Baxter Healthcare Distribution Ltd
34 Jerusalem st. Ra'anana entrance B
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נובמבר 2022

רופא/ה, רוקח/ת, נכבד/ה,

הנדון: **Sevoflurane Baxter 100 % Inhalation vapour liquid**

מרכיבים פעילים:

Sevoflurane 100% v/v

צורת מינון:

Liquid for inhalation

התוויות מאושרות:

Sevoflurane is indicated for induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient surgery.

חברת בקסטר אספקת שירותי בריאות בע"מ מבקשת להודיעכם על עדכונים בעלון לרופא של התכשיר בנדון.
העלון לרופא עודכן בתאריך נובמבר 2022. להלן העדכונים המהווים החמרה במידע הבטיחותי (מסומנים באמצעות קו תחתי):

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CLINICAL PHARMACOLOGY
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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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CONTRAINDICATIONS
- 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.

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WARNINGS
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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

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 sevoflurane, 1 case of malignant hyperthermia was reported. The risk of developing malignant hyperthermia increases with the concomitant administration of succinylcholine and volatile anesthetic agents. sevoflurane 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).**

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.

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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.

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PRECAUTIONS

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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

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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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Cases of mild, moderate, and severe hepatic dysfunction or hepatitis (e.g., jaundice associated with fever and/or eosinophilia) after anesthesia with sevoflurane have been reported.

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Labor and Delivery

Sevoflurane has been used in clinical studies, as part of general anesthesia for elective cesarean section, in 29 women.

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Sevoflurane can cause uterine smooth muscle relaxation and may contribute to uterine atony.

Nursing Mothers

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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Pediatric Use

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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 maltase 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

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of 9 having received sevoflurane) experienced arrhythmias after induction of anesthesia. Reported arrhythmias 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.

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Use in Pediatric Patients with Down Syndrome
See WARNINGS - Bradycardia in Down Syndrome.

ADVERSE REACTIONS

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Central Nervous System

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- Delirium

Cardiac

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

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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).

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העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות ,וניתן לקבלו מודפס על ידי פניה לבעל הרישום.

בברכה,
אנסטסיה דזיגרב,
מחלקת רישום ורגולציה,
בקסטר אספקת שירותי בריאות בע"מ.