup> AF 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**

	Infants (N = 26)		Children (N = 39)		Adults (N = 41)			
	1 to < 6 months	6 to < 12 months	1 to < 3 years	3 to 12 years	25 years	40 years	60 years	80 years
MAC in Oxygen	3.0%	2.8%	2.6%	2.5%	2.5%	2.1%	1.6%	1.4%
MAC in 65% N <sub>2</sub> O / 35% O <sub>2</sub>	-	-	2.0%	-	1.4%	1.1%	0.9%	0.7%

Note 1: In 12 neonates of full-term gestational age, MAC was determined to be 3.3%.

Note 2: In 1 to < 3 years old pediatric patients, 60% N<sub>2</sub>O / 40% O<sub>2</sub> was used.

## Administration

SEVORANE<sup>®</sup> AF should be administered only by persons trained in the administration of general anesthesia. See **WARNINGS AND PRECAUTIONS, General**.

## OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre for the most current information.

In the event of overdosage, or what may appear to be overdosage, the following action should be taken: discontinue administration of SEVORANE<sup>®</sup> AF (sevoflurane), maintain a patent airway, initiate assisted or controlled ventilation with oxygen and maintain adequate cardiovascular function.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Pharmacodynamics**

SEVORANE<sup>®</sup> AF (sevoflurane) is an inhalational anesthetic agent for use in induction and maintenance of general anesthesia. SEVORANE<sup>®</sup> AF has a non-pungent odour and does not cause respiratory irritability. SEVORANE<sup>®</sup> AF is suitable for mask induction in adults and pediatric. Minimum alveolar concentration (MAC) of SEVORANE<sup>®</sup> AF in oxygen for a 40 year old adult is 2.1%. The MAC of SEVORANE<sup>®</sup> AF decreases with age. See **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment** for details.

Emergence times in pediatric patients are faster for SEVORANE<sup>®</sup> AF (12 minutes) than for halothane (19 minutes). Time to first analgesia in pediatric patients is earlier in SEVORANE<sup>®</sup> AF (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 SEVORANE<sup>®</sup> AF 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<sub>2</sub>. 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 SEVORANE<sup>®</sup> AF 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 SEVORANE<sup>®</sup> AF, approximately 7% (55 out of 886) of adults evaluated for inorganic fluoride had serum concentrations greater than 50 micromolar; there were no reports of toxicity associated with elevated fluoride ion levels. See **DRUG INTERACTIONS, Drug-Drug Interactions, Table 4.**

### **Excretion**

Up to 3.5% of the SEVORANE<sup>®</sup> AF 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<sub>2</sub> absorbents (soda lime and Baralyme<sup>®</sup>) producing Compound A (pentafluoroisopropenyl fluoromethyl ether).

The concentrations of Compound A measured in the anesthesia circuit when SEVORANE<sup>®</sup> AF 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**

### **Storage**

SEVORANE<sup>®</sup> AF (sevoflurane) should be stored between 15 and 25°C.

### **Stability**

SEVORANE<sup>®</sup> AF is stable when stored under normal room lighting conditions. No discernible degradation of SEVORANE<sup>®</sup> AF occurs in the presence of strong acids or heat.

SEVORANE<sup>®</sup> AF 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<sub>2</sub> absorbent within the anesthesia machine. When used as directed with fresh absorbents, degradation of SEVORANE<sup>®</sup> AF is minimal, and degradants are undetectable or non-toxic. SEVORANE<sup>®</sup> AF degradation and subsequent degradant formation are enhanced by increasing absorbent temperature, desiccated CO<sub>2</sub> absorbent (especially those containing potassium hydroxide), increased SEVORANE<sup>®</sup> AF 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<sub>2</sub> absorbents and leads to the dissociation of sevoflurane into hexafluoroisopropanol (HFIP) and formaldehyde. HFIP is inactive, non-genotoxic, rapidly glucuronidated, cleared, and has toxicity comparable to sevoflurane. Formaldehyde is present during normal metabolic processes. Upon exposure to a highly desiccated absorbent, formaldehyde can further degrade into methanol and formate. Formate can contribute to the formation of carbon monoxide, in the presence of high temperature. Methanol can react with Compound A to form the methoxy addition product Compound B. Compound B can undergo further HF elimination to form Compounds C, D, and E. With highly desiccated absorbents, especially those containing potassium hydroxide, 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<sub>2</sub> absorbents is not unique to SEVORANE<sup>®</sup> AF. 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.

### **Lewis Acid Degradation**

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

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

### **Composition**

SEVORANE<sup>®</sup> AF (sevoflurane) is a clear, colorless, liquid. The finished product is comprised only of the active drug substance, sevoflurane (about 99.9875% v/v on anhydrous basis).

### **Availability of Dosage Forms**

SEVORANE<sup>®</sup> AF is available in 250 mL PEN (polyethylene naphthalate) plastic bottles with QUIK-FIL\* closures.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

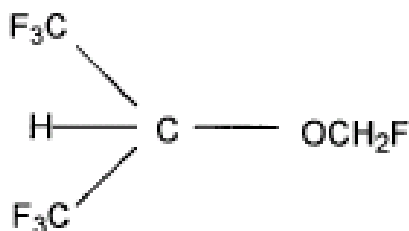
#### Drug Substance

Proper name: sevoflurane

Chemical name: fluoromethyl 2,2,2-trifluoro-1-(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. Sevoflurane is nonpungent. It is miscible with ethanol, ether, chloroform and petroleum benzene, and it is slightly soluble in water.

Sevoflurane has the following physical and chemical properties:

Boiling Point at 760 mm Hg	58.6°C
Specific Gravity at 20°C	1.520 - 1.525
Vapor Pressure*	157 mm Hg at 20°C 197 mm Hg at 25°C 317 mm Hg at 36°C
Distribution Partition Coefficients at 37°C:	
Blood/Gas	0.63 - 0.69
Water/Gas	0.36
Olive Oil/Gas	47.2 - 53.9
Brain/Gas	1.15

\* Vapor pressure (mm Hg) is calculated using the equation:  $\text{Log}_{10}P_{\text{vap}} = A+B/T$ , where  $A = 8.086$ ;  $B = -1726.68$ ;  $T = ^\circ\text{C} + 273.16^\circ\text{K}$  (Kelvin)



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

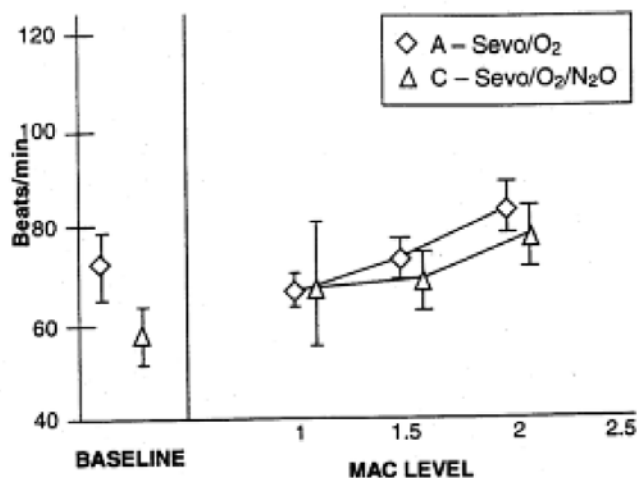
Conductive rubber	14.0
Butyl rubber	7.7
Polyvinyl chloride	17.4
Polyethylene	1.3

## CLINICAL TRIALS

### Study Results

#### Cardiovascular Effects

SEVORANE<sup>®</sup> AF (sevoflurane) was studied in 14 healthy volunteers (18 to 35 years old) comparing sevoflurane-O<sub>2</sub> (Sevo/O<sub>2</sub>) to sevoflurane-O<sub>2</sub>/N<sub>2</sub>O (Sevo/O<sub>2</sub>/N<sub>2</sub>O) during 7 hours of anesthesia. During controlled ventilation, hemodynamic parameters measured are shown in, **Figure 1, Figure 2, Figure 3, and Figure 4.**



**Figure 1.** Heart Rate – SEVORANE<sup>®</sup> AF does not produce an increase in heart rate with or without nitrous oxide at doses less than 2 MAC.

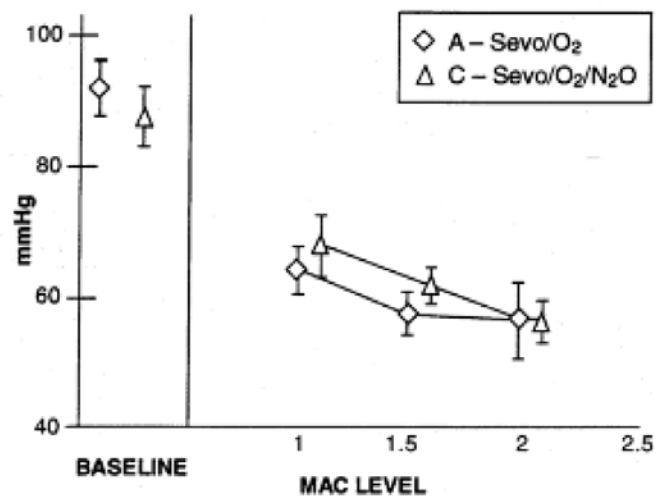


Figure 2. Mean Arterial Pressure – The decrease in mean arterial pressure seen with SEVORANE<sup>®</sup> AF with or without nitrous oxide is dose dependent at all MAC values.

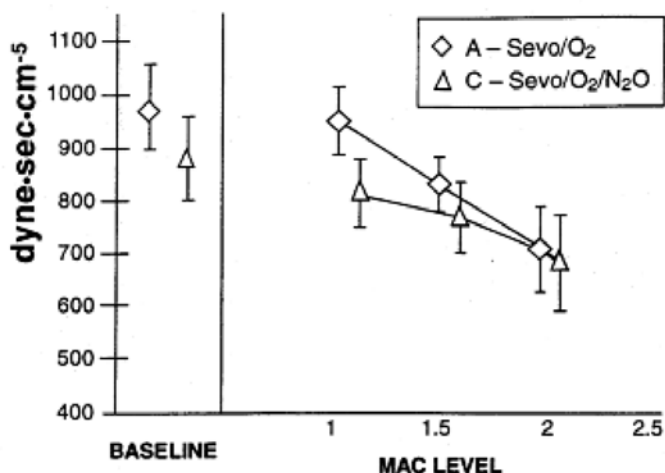
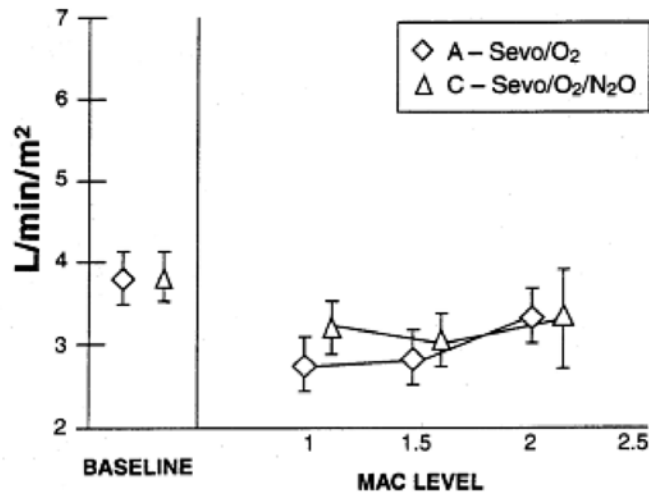


Figure 3. Systemic Vascular Resistance – The decrease in systemic vascular resistance seen with SEVORANE<sup>®</sup> AF with or without nitrous oxide is dose dependent at all MAC values.



**Figure 4.** Cardiac Index - SEVORANE<sup>®</sup> AF has a dose-related cardiac depressant effect with or without nitrous oxide.

A study investigating the epinephrine-induced arrhythmogenic effect of SEVORANE<sup>®</sup> AF 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

SEVORANE<sup>®</sup> AF 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 SEVORANE<sup>®</sup> AF and 0.53 for isoflurane. No statistical differences were observed between the two treatment groups with respect to incidence (SEVORANE<sup>®</sup> AF 7%, isoflurane 11%) and duration (SEVORANE<sup>®</sup> AF approx. 18 minutes, isoflurane approx. 17 minutes) of ischemic events, number of patients with diagnosis of myocardial infarction (SEVORANE<sup>®</sup> AF 8%, isoflurane 10%), time to hemodynamic stability (SEVORANE<sup>®</sup> AF approx. 5 hours, isoflurane approx. 6 hours), or use of cardioactive drugs (SEVORANE<sup>®</sup> AF 53%, isoflurane 47%).

### Non-Cardiac Surgery Patients at Risk for Myocardial Ischemia

Sevoflurane-N<sub>2</sub>O was compared to isoflurane-N<sub>2</sub>O 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 (SEVORANE<sup>®</sup> AF 6%, isoflurane 3%) or post-operative incidence of ischemic events (SEVORANE<sup>®</sup> AF 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 (SEVORANE<sup>®</sup> AF 60%, isoflurane 61%). There was one death in SEVORANE<sup>®</sup> AF 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 SEVORANE<sup>®</sup> AF required for maintenance of general anesthesia is age-dependent. See **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**. Incidences of bradycardia (more than 20 beats/min less than normal) is lower for SEVORANE<sup>®</sup> AF (3%) than for halothane (7%). Emergence times for SEVORANE<sup>®</sup> AF are faster than with halothane (12 vs 19 minutes, respectively). A higher incidence of agitation occurs with SEVORANE<sup>®</sup> AF (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<sub>2</sub>), 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 epinephrine-induced 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 1-hour inhalation exposure ranged from 5.8% in the rat to 10.6% in rabbits. Prolongation of exposure lowered the LC<sub>50</sub> within each species. See **Table 6**.

**Table 6.** Summary of Calculated Median Lethal Concentrations

Species	Inhalation LC <sub>50</sub>	
	1 hour	3 hours
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<sub>50</sub> 10.8 to 24.3 mL/kg) and parenterally (LD<sub>50</sub> 6.3 to 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<sub>50</sub> 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 (concentration-dependent increases in BUN, creatinine, glucose, protein/creatinine ratios and N-acetylglucosamidase/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 ( $\beta$ -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<sub>2</sub> 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<sup>®</sup> as the CO<sub>2</sub> 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

### <sup>Pr</sup>SEVORANE<sup>®</sup> AF volatile liquid sevoflurane

This leaflet is PART III of a three-part Product Monograph published when SEVORANE<sup>®</sup> AF was approved for sale in Canada and is designed specifically for consumers. This leaflet is a summary and will not tell you everything about SEVORANE<sup>®</sup> AF. Contact your doctor or pharmacist if you have any questions about the drug.

#### ABOUT THIS MEDICATION

##### What the medication is used for:

SEVORANE<sup>®</sup> AF is an inhalation general anesthetic used during surgery.

##### What it does:

SEVORANE<sup>®</sup> AF causes unconsciousness, muscle relaxation, and loss of sensation over the entire body so that surgery can be performed.

##### When it should not be used:

SEVORANE<sup>®</sup> AF should not be used in patients who:

- are allergic to SEVORANE<sup>®</sup> AF 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

##### What the non-medicinal ingredients are:

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

##### What dosage forms it comes in:

SEVORANE<sup>®</sup> AF is available as a volatile liquid that is 99.9875% pure.

#### WARNINGS AND PRECAUTIONS

Recovery of consciousness following SEVORANE<sup>®</sup> AF administration generally occurs within minutes. As with other anesthetics, small changes in moods 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 SEVORANE<sup>®</sup> AF. 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 airway 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 SEVORANE® AF, contact your doctor or pharmacist.*

**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](http://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 Web site 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**

The most recent version of this document plus the full Product Monograph, prepared for healthcare professionals can be found at:

[www.abbvie.ca](http://www.abbvie.ca)

or by contacting the sponsor, AbbVie Corporation, Saint-Laurent, Qc H4S 1Z1 at:  
1-888-704-8271

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