# NOREVELL

**Inhalation Vapour, Liquid**

**Sevoflurane**

## QUALITATIVE AND QUANTITATIVE COMPOSITION

Sevoflurane 100%. Each bottle contains 250ml of sevoflurane as active substance.

The finished product is comprised only of the active substance.

## PHARMACEUTICAL FORM

Inhalation Vapour, Liquid

Clear and colorless liquid

## CLINICAL PHARMACOLOGY

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

### Pharmacokinetics

#### *Solubility*

The low solubility of sevoflurane in blood would suggest alveolar concentrations should rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent. This was confirmed in a clinical study where inspired and end-tidal concentrations ($F_I$ and $F_A$) were measured. The $F_A/F_I$ (washin) value at 30 minutes for sevoflurane was 0.85. The $F_A/F_{AO}$ (washout) value at five minutes was 0.15.

#### *Distribution*

The effects of sevoflurane on the displacement of drugs from serum and tissue proteins have not been investigated. Other fluorinated volatile anesthetics have been shown to displace drugs from serum and tissue proteins *in vitro*. The clinical significance of this is unknown. Clinical studies have shown no untoward effects when sevoflurane is administered to patients taking drugs that are highly bound and have a small volume of distribution (e.g., phenytoin).

#### *Metabolism*

The rapid pulmonary elimination of sevoflurane minimizes the amount of anesthetic available for metabolism. In humans <5% sevoflurane absorbed is metabolized via cytochrome P450 2E1 isoform to hexafluorisopropanol (HFIP), with release of inorganic fluoride and carbon dioxide (or a one carbon fragment). Once formed HFIP is rapidly conjugated with glucuronic acid and eliminated as a urinary metabolite. No other metabolic pathways for sevoflurane have been identified. It is the only fluorinated volatile anesthetic which is not metabolized to trifluoroacetic acid.

***Fluoride Ion***

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

The defluorination of sevoflurane is not inducible by barbiturates.

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

**Pharmacodynamics**

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

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

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

In both dogs and humans, the epinephrine-induced arrhythmogenic threshold for sevoflurane was comparable to that of isoflurane and higher than that of halothane. Studies in dogs have demonstrated sevoflurane does not reduce collateral myocardial perfusion. In clinical studies, the incidence of myocardial ischemia and myocardial infarction in patients at risk for myocardial ischemia was comparable between sevoflurane and isoflurane.

Animal studies have shown regional blood flow (*e.g.*, hepatic, renal, cerebral circulations) is wellmaintained with sevoflurane. In both animal studies (dogs, rabbits) and clinical studies, changes in neurohemodynamics (intracranial pressure, cerebral blood flow/blood flow velocity, cerebral metabolic rate for oxygen, and cerebral perfusion pressure) were comparable between sevoflurane and isoflurane. Sevoflurane has minimal effect on ICP (intracranial pressure) and preserves $CO_2$ responsiveness.

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

***Minimum Alveolar Concentration***

The minimum alveolar concentration (MAC) is the concentration at which 50% of the population tested does not move in response to a single stimulus of skin incision. For MAC equivalents for sevoflurane for various age groups, (see **DOSAGE AND ADMINISTRATION)**.

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

## INDICATIONS

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

## DOSAGE AND ADMINISTRATION

**Route of Administration: Inhalation**

***Premedication***

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

***Surgical Anesthesia***

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

***Induction***

Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. A short acting barbiturate or other intravenous induction agent may be administered followed by inhalation of sevoflurane. Induction with sevoflurane may be achieved in oxygen or in combination with oxygen-nitrous oxide mixtures. For induction of anesthesia, inspired concentrations of up to 8% sevoflurane usually produces surgical anesthesia in less than two minutes in both adults and children.

***Maintenance***

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

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

| **Age of Patient (Years)** | **Sevoflurane in Oxygen** | **Sevoflurane in 65% $N_2O$/35% $O_2$** |
|---|---|---|
| 0 – 1 months* | 3.3% | |
| 1 – < 6 months | 3.0% | |
| 6 – < 3 years | 2.8% | 2.0%@ |
| 3 – 12 | 2.5% | |
| 25 | 2.6% | 1.4% |
| 40 | 2.1% | 1.1% |
| 60 | 1.7% | 0.9% |
| 80 | 1.4% | 0.7% |

*Neonates are full-term gestational age. MAC in premature infants has not been determined.
@ In 1 – < 3 years old pediatric patients, 60% $N_2O$/40% $O_2$

**Emergence**

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

**Elderly**

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

## CONTRAINDICATIONS

Sevoflurane should not be used in patients with known or suspected genetic susceptibility to malignant hyperthermia.

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

## WARNINGS AND PRECAUTIONS

Sevoflurane may cause respiratory depression, which may be augmented by narcotic premedication or other agents causing respiratory depression. Respiration should be supervised and if necessary, assisted.

Sevoflurane should be administered only by persons trained in the administration of general anesthesia. Facilities for maintenance of a patent airway, artificial ventilation and oxygen enrichment, and circulatory resuscitation must be immediately available.

The concentration of sevoflurane being delivered from a vaporizer must be known exactly. As volatile anaesthetics differ in their physical properties, only vaporizers specifically calibrated for sevoflurane must be used. The administration of general anaesthesia must be individualized based on the patient’s response. Hypotension and respiratory depression increase as anesthesia is deepened.

Isolated reports of QT prolongation, very rarely associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering sevoflurane to susceptible patients.

Isolated cases of ventricular arrhythmia were reported in pediatric patients with Pompe's disease.

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

***Hepatic***

Very rare cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice have been reported from postmarketing experiences.

Clinical judgment should be exercised when sevoflurane is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction (see **ADVERSE REACTIONS**).

It has been reported that previous exposure to halogenated hydrocarbon anesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury.

***Malignant Hyperthermia***

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

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

Treatment of malignant hyperthermia includes discontinuation of triggering agents (e.g. sevoflurane), administration of intravenous dantrolene sodium (consult prescribing

information for intravenous dantrolene sodium for additional information on patient management), and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base abnormalities. Renal failure may appear later, and urine flow should be monitored and sustained if possible.

***Perioperative Hyperkalemia***

Use of inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the postoperative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. Concomitant use of succinylcholine has been associated with most, but not all, of these cases.

These patients also experienced significant elevations in serum creatine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

***General***

During maintenance of anesthesia, increasing the concentration of sevoflurane produces dose-dependent decreases in blood pressure. Excessive decrease in blood pressure may be related to depth of anesthesia and in such instances may be corrected by decreasing the inspired concentration of sevoflurane.

As with all anesthetics, maintenance of hemodynamic stability is important to the avoidance of myocardial ischemia in patients with coronary artery disease.

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

Although recovery of consciousness following sevoflurane administration generally occurs within minutes, the impact on intellectual function for two or three days following anesthesia

has not been studied. As with other anesthetics, small changes in moods may persist for several days following administration. 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.

***Replacement of Desiccated $CO_2$ Absorbents:***

Rare cases of extreme heat, smoke, and/or spontaneous fire in the anesthesia machine have been reported during sevoflurane use in conjunction with the use of desiccated 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 (see DESCRIPTION) can occur when the CO2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO2 absorbent canisters. Sevoflurane degradants (methanol, formaldehyde, carbon monoxide, and Compounds A, B, C, and D) were observed in the respiratory circuit of an experimental anesthesia machine using desiccated CO2 absorbents and maximum sevoflurane concentrations (8%) for extended periods of time ($\geq$ 2 hours). Concentrations of formaldehyde observed at the anesthesia respiratory circuit (using sodium hydroxide containing absorbents) were consistent with levels known to cause mild respiratory irritation. The clinical relevance of the degradants observed under this extreme experimental model is unknown.

When a clinician suspects that the CO2 absorbent may be desiccated, it should be replaced before administration of sevoflurane. 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.

***Renal Impairment***

Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 1.5 mg/dL) studied, the safety of sevoflurane administration in this group has not yet been fully established. Therefore, sevoflurane should be used with caution in patients with renal insufficiency.

***Neurosurgery***

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

***Seizures***

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

***Pediatric Use***

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

**DRUG INTERACTIONS**

Beta-sympathomimetic agents like isoprenaline and alpha- and beta- sympathomimetic agents like adrenaline and noradrenaline should be used with caution during Sevoflurane narcosis, due to a potential risk of ventricular arrhythmia.

Non-selective MAO-inhibitors: Risk of crisis during the operation. It is generally recommended that treatment should be stopped 2 weeks prior to surgery.

Sevoflurane may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivates.

Caution should be exercised when calcium antagonists are used concomitantly with inhalation anesthetics due to the risk of additive negative inotropic effect.

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

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

***Barbiturates***

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

***Benzodiazepines and Opioids***

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

***Inducers of CYP2E1***

Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of sevoflurane and lead to significant increases in plasma fluoride concentrations (see **CLINICAL PHARMACOLOGY, Pharmacokinetics,** ***Metabolism*** and ***Fluoride Ion***).

***Nitrous Oxide***

As with other halogenated volatile anesthetics, the MAC of sevoflurane is decreased when administered in combination with nitrous oxide. The MAC equivalent is reduced approximately 50% in adult and approximately 25% in pediatric patients (see **DOSAGE AND ADMINISTRATION,** ***Maintenance***).

***Neuromuscular Blocking Agents***

As with other inhalational anesthetic agents, sevoflurane affects both the intensity and duration of neuromuscular blockade by non-depolarizing muscle relaxants. When used to supplement alfentanil-$N_2O$ anesthesia, sevoflurane potentiates neuromuscular block induced with pancuronium, vecuronium or atracurium. The dosage adjustments for these muscle relaxants when administered with sevoflurane are similar to those required with isoflurane.

The effect of sevoflurane on succinylcholine and the duration of depolarizing neuromuscular blockade has not been studied.

Dosage reduction of neuromuscular blocking agents during induction of anesthesia may result in delayed onset of conditions suitable for endotracheal intubation or inadequate muscle relaxation because potentiation of neuromuscular blocking agents is observed a few minutes after the beginning of sevoflurane administration.

Among non-depolarizing agents, vecuronium, pancuronium and atracurium interactions have been studied. In the absence of specific guidelines: (1) for endotracheal intubation, do not reduce the dose of nondepolarizing muscle relaxants; and, (2) during maintenance of anesthesia, the dose of non-depolarizing muscle relaxants is likely to be reduced compared to that during $N_2O$/opioid anesthesia. Administration of supplemental doses of muscle relaxants should be guided by the response to nerve stimulation.

## PREGNANCY AND LACTATION

### Preg and Lact - Pregnancy

***Pregnancy Category B***

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

Published animal studies of some anesthetic/sedation drugs have reported adverse effects on brain development in early life.

***Labor and Delivery***

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

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.

**Lactation**

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

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

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

**ADVERSE REACTIONS**

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

**ADR - Clinical Trials**

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

The most commonly reported adverse reactions were as follows:
In adult patients: hypotension, nausea and vomiting;
In elderly patients: bradycardia, hypotension and nausea; and
In paediatric patients: agitation, cough, vomiting and nausea.

All events, at least possibly related to sevoflurane from clinical trials, are displayed in the Table below by MedDRA System Organ Class, Preferred Term and frequency. The following

frequency groupings are used: very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000); very rare (<1/10,000), including isolated reports. The type, severity, and frequency of adverse events in sevoflurane patients were comparable to adverse events in reference-drug patients.

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

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

**Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anesthesia. Concentrations of inorganic fluoride generally peak within two hours of the end of sevoflurane anesthesia and return within 48 hours to preoperative levels. In clinical trials, elevated fluoride concentrations were not associated with impairment of renal function.

**ADR - Post Marketing Experience**

Adverse events have been spontaneously reported during post-approval use of sevoflurane. These events are reported voluntarily from a population of an unknown rate of exposure. Therefore it is not possible to estimate the true incidence of adverse events or establish a causal relationship to sevoflurane exposure.

| **Summary of Post-Marketing Adverse Drug Events** | |
|---|---|
| **System Organ Class** | **Adverse Reaction** |
| Immune system disorders | Anaphylactic reaction*** |
| | Anaphylactoid reaction |
| | Hypersensitivity*** |
| Nervous system disorders | Convulsion |
| | Dystonia |
| Cardiac disorders | Cardiac arrest[#] |
| Respiratory, thoracic and mediastinal disorders | Bronchospasm |
| | Dyspnoea |
| | Wheezing*** |
| Hepato-biliary disorders | Hepatitis |
| | Hepatic failure |
| | Hepatic necrosis |
| Skin and subcutaneous tissue disorders | Rash*** |
| | Urticaria |
| | Pruritus |
| | Dermatitis contact*** |
| | Swelling Face*** |
| General disorders and administration site conditions | Hyperthermia malignant |
| | Chest discomfort*** |

*** May be associated with hypersensitivity reactions, particularly in association with long-term occupational exposure to inhaled anesthetic agents

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

## OVERDOSAGE

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

### How supplied

Sevoflurane 100%, Inhalation Vapour, Liquid, is packaged in amber colored bottles containing 250 mL sevoflurane.

### Storage

Sevoflurane should be stored at room temperature below 30°C (86ºF).

Sevoflurane has been demonstrated to be stable for the period defined by the expiration date on the label.

Shelf life : 3 years

**Manufactured by:**

**PT. Novell Pharmaceutical Laboratories**

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Product Registration Holder :

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