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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.

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

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WARNINGS

Risk of Renal Injury

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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**).

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Malignant Hyperthermia

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In clinical ~~trials~~ studies, one case of malignant hyperthermia was reported. In addition, there have been post-marketing 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).**

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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

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**).

…

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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.

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Hepatic Function
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~~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.

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.

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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

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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).

השינויים המודגשים ברקע צהוב מהווים החמרה. בעלון בוצעו שינויים נוספים אשר מהווים תוספת מידע.

העלון מפורסם במאגר התרופות שבאתר משרד הבריאות:
https://data.health.gov.il/drugs/index.html#!/byDrug
ניתן לקבלו מודפס באמצעות פניה לבעל הרישום, חברת פארמה-מדיס, פייירברג 4 חולון.

בברכה,

מירי חזן
רוקחת ממונה