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רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

**SOJOURN SEVOFLURANE USP**

חברת פארמה מדיס מבקשת להודיע על עדכונים בעלון לרופא של התכשיר שבנדון.

**התווית התכשיר:**
Induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery

**מרכיב פעיל:** SEVOFLURANE 100%
**צורת המתן של התכשיר :** INHALATION

**להלן העדכונים העיקריים בעלון לצרכן (במתכונת עלון לרופא):**

**THERAPEUTIC INDICATIONS ~~AND USAGE~~**
Sevoflurane is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

**Pharmacogenomics**
*RYR1* and *CACNA1S* are polymorphic genes, and multiple pathogenic variants have been associated with malignant hyperthermia susceptibility (MHS) in patients receiving volatile anesthetic agents, including sevoflurane. Case reports as well as ex-vivo studies have identified multiple variants in *RYR1* and *CACNA1S* associated with MHS. Variant pathogenicity should be assessed based on prior clinical experience, functional studies, prevalence information, or other evidence (see **CONTRAINDICATIONS, WARNINGS - Malignant Hyperthermia)**.

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## CLINICAL STUDIES
~~**Clinical Trials**~~

Sevoflurane was administered to a total of 3185 patients. The types of patients are summarized as follows:

**Table 5. Patients Receiving Sevoflurane in Clinical ~~Trials~~ Studies**

| Type of Patients | Number | Studied |
|---|---|---|
| **ADULT** | 2223 | |
| Cesarean Delivery | | 29 |
| Cardiovascular and patients at risk of myocardial ischemia | | 246 |
| Neurosurgical | | 22 |
| Hepatic impairment | | 8 |
| Renal impairment | | 35 |
| **PEDIATRIC** | 962 | |

Clinical experience with these patients is described below.

## CONTRAINDICATIONS

- ~~Sevoflurane can cause malignant hyperthermia. It should not be used in patients with known sensitivity to sevoflurane or to other halogenated agents nor in patients with known or suspected susceptibility to malignant hyperthermia~~. Known or suspected genetic susceptibility to malignant hyperthermia. (see WARNINGS - Malignant Hyperthermia, CLINICAL PHARMACOLOGY - Pharmacogenomics).

- Known or suspected sensitivity to sevoflurane or to other halogenated inhalational anesthetics.

## WARNINGS
### Risk of Renal Injury

…

### Risk of Respiratory Depression

Sevoflurane may cause respiratory depression, which may be augmented by opioid premedication or other agents causing respiratory depression. Monitor respiration and, if necessary, assist with ventilation (see **PRECAUTIONS**).

…

**Malignant Hyperthermia**

In susceptible individuals, volatile anesthetic agents, including sevoflurane, may trigger malignant hyperthermia, a skeletal muscle hypermetabolic state leading to high oxygen demand. Fatal outcomes of malignant hyperthermia have been reported. In clinical studies of SEVORANE, 1 case of malignant hyperthermia was reported.

The risk of developing malignant hyperthermia increases with the concomitant administration of succinylcholine and volatile anesthetic agents. SEVORANE can induce malignant hyperthermia in patients with known or suspected susceptibility based on genetic factors or family history, including those with certain inherited ryanodine receptor (RYR1) or dihydropyridine receptor (CACNA1S) variants (see CONTRAINDICATIONS, CLINICAL PHARMACOLOGY - Pharmacogenomics).

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Signs consistent with malignant hyperthermia may include hyperthermia, hypoxia, hypercapnia, muscle rigidity (e.g., jaw muscle spasm), tachycardia (e.g., particularly that unresponsive to deepening anesthesia or analgesic medication administration), tachypnea, cyanosis, arrhythmias, hypovolemia, and hemodynamic instability. Skin mottling, coagulopathies, and renal failure may occur later in the course of the hypermetabolic process.

Successful treatment of malignant hyperthermia depends on early recognition of the clinical signs. If malignant hyperthermia is suspected, discontinue all triggering agents (i.e., volatile anesthetic agents and succinylcholine), administer intravenous dantrolene sodium, and initiate supportive therapies. Consult prescribing information for intravenous dantrolene sodium for additional information on patient management. Supportive therapies include administration of supplemental oxygen and respiratory support based on clinical need, maintenance of hemodynamic stability and adequate urinary output, management of fluid and electrolyte balance, correction of acid base derangements, and institution of measures to control rising temperature.

~~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. Sevoflurane can induce malignant hyperthermia in genetically susceptible individuals, such as those with certain inherited ryanodine receptor mutations. 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 studies, one case of malignant hyperthermia was reported. In addition, there have been postmarketing reports of malignant hyperthermia. Some of these cases 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. Supportive therapy may include efforts to restore body temperature, 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.~~

**Pediatric Neurotoxicity**
Published animal studies demonstrate that the administration of anesthetic and sedation drugs that block NMDA receptors and/or potentiate GABA activity increase neuronal apoptosis in the developing brain and result in long-term cognitive deficits when used for longer than 3 hours. The clinical significance of these findings is not clear. However, based on the available data, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester of gestation through the first several months of life, but may extend out to approximately three years of age in humans (see **PRECAUTIONS - Pregnancy, PRECAUTIONS - Pediatric Use, ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY).**

…

**Bradycardia in Down Syndrome**
Episodes of severe bradycardia and cardiac arrest, not related to underlying congenital heart disease, have been reported during anesthesia induction with sevoflurane in pediatric patients with Down syndrome. In most cases, bradycardia improved with decreasing the concentration of sevoflurane, manipulating the airway, or administering an anticholinergic or epinephrine.
During induction, closely monitor heart rate, and consider incrementally increasing the inspired sevoflurane concentration until a suitable level of anesthesia is achieved. Consider having an anticholinergic and epinephrine available when administering sevoflurane for induction in this patient population.

**Risk of Driving and Operating Machinery**
Performance of activities requiring mental alertness, such as driving or operating machinery, may be impaired after sevoflurane anesthesia.

…

**Information for Patients**

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Risk of Driving and Operating Machinery
Advise patients that performance of activities requiring mental alertness, such as driving or operating machinery, may be impaired after sevoflurane anesthesia (see **WARNINGS**).

…

**Drug Interactions**
In clinical ~~trials~~ studies, no significant adverse reactions occurred with other drugs commonly used in the perioperative period, including central nervous system depressants, autonomic drugs, skeletal muscle relaxants, anti-infective agents, hormones and synthetic substitutes, blood derivatives, and cardiovascular drugs.
Epinephrine
Epinephrine administered with sevoflurane may increase the risk of ventricular arrhythmias. Monitor the electrocardiogram and blood pressure and ensure emergency medications to treat ventricular arrhythmias are readily available.

Calcium antagonists
Sevoflurane may lead to marked hypotension in patients treated with calcium antagonists. Blood pressure should be closely monitored and emergency medications to treat hypotension should be readily available when calcium antagonists are used concomitantly with sevoflurane.

In animals, impairment of atrioventricular conduction has been observed when verapamil and sevoflurane are administered concomitantly.

Succinylcholine

See **WARNINGS - Perioperative Hyperkalemia**.

Non-selective MAO-inhibitors

Concomitant use of MAO inhibitors and inhalational anesthetics may increase the risk of hemodynamic instability during surgery or medical procedures.

…

**Hepatic Function**
….

~~Very rare~~ Cases of mild, moderate and severe ~~post operative~~ hepatic dysfunction or hepatitis ~~with or without~~ (e.g., jaundice associated with fever and/or eosinophilia) after anesthesia with sevoflurane have been reported ~~reports from post marketing experiences~~.
…

**Labor and Delivery**
Sevoflurane has been used in clinical studies as part of general anesthesia for elective cesarean section in 29 women. There were no untoward effects in mother or neonate (see ~~**PHARMACODYNAMICS**~~ **CLINICAL ~~Trials~~ STUDIES).** The safety of sevoflurane in labor and delivery has not been demonstrated.
Sevoflurane can cause uterine smooth muscle relaxation and may contribute to uterine atony.

**Nursing Mothers**
~~The concentrations of sevoflurane in milk are probably of no clinical importance 24 hours after anesthesia. Because of rapid washout, sevoflurane concentrations in milk are predicted to be below those found with many other volatile anesthetics.~~
It is not known whether sevoflurane or its metabolites are present in human milk. To minimize infant exposure to sevoflurane or its metabolites, a nursing mother may temporarily pump, and discard breast milk produced during the first 24 hours after administration of sevoflurane.
Exercise caution when administering sevoflurane to a nursing mother.

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**Geriatric Use**
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.

**Pediatric Use**
…
Cases of life-threatening ventricular arrhythmias have been reported in pediatric patients with Pompe disease (also commonly known as glycogen storage disease type II or acid altase deficiency). In a published case series about a clinical trial of patients with infantile-onset Pompe disease, six percent of patients (9 of 139, with 6 of 9 having received sevoflurane) experienced arrhythmias after induction of anesthesia. Reported arrythmias included severe bradycardia, torsade de pointes, and fatal ventricular fibrillation, which usually resolved after treatment with pharmacologic agents and defibrillation. Avoid induction and maintenance of anesthesia using sole agents, such as sevoflurane, that decrease systemic vascular resistance or diastolic blood pressure.

## ADVERSE REACTIONS

…
Central Nervous System
- Delirium

Cardiac
- Cardiac arrest
- QT prolongation associated with Torsade de Pointe
- Bradycardia in patients with Down syndrome

## ANIMAL TOXICOLOGY AND/OR PHARMACOLOGY

Published studies in animals 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, exposure to 3 hours of an anesthetic regimen that produced a light surgical plane of anesthesia did not increase neuronal cell loss; however, treatment regimens of 5 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. The clinical significance of these nonclinical findings is not known, and healthcare providers should balance the benefits of appropriate anesthesia in pregnant women, neonates and young children who require procedures against the potential risks suggested by the nonclinical data (see WARNINGS - Pediatric Neurotoxicity, PRECAUTIONS - Pregnancy, PRECAUTIONS - Pediatric Use).

**בהודעה זו מצוינים סעיפים בהם נעשה שינוי מהותי או שינוי המהווה החמרה. מידע שהתווסף מצוין באדום**
העלון מפורסם במאגר התרופות שבאתר משרד הבריאות
ניתן לקבלו מודפס באמצעות פניה לבעל הרישום, חברת פארמה-מדיס, פייירברג 4 חולון.

בברכה,

מירי חזן

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רוקחת ממונה