

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrSEVOFLURANE

Sevoflurane

Liquid, 99.97% v/v sevoflurane (on anhydrous basis), Inhalation

USP

Inhalation Anesthetic

Volatile Liquid

Baxter Corporation
Mississauga, Ontario L5N 0C2

Date of Initial Authorization:
March 15, 2005

Date of Revision:
March 08, 2023

Submission Control Number: 267081

Baxter is a registered trademark of Baxter International Inc.

RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, 7.1.3 Pediatrics

03/2023

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

RECENT MAJOR LABEL CHANGES	2
TABLE OF CONTENTS	2
PART I: HEALTH PROFESSIONAL INFORMATION	4
1 INDICATIONS.....	4
1.1 Pediatrics.....	4
1.2 Geriatrics	4
2 CONTRAINDICATIONS.....	4
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	4
4 DOSAGE AND ADMINISTRATION.....	4
4.1 Dosing Considerations	4
4.2 Recommended Dose and Dosage Adjustment	5
4.4 Administration	5
5 OVERDOSAGE.....	5
6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING	6
7 WARNINGS AND PRECAUTIONS.....	6
7.1 Special Populations	9
7.1.1 Pregnant Women.....	10
7.1.2 Breast-feeding.....	10
7.1.3 Pediatrics.....	10
7.1.4 Geriatrics	10
8 ADVERSE REACTIONS.....	11
8.1 Adverse Reaction Overview	11
8.2 Clinical Trial Adverse Reactions	11
8.3 Less Common Clinical Trial Adverse Reactions.....	14

8.4	Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data.....	14
8.5	Post-Market Adverse Reactions.....	15
9	DRUG INTERACTIONS	16
9.2	Drug Interactions Overview	16
9.3	Drug-Behavioural Interactions	16
9.4	Drug-Drug Interactions.....	16
9.5	Drug-Food Interactions	18
9.6	Drug-Herb Interactions.....	18
9.7	Drug-Laboratory Test Interactions	18
10	CLINICAL PHARMACOLOGY.....	18
10.1	Mechanism of Action	18
10.2	Pharmacodynamics.....	18
10.3	Pharmacokinetics.....	19
11	STORAGE, STABILITY AND DISPOSAL.....	21
12	SPECIAL HANDLING INSTRUCTIONS.....	21
PART II: SCIENTIFIC INFORMATION		22
13	PHARMACEUTICAL INFORMATION	22
14	CLINICAL TRIALS	23
14.1	Trial Design and Study Demographics	23
14.2	Study Results.....	23
15	MICROBIOLOGY	26
16	NON-CLINICAL TOXICOLOGY.....	26
17	SUPPORTING PRODUCT MONOGRAPHS.....	28
PATIENT MEDICATION INFORMATION		29

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

SEVOFLURANE (sevoflurane) is indicated for:

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

1.1 Pediatrics

Pediatrics (< 18 years of age): For a brief discussion, see [7.1.3 Pediatrics](#).

1.2 Geriatrics

Geriatrics (> 65 years of age): For a brief discussion, see [7.1.4 Geriatrics](#).

2 CONTRAINDICATIONS

- SEVOFLURANE is contraindicated in patients with known sensitivity to sevoflurane or to other halogenated inhalation anesthetics.
- 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 [7 WARNINGS AND PRECAUTION, Hepatic/Biliary/Pancreatic](#).
- 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.
- SEVOFLURANE should not be used when general anesthesia is contraindicated.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- 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 [7 WARNINGS AND PRECAUTIONS, General, Safe Use of CO₂ Absorbents](#).

4 DOSAGE AND ADMINISTRATION

4.1 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. See [9.4 Drug-Drug Interactions](#).

Table 6. Sevoflurane can be administered with any type of anesthesia circuit.

4.2 Recommended Dose and Dosage Adjustment

Minimum alveolar concentration (MAC) values according to age are presented in [Table 1](#).

Table 1 - 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 ₂ O / 35% O ₂	-	-	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% N₂O / 40% O₂ was used.

4.4 Administration

SEVOFLURANE should be administered only by persons trained in the administration of general anesthesia. See [7 WARNINGS AND PRECAUTIONS, General](#).

5 OVERDOSAGE

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.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2– Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Inhalation	volatile liquid / 99.97% v/v sevoflurane, USP (on anhydrous basis)	none

Composition:

SEVOFLURANE is a clear, colorless, liquid containing no additives or chemical stabilizers. The finished product is comprised only of the active drug substance, sevoflurane, USP (about 99.975% v/v on anhydrous basis).

Availability of Dosage Forms:

SEVOFLURANE, is available in a 250 mL aluminum bottle and a plastic screw-on cap, with or without an integrated crimped-on valve closure.

7 WARNINGS AND PRECAUTIONS

Please see **3 SERIOUS WARNINGS AND PRECAUTIONS BOX**.

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 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 CO₂ 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) CO₂ absorbents. The color indicator of most CO₂ 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. CO₂ absorbents should be replaced routinely regardless of the state of the color indicator.

Compound A is produced when sevoflurane interacts with soda lime and Baralyme®. See

10.3 Pharmacokinetics, Elimination, Compound A Production in Anesthesia Circuit. 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.

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 CO₂ 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 CO₂ absorbent canister.

An exothermic reaction, enhanced sevoflurane degradation, and production of degradation products can occur when the CO₂ absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO₂ absorbent canisters. See [11 STORAGE, STABILITY AND DISPOSAL, 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 CO₂ absorbents and maximum sevoflurane concentrations (8%) for extended periods of time (≥ 2 hours). Concentrations of formaldehyde observed at the anesthesia respiratory circuit (using sodium hydroxide containing absorbents) were consistent with levels known to cause respiratory irritation.

Carcinogenesis and Mutagenesis:

Studies on carcinogenesis have not been performed. No mutagenic effect was noted in the Ames test, see [16 NON-CLINICAL TOXICOLOGY, Genotoxicity](#).

Cardiovascular:

Caution should be exercised when administering SEVOFLURANE to susceptible patients. Sevoflurane 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.

Driving and Operating Machinery:

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.

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.

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 post-marketing 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 sevoflurane from post-marketing experiences.

As with other halogenated anesthetics, sevoflurane 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 SEVOFLURANE is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction. See [2 CONTRAINDICATIONS](#) and [8.5 Post-Market Adverse 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 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:

- **Seizures**

Cases of seizures have been reported in association with sevoflurane. See [7.1.3 Pediatrics and 8.5 Post-Market Adverse Reactions, Seizures](#).

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 minimum alveolar concentration (MAC) inspired concentrations of volatile agent during N₂O-O₂-fentanyl anesthesia. During progressive hyperventilation from PaCO₂ = 40 to PaCO₂ = 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.

Psychiatric:

Sevoflurane, 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.

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 [10 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.

7.1 Special Populations

SEVOFLURANE should only be used in pregnant women, including women in labour and delivery, or young children when its benefits outweigh potential risks. Patients should be followed up post-operatively after exposure to SEVOFLURANE as appropriate to identify potential adverse effects. See [16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology](#).

7.1.1 Pregnant Women

There are no adequate and well-controlled studies in pregnant women.

- **Labour and Delivery**

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

- **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.

7.1.2 Breast-feeding

It is not known whether sevoflurane or its metabolites are 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.

7.1.3 Pediatrics

The concentration of SEVOFLURANE required for maintenance of general anesthesia is age-dependent. See [4.2 Recommended Dose and Dosage Adjustment](#).

- **Risk of seizures**

The use of sevoflurane 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 SEVOFLURANE in patients who may be at risk for seizures. See [8.5 Post-Market Adverse Reactions, Seizures](#).

- **Congenital, Familial and Genetic Disorders**

- **Pompe's disease:** 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 Pompe's disease.
- **Down syndrome:** Caution should be exercised when inducing general anesthesia with SEVOFLURANE in pediatric patients with Down Syndrome (DS). Information from published observational studies and post-market spontaneous reports suggests a greater risk (higher frequency and degree) of bradycardia in children with DS exposed to sevoflurane for induction compared to healthy children.

7.1.4 Geriatrics

Minimum alveolar concentration (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.

8 ADVERSE REACTIONS

8.1 Adverse 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 post-operative 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

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 3, Table 4 and Table 5. One case of malignant hyperthermia was reported in pre-registration clinical trials.

Table 3 - 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

Body System	Adult Patients N = 118 (%)	Pediatric Patients N = 507 (%)
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 4 - Adverse Events for All Patients During All Anesthetic Periods with Possibly or Probably Related Incidence $\geq 1\%$

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

Body System	Sevoflurane N = 2906 (%)
Nervous System	
Agitation	9
Dizziness	4
Increased salivation	4
Somnolence	9
Respiratory System	
Breath-holding	2
Cough increased	11
Laryngospasm	2

Table 5 - 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

Body System	Sevoflurane N = 2906 (%)	Reference Agent N = 2276 (%)
Nervous System		
Agitation	11	9
Dizziness	8	9
Increased salivation	7	11
Somnolence	14	17
Respiratory System		
Breath-holding	3	3
Cough increased	24	29
Laryngospasm	2	3

8.3 Less Common Clinical Trial Adverse Reactions

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 atrioventricular (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 alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), lactate dehydrogenase (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

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

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

8.5 Post-Market Adverse 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 post-market reports that link sevoflurane with QT prolongation. Very rare cases of torsade de pointes, some resulting in deaths, have been reported. See [7 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 [2 CONTRAINDICATIONS](#) and [7 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 [2 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 sevoflurane. 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 electroencephalogram (EEG). Although many cases resolved spontaneously or after treatment, cases of multiple seizures have also been reported. Seizures have occurred during or soon after sevoflurane induction, during emergence, and during post-operative recovery up to a day following anesthesia. See [7 WARNINGS AND PRECAUTIONS, Neurologic, Seizures](#).

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.

Bradycardia:

There have been reports of bradycardia, including cases of cardiac arrest, in pediatric patients with Down syndrome following induction of general anesthesia with sevoflurane. See [7.1.3 Pediatrics](#).

9 DRUG INTERACTIONS

9.2 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.

9.3 Drug-Behavioural 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 [7 WARNINGS AND PRECAUTIONS, Driving and operating machinery](#).

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6 - 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 minimum alveolar concentration (MAC) of sevoflurane in the same manner as with other inhalational anesthetics. SEVOFLURANE administration is compatible with benzodiazepines as commonly used in surgical practice.
Calcium antagonists	↓ blood pressure	Sevoflurane may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivates. Caution should be exercised when calcium antagonists are used concomitantly with inhalation anesthetics due to the risk of additive negative inotropic effect.

Drug	Effect	Clinical comment
Inducers of CYP2E1	↑ metabolism of sevoflurane ↑ 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 sevoflurane 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, 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 ₂ O, the MAC equivalent dose requirement is reduced approximately 50% in adults, and approximately 25% in pediatric patients. See 4.2 Recommended Dose and Dosage Adjustment .
Non-selective MAO-inhibitors	↑ blood pressure	Risk of hypertensive crisis during the operation. It is generally recommended that treatment should be stopped 2 weeks prior to surgery.
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.
Succinylcholine	↑ serum potassium levels	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 7 WARNINGS AND PRECAUTIONS .

Drug	Effect	Clinical comment
Sympathomimetic Agents	↑ risk of ventricular arrhythmia	Beta-sympathomimetic agents like isoprenaline and alpha- and beta- sympathomimetic agents like adrenaline and noradrenaline should be used with caution during SEVOFLURANE narcosis, due to a potential risk of ventricular arrhythmia.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

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).

10.2 Pharmacodynamics

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 [4.2 Recommended Dose and Dosage Adjustment for details](#).

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.

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.

Equipotent doses of sevoflurane and isoflurane produce similar effects on cerebral blood flow (CBF), cerebral metabolic rate for oxygen (CMRO₂), intracranial pressure (ICP) and electroencephalogram patterns (EEG). In contrast, after short-term exposure, sevoflurane administration (1 minimum alveolar concentration: MAC) produces a smaller increase in ICP than does an equipotent concentration of halothane.

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.

10.3 Pharmacokinetics

Absorption

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 (FA) toward the inspired concentration (FI) 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 CO₂. 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 micromolar; there were no reports of toxicity associated with elevated fluoride ion levels. See [9.4 Drug-Drug Interactions](#), Table 6.

Elimination

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 CO₂ 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.

- **Sex**

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

- **Ethnic Origin**

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.

11 STORAGE, STABILITY AND DISPOSAL

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 CO₂ 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 CO₂ 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 pentafluoroisopropyl fluoromethyl ether (PIFE or more commonly known as Compound A). The second occurs only in the presence of desiccated CO₂ 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 CO₂ 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.

Temperature:

Store between 15 and 30°C.

12 SPECIAL HANDLING INSTRUCTIONS

No Special Handling Instructions are required for this drug product.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance:

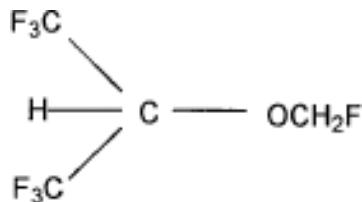
Proper name: sevoflurane

Chemical name: fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether

Molecular formula and

Molecular mass: C₄H₃F₇O 200.05 g/mol

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

*Vapor pressure (mm Hg) is calculated using the equation: Log10P_{vap} = A+B/T, where A = 8.086; B = -1726.68; T = °C + 273.16°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

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

For information regarding the trial design and study demographics, refer to 14.2 Study Results.

14.2 Study Results

Cardiovascular Effects:

Sevoflurane was studied in 14 healthy volunteers (18 to 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 [Figure 1](#), [Figure 2](#), [Figure 3](#), and [Figure 4](#).

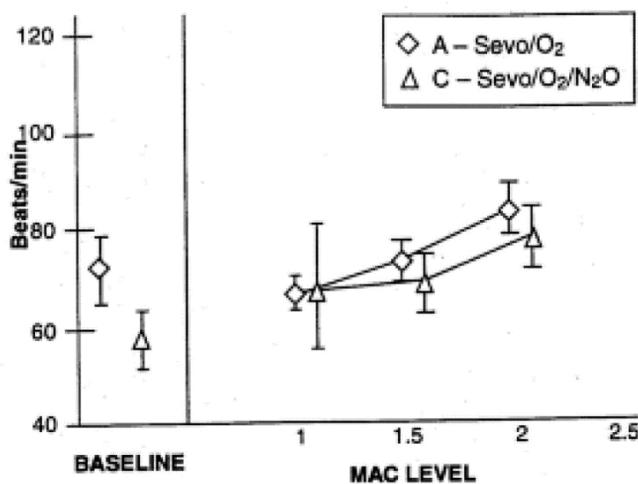


Figure 1 - Heart Rate –Sevoflurane does not produce an increase in heart rate with or without nitrous oxide at doses less than 2 minimum alveolar concentration (MAC).

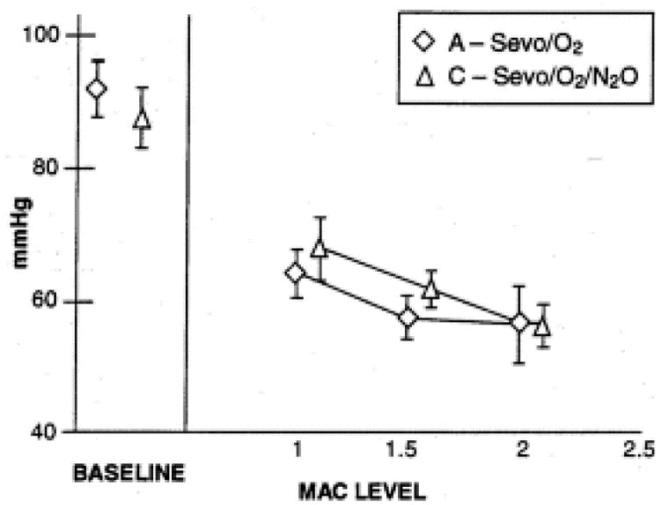


Figure 2 - Mean Arterial Pressure – The decrease in mean arterial pressure seen with sevoflurane with or without nitrous oxide is dose dependent at all MAC values.

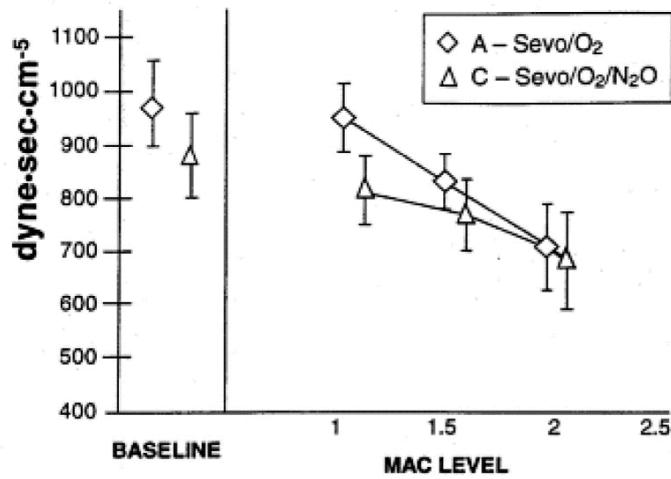


Figure 3 - Systemic Vascular Resistance – The decrease in systemic vascular resistance seen with sevoflurane with or without nitrous oxide is dose dependent at all MAC values.

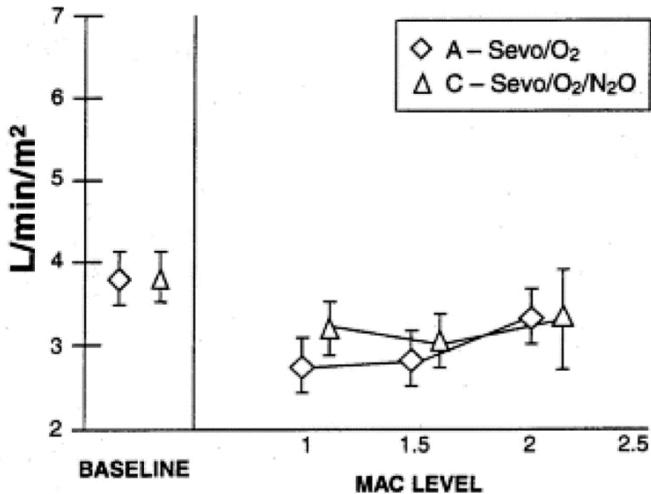


Figure 4 - Cardiac Index - Sevoflurane has a dose-related cardiac depressant effect with or without nitrous oxide.

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 hours, isoflurane approx. 6 hours), or use of cardioactive drugs (sevoflurane 53%, isoflurane 47%).

Non-Cardiac Surgery Patients at Risk for Myocardial Ischemia:

Sevoflurane-N₂O was compared to isoflurane-N₂O 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 4.2 Recommended Dose and Dosage Adjustment. 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%).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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 LC₅₀ within each species. See Table 7.

Table 7 - Summary of Calculated Median Lethal Concentrations

Species	Inhalation LC ₅₀	
	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 (LD₅₀ 10.8 to 24.3 mL/kg) and parenterally (LD₅₀ 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 minimum alveolar concentration

(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.

Carcinogenicity:

Studies on carcinogenesis have not been performed.

Genotoxicity:

Mutagenicity studies indicate that sevoflurane is not mutagenic when tested both in vitro and in vivo.

Reproductive and Developmental Toxicology:

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 were observed.

In rabbits, no developmental toxicity was observed at maternally toxic concentrations of up to 1.0 MAC (1.8%).

Studies in rodents demonstrate that the use of anesthetic agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, three hours exposure to an anesthetic regimen that produced a light surgical plane of anesthesia did not increase neuronal cell loss; however, treatment regimens of five hours or longer increased neuronal cell loss.

Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with subtle but prolonged cognitive deficits in learning and memory.

Inhalation Toxicology:

- **Compound A**

In Wistar rats the LC₅₀ 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 blood urea nitrogen (BUN), creatinine, glucose, protein/creatinine ratios and N-acetyl-glucosamidase (NAG)/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 CO₂ 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 CO₂ 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.

17 SUPPORTING PRODUCT MONOGRAPHS

SEVORANE AF (sevoflurane volatile liquid; 99.9875% sevoflurane on anhydrous basis) submission control 246821, Product Monograph, AbbVie Corporation, May 13, 2021.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr SEVOFLURANE

Sevoflurane, USP

Read this carefully before the administration of **SEVOFLURANE**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **SEVOFLURANE**.

Serious Warnings and Precautions

- SEVOFLURANE should only be administered by a healthcare professional trained in using general anesthesia.
- SEVOFLURANE must only be used in a medical setting where you can be properly monitored and cared for.

What is SEVOFLURANE used for?

- SEVOFLURANE is used in adults and children to put them to sleep during surgery (general anesthesia).

How does SEVOFLURANE work?

SEVOFLURANE contains the medicinal ingredient sevoflurane which belongs to a group of medicines called general anesthetics. Sevoflurane is a liquid, that when put into a special machine becomes a gas.

This gas mixes with the oxygen you will be breathing in during surgery. Sevoflurane works by temporarily reducing the activity of the body's central nervous system. This causes a loss of consciousness, muscle relaxation and loss of sensation. This allows surgery to be carried out without pain or distress.

What are the ingredients in SEVOFLURANE?

Medicinal ingredient: sevoflurane

Non-medicinal ingredient: none

SEVOFLURANE comes in the following dosage forms:

volatile liquid: 99.97% v/v

Do not use SEVOFLURANE if you:

- are allergic to sevoflurane or any other general anesthetic medicines.
- have had liver problems, jaundice (yellowing of the skin or eyes), unexplained fever, or

- certain types of inflammation reactions after having a general anesthetic.
- or a family member have had malignant hyperthermia (a serious, sometimes deadly, reaction to anesthesia where your body temperature becomes dangerously high and your muscles contract).
- have been told that you should not receive general anesthesia.

To help avoid side effects and ensure proper use, talk to your anesthesia professional prior to surgery. Talk about any health conditions or problems you may have, including if you:

- have difficulty with airway intubations (having a tube put down your throat to help you breathe).
- have kidney or liver problems.
- have heart problems.
- have a neuromuscular disease such as Duchenne muscular dystrophy.
- have a history of seizures or fits.
- have a mitochondrial disorder.
- are pregnant.
- are breastfeeding. You should not breastfeed for 48 hours after receiving SEVOFLURANE.

Other warnings you should know about:

Once you have stopped receiving SEVOFLURANE you should regain consciousness within minutes. Like with other anesthetics, you might notice small changes in your mood. This might last for several days after you have had SEVOFLURANE. Talk to your healthcare professional if this becomes severe.

Pompe's disease and Down syndrome: If your child has Pompe's disease or Down syndrome it is important to let their healthcare professional know before they are given SEVOFLURANE.

Driving and using machines: Give yourself time after being given SEVOFLURANE to see how you feel before driving a vehicle or using machinery. It might take some time for you to become fully alert.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with SEVOFLURANE:

- alcohol
- benzodiazepines (a type of sedative)
- calcium antagonists (high blood pressure and heart medicine)
- isoniazid (an antibiotic used to treat tuberculosis)
- non-selective MAO-inhibitors (a type of antidepressant)
- opioids (pain medicine)

Tell your healthcare professional if you have a history of drug interactions. Your healthcare professional will manage this according to your condition.

How to take SEVOFLURANE:

SEVOFLURANE will always be given to you by a healthcare professional trained in the administration of general anesthesia.

Usual dose:

Your healthcare professional will decide on the dose that is right for you.

Overdose:

If you think you, or a person you are caring for, have been given too much SEVOFLURANE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using SEVOFLURANE?

These are not all the possible side effects you or your child may have after being given SEVOFLURANE. If you or your child experience any side effects not listed here, tell your healthcare professional.

Side effects when you wake up may include:

- feeling agitated
- increased cough
- nausea
- vomiting
- chills
- dizziness

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Low blood pressure: dizziness, fainting, lightheadedness (may occur when you go from lying or sitting to standing up)		✓	
COMMON			
Heart rate problems: change in heartbeat (slow or fast)		✓	
High blood pressure: headaches, dizziness, shortness of breath		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
UNCOMMON			
Breathing problems: difficulty breathing/choking, wheezing		✓	
High blood sugar: frequent urination, thirst, and hunger		✓	
UNKNOWN			
Allergic reaction: rash, itching, hives, swelling of the face, lips, tongue or throat, difficulty breathing or swallowing			✓
Liver problems: yellowing of the skin or eyes, dark urine, abdominal pain, nausea, vomiting, loss of appetite		✓	
Malignant hyperthermia: sudden fever, stiffness, pain and weakness in the muscles			✓
Seizures or fits			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

SEVOFLURANE will be stored by your healthcare professional.

If you want more information about SEVOFLURANE:

- Talk to your healthcare professional.

- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website (www.baxter.ca), or by calling 1-888-719-9955

This leaflet was prepared by Baxter Corporation, Mississauga, Ontario L5N 0C2.

Baxter is a registered trademark of Baxter International Inc.

Last Revised: March 08, 2023