INSTRUCTIONS

for medical use of the medicinal product

Sevoflurane U-FILL

Composition:

- active substance: sevoflurane;
- 1 bottle contains 100% sevoflurane.

Dosage form. Vapor for inhalation, liquid.

Main physicochemical properties: clear, colorless, volatile liquid.

Pharmacotherapeutic group. General anesthetics. Halogenated hydrocarbons. Sevoflurane. ATX code N01A B08.

Pharmacological properties.

Pharmacodynamics.

Inhalation use of the medicinal product for induction anesthesia causes rapid loss of consciousness, which is quickly restored after the end of anesthesia. Induction of anesthesia is accompanied by minimal excitement or signs of upper respiratory tract irritation and does not cause increased secretion in the tracheobronchial tree and stimulation of the central nervous system (CNS). In studies in pediatric practice (induction of anesthesia by mask), the incidence of cough with sevoflurane was significantly lower than with halothane. Like other inhalation anesthetics, sevoflurane causes dose-dependent depression of respiratory function and a decrease in blood pressure. In humans, the adrenaline-induced arrhythmogenic threshold of sevoflurane corresponds to the same level as isoflurane and exceeds the threshold of halothane. Sevoflurane has minimal effects on intracranial pressure and does not reduce the response to CO2.

Sevoflurane has no clinically significant effect on liver or kidney function and does not cause exacerbation of renal and hepatic failure. Sevoflurane does not affect the renal concentrating function even during prolonged anesthesia (up to approximately 9 hours).

Pharmacokinetics.

As a result of the low solubility of sevoflurane in the blood, the alveolar concentration increases rapidly after administration and decreases rapidly after the anesthetic agent is discontinued.

The rapid and extensive elimination of sevoflurane by the lungs helps to minimize the amount of anesthetic agent that can be metabolized. In humans, < 5% of absorbed sevoflurane is metabolized by cytochrome P450 (CYP) 2E1 to form hexafluoroisopropanol (HFIP) with the release of inorganic fluoride and carbon dioxide (or one carbohydrate moiety). HFIP is then rapidly conjugated with glucuronic acid and excreted in the urine. No other metabolic pathways for sevoflurane have been identified. It is the only fluorinated volatile anesthetic that is not metabolized to trifluoroacetic acid.

The concentration of fluoride ion depends on the duration of anesthesia, the concentration of sevoflurane, and the composition of the anesthetic mixture. Defluorination of sevoflurane is not induced by barbiturates. Approximately 7% of adult patients were found to have inorganic fluoride concentrations greater than 50 µmol during the clinical program, but no clinical effect on renal function was observed.

Clinical Studies

Efficacy Studies

Numerous clinical studies of sevoflurane as an anesthetic agent have been conducted in pediatric and adult patients. The results of the studies have demonstrated that sevoflurane provides a smooth, rapid induction, as well as a rapid recovery from anesthesia.

Sevoflurane was associated with faster induction and recovery from anesthesia, response to commands, and orientation than comparison groups.

Adult Anesthesia

In adult patients who underwent mask induction, sevoflurane provided smooth and rapid induction of anesthesia. In outpatient and inpatient studies involving adult patients (using sevoflurane, isoflurane, enflurane, and propofol), sevoflurane has been shown to be an effective agent for maintenance of anesthesia. Sevoflurane has been shown to be adequate for use in neurosurgery, cesarean section, coronary artery bypass grafting, and in patients without cardiac disease at risk of myocardial ischemia.

Pediatric Anesthesia

In outpatient and inpatient studies in children (children received sevoflurane and halothane), sevoflurane has been shown to be an effective agent for induction and maintenance of anesthesia. In pediatric studies (mask induction), induction time was statistically significantly shorter and cough incidence was significantly lower with sevoflurane than with halothane.

Safety Studies

Clinical studies in various patient populations (children, adults, elderly, renally or hepatically impaired, obese, patients undergoing cardiac bypass surgery, patients receiving aminoglycosides or metabolic inducers, patients undergoing repeat surgery, patients undergoing surgery lasting more than 6 hours) and laboratory parameters [such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, serum creatinine, blood urea nitrogen], along with the incidence of adverse reactions (in studies) related to hepatic or renal function, have shown that sevoflurane does not cause clinically significant effects on hepatic or renal function or worsen pre-existing renal or hepatic impairment in the patients studied. population (see sections “Special warnings and precautions for use” and “Adverse reactions”). The data from the studies also demonstrated that there was no statistically significant difference in the number of patients who had changes in any clinical and chemical parameters when using sevoflurane compared to other inhalational anesthetics. The effect on renal function was comparable between sevoflurane and other inhalational anesthetics, with different types of anesthetic circuits, with different anesthetic delivery rates, and in patients with inorganic fluoride concentrations ≥ 50 µmol and < 50 µmol. The incidence of renal dysfunction in comparative studies was < 1% for both sevoflurane (0.17%) and other inhalational anesthetics (0.22% isoflurane, halothane, enflurane, propofol). This incidence is consistent with the incidence in general surgical practice. In all cases, either an alternative cause or a reasonable explanation for the development of renal dysfunction was available.

Children

Some published studies in children have reported cognitive deficits following repeated or prolonged exposure to anesthetic agents early in life. These studies have significant limitations and it remains unclear whether the effects observed were due to the anesthetic/sedative agents or to other factors such as surgery or underlying disease. Furthermore, these findings have not been confirmed in later published registration studies. Published animal studies investigating some anesthetic/sedative agents have reported adverse effects on brain development early in life (see “Preclinical safety data” below).

Patients with hepatic impairment

In clinical studies, sevoflurane was effective and well tolerated when used as the primary agent for maintenance of anesthesia in patients with Child-Pugh Class A and B hepatic impairment. Sevoflurane did not

worsen pre-existing hepatic impairment. For hepatic adverse reactions observed in post-marketing studies, see sections 4.4 and 4.8.

Patients with renal impairment

The effects of sevoflurane were evaluated in patients with renal impairment with serum creatinine ≥ 1.5 mg/dL (130 µmol/L). Based on the frequency and magnitude of changes in creatinine concentration, sevoflurane did not impair renal function.

Pharmaceutical characteristics

Formula for calculating saturated vapor pressure: Log10 Pvapor = A + B/T,

where A = 8.086,

B = –1726.68,

T = °C + 273.16 °K (temperature on the Kelvin scale).

Partition coefficients at 37 °C:

water/gas 0.36

blood/gas 0.63–0.69

olive oil/gas 47.2–53.9

brain/gas 1.15

Average component/gas partition coefficients at 25 °C for polymers used for medical purposes:

electrically conductive rubber 14.0

butyl rubber 7.7

polyvinyl chloride 17.4

polyethylene 1.3

Sevoflurane is a non-flammable, non-explosive liquid that is administered by inhalation of the vaporized liquid using a vaporizer. Sevoflurane is chemically stable. No appreciable chemical decomposition occurs in the presence of strong acids or elevated temperatures.

Degradation of Sevoflurane

Sevoflurane is stable when stored under normal room light. No significant degradation occurs in the presence of strong acids or heat. Sevoflurane is not corrosive to stainless steel, brass, aluminum, nickel-plated copper, chromium-plated copper, or copper-beryllium alloy. Chemical degradation may occur due to the anesthetic being exposed to the CO2 absorbent of the anesthesia machine. When fresh absorbents are used, degradation of sevoflurane is minimal and the degradation products are undetectable or nontoxic. Degradation of sevoflurane and subsequent formation of degradation products are enhanced by increasing the temperature of the absorbent, drying of the CO2 absorbent (especially that containing potassium hydroxide, e.g. Baralyme®), increasing the concentration of sevoflurane, and decreasing the fresh gas flow. Sevoflurane can undergo alkaline degradation in two ways. The first way is through the loss of hydrogen fluoride to form compound A. The second way of degradation occurs only in the presence of a dry CO2 absorbent and results in the dissociation of sevoflurane to HFIP and formaldehyde. HFIP is an inactive, non-genotoxic substance that is rapidly glucuronized and excreted, and is comparable in toxicity to sevoflurane. Formaldehyde is present in normal metabolic processes. When used with a very dry absorbent, formaldehyde can decompose to methanol and formate. Formate (residual formic acid) can contribute to the formation of

carbon monoxide at high temperature. Methanol can react with compound A to form compound B. Compound B is subject to further HF-elimination to form compounds C, D, E. When using very dry absorbents, especially those containing potassium hydroxide (e.g. Baralyme®), formaldehyde, methanol, carbon monoxide, compound A and some of its degradants, compounds B, C and D, may be formed.

Lewis acid degradation

The formulation contains at least 0.3‰ of water as a Lewis acid inhibitor. No other chemical stabilizers are used.

Preclinical safety data

Animal studies have shown that hepatic and renal circulation are well preserved with sevoflurane.

Sevoflurane reduces cerebral oxygen metabolism (CMRO2) in a manner similar to that observed with isoflurane. CMRO2 is reduced by approximately 50% at sevoflurane concentrations approaching

2.0 MAC. Animal studies have shown that sevoflurane has no significant effect on cerebral blood flow.

In animals, sevoflurane significantly suppresses electrical brain activity (as measured by electroencephalography (EEG)), comparable to that seen with equivalent doses of isoflurane. There is no evidence that sevoflurane is associated with epileptiform activity under normocapnic or hypocapnic conditions. In contrast to enflurane, attempts to elicit seizure-like EEG activity during hypocapnic conditions using rhythmic auditory stimuli have not been successful. Compound A was minimally nephrotoxic at concentrations of 50–114 ppm for 3 hours in a series of rat studies. Toxicity was characterized by sporadic single-cell necrosis of proximal tubular cells. The mechanism of this renal toxicity in rats is unknown and its relevance to humans has not been established. In humans, the comparative threshold for nephrotoxicity associated with Compound A is predicted to be 150–200 ppm. Concentrations of Compound A reported in clinical practice average 19 ppm in adults (maximum 32 ppm) when soda lime is used as a CO2 absorbent.

Published studies in pregnant and juvenile animals indicate that the use of anesthetics and sedatives that block NMDA (N-methyl-D-aspartate) receptors and/or enhance GABA (gamma-aminobutyric acid) activity during periods of rapid brain growth or synaptogenesis may result in desensitization of neuronal and oligodendrocyte cells in the developing brain and changes in synaptic morphology and neurogenesis when used for more than 3 hours. These studies included anesthetic agents from different drug classes. The clinical significance of these nonclinical data is still being determined (see Pharmacodynamics section).

Clinical characteristics.

Indications.

Induction and maintenance of general anesthesia in adult and pediatric patients for inpatient and outpatient procedures.

Contraindications.

Known or suspected hypersensitivity to sevoflurane or other halogenated anesthetics (e.g., history of unexplained liver dysfunction, usually with elevated liver enzymes, fever, leukocytosis, and/or eosinophilia, following administration of halogenated anesthetics).

- Known or suspected genetic predisposition to malignant hyperthermia.
- If general anesthesia is contraindicated.

Interaction with other medicinal products and other forms of interaction.

During sevoflurane anaesthesia, beta-sympathomimetics such as isoprenaline and alpha- and beta-sympathomimetics such as adrenaline and noradrenaline should be used with caution due to the potential risk of ventricular arrhythmia.

Non-selective monoamine oxidase inhibitors (MAOIs). There is a risk of a crisis during surgery. It is generally recommended to discontinue MAOI therapy 2 weeks before surgery.

Sevoflurane may cause marked hypotension in patients treated with calcium channel antagonists, particularly dihydropyridine derivatives.

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

Concomitant use of succinylcholine and inhalational anesthetics has been associated with an increase in serum potassium levels, resulting in cardiac arrhythmias and death in pediatric patients during the postoperative period.

As with other drugs, lower concentrations of sevoflurane may be required following the use of an intravenous anesthetic such as propofol.

Sevoflurane is safe and effective when administered with drugs commonly used in surgical practice, such as central nervous system agents, autonomic nervous system depressants, muscle relaxants, antimicrobials including aminoglycosides, hormones, synthetic substitutes, blood derivatives, and cardiovascular drugs including epinephrine.

Epinephrine/Adrenaline. Sevoflurane, like isoflurane, increases myocardial sensitivity to the arrhythmogenic effect of exogenously administered adrenaline.

Indirect-acting sympathomimetics. When sevoflurane interacts with sympathomimetics (amphetamine, ephedrine), there is a risk of developing acute hypertensive episodes.

Beta-blockers. Sevoflurane may increase the negative inotropic, chronotropic and dromotropic effects of beta-blockers (by blocking cardiovascular compensatory mechanisms).

Verapamil. Atrioventricular conduction disorders have been observed with the simultaneous use of verapamil with sevoflurane.

St. John's wort. Cases of severe hypotension and delayed recovery from anesthesia have been reported in patients who have taken St. John's wort for a long time.

Barbiturates. Sevoflurane is compatible with barbiturates, which are widely used in surgical practice.

Benzodiazepines and opioids. A decrease in the minimum alveolar concentration (MAC) of sevoflurane is expected, as with other inhalational anesthetics. Sevoflurane is compatible with benzodiazepines and opioids commonly used in surgical practice. The use of opioids such as alfentanil and sufentanil in combination with sevoflurane may result in synergistic decreases in heart rate, blood pressure and respiratory rate.

CYP2E1 inducers. Drugs and compounds that increase the activity of the 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 section 5.1). Concomitant use of sevoflurane and isoniazid may potentiate the hepatotoxic effects of isoniazid.

Nitrous oxide. As with other inhalation anesthetics, the MAC of sevoflurane is reduced (by 50% in adults and 25% in children).

Neuromuscular blocking agents. As with other inhalation anesthetics, sevoflurane affects both the intensity and duration of neuromuscular blockade induced by non-depolarizing neuromuscular blocking agents.

In cases of additional alfentanil-N2O anesthesia, sevoflurane enhances neuromuscular blockade induced by pancuronium, vecuronium, atracurium. Dose adjustments for these neuromuscular blocking agents when administered with sevoflurane are similar to those required for isoflurane. The effect of sevoflurane on succinylcholine and the duration of action of depolarizing neuromuscular blocking agents have not been studied.

Reducing the dose of neuromuscular blocking agents during induction of anesthesia may delay the time to tracheal intubation or result in inadequate muscle relaxation, as potentiation of the action of muscle relaxants occurs within minutes of the start of sevoflurane administration.

Interactions with non-depolarizing neuromuscular blocking agents such as pancuronium, vecuronium, atracurium have been studied. Unless otherwise indicated, the dose of non-depolarizing muscle relaxants should not be reduced for endotracheal intubation; the dose of non-depolarizing muscle relaxants should be reduced during maintenance of anesthesia, as in N2O-opioid anesthesia. Additional doses of muscle relaxants should be administered only after assessment of the response to neurostimulation.

A significant increase in plasma fluoride concentrations was observed after increasing CYP 2E1 activity.

Special precautions for use.

Sevoflurane may cause respiratory depression, which is exacerbated by premedication with narcotics or other drugs that cause respiratory depression.

Breathing should be monitored and emergency medical care should be sought if necessary.

Sevoflurane should only be administered by persons trained in general anesthesia. Equipment for maintaining a patent airway, providing artificial ventilation, oxygenation, and reperfusion must be available. The concentration of sevoflurane delivered from the vaporizer must be accurately known. Since volatile anesthetics have different physical properties, only vaporizers specifically calibrated for sevoflurane should be used. The use of general anesthesia should be individualized based on the patient's response to anesthesia. Hypotension and respiratory depression increase with increasing anesthesia.

There have been isolated reports of QT prolongation, very rarely associated with torsades de pointes, which in exceptional cases have been fatal. Sevoflurane should be used with caution in patients predisposed to this condition.

Isolated cases of ventricular extrasystoles have been reported in children with Pompe disease.

General anaesthesia, including sevoflurane, should be used with caution in patients with mitochondrial disorders.

All patients undergoing anaesthesia with sevoflurane should be monitored closely, including electrocardiogram (ECG), blood pressure, oxygen saturation and end-tidal CO2. The presence of concomitant risk factors should be considered.

During maintenance of anaesthesia, increasing sevoflurane concentrations result in a dose-dependent decrease in blood pressure. Excessive hypotension may be related to the depth of anesthesia and can be corrected by reducing the inhaled concentration of sevoflurane. Special care should be taken when selecting the dose in patients with hypovolemia, hypotension, or other hemodynamic compromise, e.g., due to concomitant medications. As with any anesthetic agent, it is important to maintain hemodynamic stability in patients with ischemic heart disease to prevent myocardial ischemia.

Recovery from anesthesia should be carefully assessed before the patient is discharged from the recovery room.

Although recovery from sevoflurane usually occurs within minutes, the effect on intellectual performance for 2 to 3 days following anesthesia has not been studied. As with other anaesthetics, slight mood changes may occur for a few days after anaesthesia (see section 4.8).

Sevoflurane should be used with caution in obstetric anaesthesia as the uterine relaxant effect may increase the risk of uterine bleeding (see section 4.8).

Hepatic impairment

Very rare cases of mild, moderate and severe postoperative hepatic impairment or hepatitis with or without jaundice have been reported in post-marketing studies. Clinical judgment should be exercised when administering sevoflurane to patients with underlying hepatic impairment or with medicinal products known to cause hepatic impairment (see section 4.8).

It has been reported that previous use of halogenated hydrocarbon anaesthetics may increase the risk of hepatic injury, particularly if the interval between administrations is less than 3 months.

Malignant hyperthermia

In susceptible individuals, potent inhalational anaesthetics may induce a musculoskeletal hypermetabolic state, resulting in increased oxygen demand and the development of a clinical syndrome known as malignant hyperthermia. This clinical syndrome is characterized by hypercapnia and may include nonspecific signs such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmia, and/or unstable blood pressure (some of these symptoms may also occur with superficial anesthesia, acute hypoxia, hypercapnia, and hypovolemia).

One case of malignant hyperthermia has been reported in clinical trials. Malignant hyperthermia has also been observed in postmarketing studies. In some cases, fatalities have been reported.

Treatment of malignant hyperthermia includes discontinuation of initiating agents (e.g., sevoflurane), intravenous administration of dantrolene sodium (see the dantrolene sodium SPC), and supportive care consisting of vigorous measures to normalize body temperature, maintain respiratory and circulatory function, and correct fluid and electrolyte imbalances.

Renal failure may develop later, so diuresis should be monitored and maintained if possible.

Perioperative hyperkalemia

The use of inhalation anesthetics has been associated with rare cases of elevated plasma potassium, which may manifest as arrhythmias. There have been fatalities in children in the postoperative period. Patients with latent or overt neuromuscular diseases, especially Duchenne neuromuscular dystrophy, are particularly susceptible. In most of these cases, succinylcholine was used concomitantly. These patients also had marked increases in plasma creatine phosphokinase (CPK) levels, and in some cases myoglobinuria. Although these manifestations are similar to malignant hyperthermia, no patient had signs or symptoms of muscle rigidity or a hypermetabolic state. Early and intensive correction of hyperkalemia and treatment of resistant arrhythmias are recommended, followed by examination for latent neuromuscular diseases.

Patients with renal impairment

Due to the small number of patients with renal impairment studied [baseline serum creatinine above 133 µmol/L (1.5 mg/dL)], the safety of sevoflurane in this group has not been fully established. Therefore, sevoflurane should be administered with caution to patients with renal impairment.

When sevoflurane comes into direct contact with CO2 absorbents, a small amount of Compound A (pentafluoroisopropenylfluoromethyl ether (PFE)) and a small amount of Compound B (pentafluoromethoxyisopropylfluoromethyl ether (PMFE)) are formed. Compound A levels increase with increasing canister temperature, increasing anesthetic concentration, decreasing gas flow rate, and are increased more with potassium hydroxide (e.g., Baralyme®) than soda lime.

Compound A concentrations reported in clinical practice average 19 ppm in adults (maximum 32 ppm) with soda lime as the CO2 absorbent.

Although the exposure of sevoflurane in low-flow systems is limited, there is no evidence of renal impairment associated with the compound. A.

Neurosurgery

Sevoflurane should be used with caution in patients at risk of increased intracranial pressure and measures to reduce intracranial pressure, such as hyperventilation, should be used.

Seizures

Seizures have been reported rarely with sevoflurane (see sections 4.4 and 4.8).

There has been an association between sevoflurane and seizures, which have been observed in children and young patients, as well as in elderly patients, with and without risk factors for seizures. Clinical assessment of the risk of seizures in patients with risk factors should be considered before sevoflurane is administered. Depth of anaesthesia should be limited in children. EEG monitoring may help to optimise the dose of sevoflurane and help to avoid seizures in patients predisposed to them.

Children.

Seizures have been associated with the use of sevoflurane. Many of these have occurred in children as young as two months of age and young adults, most of whom had no risk factors for seizures. Clinical judgment should be exercised when using sevoflurane in patients who may be at risk for seizures (see section 4.8).

Bradycardia in Down syndrome

Episodes of severe bradycardia and cardiac arrest, not associated with congenital heart disease, have been reported during induction of anesthesia with sevoflurane in children with Down syndrome. In most cases, bradycardia improved with decreasing sevoflurane concentrations, airway manipulation, or administration of anticholinergics or adrenaline.

Monitor heart rate closely during induction and consider gradually increasing the inspired sevoflurane concentration until adequate anesthesia is achieved. Consider anticholinergics and epinephrine when administering sevoflurane for induction in this patient group.

Replacement of dried CO2 absorbents

Rare cases of excessive heat, smoke, and/or spontaneous combustion in the anesthesia machine have been reported when sevoflurane is used in conjunction with the use of dried CO2 absorbents, particularly those containing potassium hydroxide (e.g., Baralyme®). An unusually slow rise or unexpected decrease in the inspired sevoflurane concentration compared to the vaporizer setting may be due to excessive heating of the CO2 absorbent canister.

An exothermic reaction, increased decomposition of sevoflurane, and formation of degradation products may occur when the CO2 absorbent becomes desiccated, such as after prolonged periods of dry gas flow through CO2 absorbent canisters. Sevoflurane degradation products (methanol, formaldehyde, carbon monoxide, and compounds A, B, C, and D) were observed in the breathing circuit of an experimental anesthesia machine using dried CO2 absorbents and maximum sevoflurane concentrations (8%) for extended periods of time (≥ 2 hours). The formaldehyde concentrations observed in the anesthesia breathing circuit (using absorbents containing sodium hydroxide) were within levels known to cause mild respiratory irritation. The clinical significance of the degradation products observed in this extreme experimental model is unknown. The following are clinical manifestations that have been reported in association with these rare cases: failed induction of anesthesia or insufficient level of anesthesia with sevoflurane; signs of airway irritation in the patient, such as coughing, oxygen starvation, increased airway pressure, labored breathing, marked edema and hyperemia of the airways, and increased carboxyhemoglobin levels.

If excessive heating of the CO2 absorbent canister is observed, the clinical situation should be assessed and the patient should be considered for weaning from anesthesia.

If the healthcare professional suspects that the CO2 absorbent has dried out, it should be replaced before further use of volatile anesthetics (such as sevoflurane). It should be noted that the color indicator does not always change after drying. Therefore, the absence of a significant color change should not be taken as a

guarantee of adequate hydration. CO2 absorbents should be replaced regularly regardless of the color indicator.

Anaesthesia machines should be completely switched off after use, the integrity of the packaging of new CO2 absorbents should be checked before use, and the temperature of CO2 absorbent canisters should be monitored during use.

Use during pregnancy or breastfeeding.

Pregnancy

There are no adequate and well-controlled studies of sevoflurane in pregnant women, and it should be used during pregnancy only if clearly indicated.

Animal studies have been published with some anaesthetics/sedatives that have reported adverse effects on early brain development (see section 5.1).

The safety of sevoflurane for the mother and neonate has been demonstrated in clinical studies during caesarean section. Safety during labour has not been studied.

Sevoflurane, like other inhalation agents, has a relaxing effect on the uterus with a potential risk of uterine bleeding, as reported in a study of its use during termination of pregnancy. Use during labour is limited to one small study in caesarean section. Clinical judgment should be exercised when using sevoflurane during obstetric anesthesia.

Breastfeeding

It is not known whether sevoflurane or its metabolites are excreted in human milk. In the absence of documented experience, breastfeeding should be discontinued for 48 hours after administration of sevoflurane.

Fertility

Animal studies have not shown any evidence of impaired fertility when sevoflurane is administered at doses up to 1 MAC.

Ability to influence the speed of reactions when driving or using other mechanisms.

As with other drugs, patients should be warned that the performance of tasks requiring mental alertness, such as driving or operating dangerous machinery, may be impaired for some time after general anesthesia (see section 4.4).

After anesthesia with sevoflurane, patients should not drive or operate machinery for a period of time to be determined individually by the physician.

Method of administration and dosage.

Sevoflurane should be administered using a vaporizer specifically calibrated for the use of sevoflurane so that the concentration delivered can be precisely controlled.

Induction

The dose should be individualized and titrated to the desired effect according to the age and clinical status of the patient. A short-acting barbiturate or other intravenous agent may be administered for induction, followed by inhalation of sevoflurane. Sevoflurane may be administered in oxygen or in a mixture of oxygen and nitrous oxide for induction.

In adults, inhalation of sevoflurane at concentrations up to 5% usually produces surgical anesthesia in less than 2 minutes. In children, inhalation of sevoflurane at concentrations up to 7% usually produces surgical anesthesia in less than 2 minutes.

Alternatively, inhalation of sevoflurane at concentrations up to 8% can be used for induction in patients who have not received premedication.

Maintenance

Surgical anesthesia can be maintained with concentrations of 0.5% to 3% sevoflurane with or without nitrous oxide (see Interactions with other medicinal products and other forms of interaction).

The MAC of sevoflurane decreases with age and with the addition of nitrous oxide. The average sevoflurane concentration required to achieve MAC in patients aged 80 years is approximately 50% of that required in patients aged 20 years.

The table shows the average MAC values for different age groups.

MAC of sevoflurane for adults and children depending on the patient's age		
Age of patients	Sevoflurane in oxygen	Sevoflurane in 65% N2O/35% O2*
0–1 month**	3,3 %	2,0 %
1 month – < 6 months	3,0 %	
6 months – < 3 years	2,8 %	
3–12 years	2,5 %	
25 years	2,6 %	1,4 %
40 years	2,1 %	1,1 %
60 years	1,7 %	0,90 %
80 years	1,4 %	0,70 %

* For children aged 1 – < 3 years, 60% N2O/40% O2 was used.

** Term neonates. The MAC has not been determined in preterm neonates.

Recovery from anaesthesia

After sevoflurane anaesthesia, recovery time is usually short. Therefore, patients may require early post-operative analgesia.

Any unused medicinal product or residues should be disposed of in accordance with local requirements.

Children.

Sevoflurane can be used in term neonates from birth.

Overdose.

In the event of overdose (respiratory and cardiac depression), the following measures should be taken: discontinue administration, establish a patent airway, initiate artificial assisted or controlled ventilation with oxygen and maintain adequate cardiovascular function.

Adverse reactions.

As with all potent inhalation anesthetics, sevoflurane may cause dose-dependent respiratory and cardiac depression. Most adverse reactions are mild to moderate in severity and transient. Postoperative nausea, vomiting, and delirium are common and are often secondary to surgery and general anesthesia and may be related to the inhalation anesthetic, other drugs administered intra- or postoperatively, and the patient's response to the surgical procedure; the incidence is similar to that seen with other inhalation anesthetics.

Adverse reactions observed in patients during clinical trials

Adverse reactions are listed by system organ class and frequency (more than 10% - very common, 1-10% - common, 0.1-1% - uncommon, 0.1-0.01% - rare, less than 0.01% - very rare, including isolated reports), frequency unknown (cannot be estimated from the available data).

In adult patients, nausea, vomiting, hypotension were very common; in elderly patients - hypotension, nausea, bradycardia; in children, nausea, vomiting, agitation, cough may occur very often. The type, severity and frequency of adverse reactions in patients treated with sevoflurane are the same as in patients treated with other anesthetic agents.

Blood and lymphatic system disorders

Uncommon: leukopenia, leukocytosis.

Psychiatric disorders

Very common: agitation

Uncommon: confusion

Neurological disorders

Common: dizziness, somnolence, headache

Cardiac disorders

Very common: bradycardia

Common: tachycardia

Uncommon: complete atrioventricular block, atrial fibrillation, arrhythmia, ventricular extrasystoles, supraventricular extrasystoles, extrasystoles

Frequency unknown: QT prolongation associated with torsade de pointes

Vascular disorders

Very common: hypotension

Common: hypertension

Respiratory, thoracic and mediastinal disorders

Very common: cough

Common: respiratory distress, laryngospasm

Uncommon: apnoea, hypoxia, asthma

Gastrointestinal disorders

Very common: nausea, vomiting

Common: hypersalivation

Urinary disorders

Uncommon: urinary retention, glycosuria

General disorders

Common: chills, fever, hypothermia

Laboratory investigations

Common: changes in serum glucose levels, changes in liver function tests5, increases in ALT, AST, changes in white blood cell count, transient increases in serum inorganic fluorides1

Uncommon: increases in creatinine, lactate dehydrogenase

Injuries, poisoning and procedural complications

Common: hypothermia

Post-marketing experience with sevoflurane

Adverse reactions have been reported from spontaneous reporting, frequency and causality cannot be established.

Immune system disorders: anaphylactic reactions1, hypersensitivity1, anaphylactoid reactions.

Neurological disorders: convulsions2, 3, muscular dystonia.

Cardiac disorders: cardiac arrest4, QT prolongation associated with torsade de pointes, bradycardia in patients with Down syndrome.

Respiratory, thoracic and mediastinal disorders: dyspnoea1, wheezing1, bronchospasm, pulmonary oedema, apnoea.

Urinary disorders: acute renal failure.

Hepatobiliary disorders: hepatitis1, 2, hepatic failure1, 2, hepatic necrosis1, 2.

Skin and subcutaneous tissue disorders: rash1, contact dermatitis1, facial oedema1, urticaria, pruritus.

General disorders: chest discomfort1, malignant hyperthermia.

Musculoskeletal disorders: muscle twitching.

1 See section “Adverse reactions. Description of selected adverse reactions”.

2 See section “Special warnings and precautions for use”.

3 See section “Adverse reactions. Children”.

4 Very rare cases of cardiac arrest have been reported with sevoflurane.

5 Transient changes in liver function tests have been observed in rare cases with sevoflurane and similar drugs.

Description of selected adverse reactions

Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anaesthesia. Inorganic fluoride concentrations usually peak 2 hours after the end of sevoflurane anaesthesia and return to preoperative levels within 48 hours; elevated fluoride concentrations were not associated with deterioration of renal function in clinical studies.

Rare cases of hepatitis have been reported in the postoperative period. In addition, there have been rare post-marketing reports of hepatic failure and hepatic necrosis associated with the use of potent volatile anaesthetics, including sevoflurane, although the association with sevoflurane has not been conclusively established (see section 4.4).

Rare cases of hypersensitivity (including contact dermatitis, rash, dyspnoea, wheezing, chest discomfort, facial oedema or anaphylactic reaction) have been reported, particularly with prolonged use of inhalation anaesthetics, including sevoflurane.

In susceptible individuals, potent inhalation anaesthetics may induce a musculoskeletal hypermetabolic state, resulting in increased oxygen demand and the development of a clinical syndrome known as malignant hyperthermia (see section 4.4).

Children

Sevoflurane has been associated with convulsions. Many of these have occurred in children as young as two months of age and young adults, most of whom had no risk factors for seizures. Clinical judgment should be exercised when using sevoflurane in patients who may be at risk of seizures (see section 4.4).

Reporting of adverse reactions

Reporting adverse reactions after the registration of a medicinal product is important. This allows monitoring of the benefit/risk ratio of this medicinal product. Healthcare professionals, as well as patients or their legal representatives, should report all suspected adverse reactions and lack of efficacy of the medicinal product via the Automated Pharmacovigilance Information System at the following link: https://aisf.dec.gov.ua.

Shelf life. 2 years.

Storage conditions.

Keep out of reach of children. Store at a temperature not exceeding 25 °C in the original packaging. Do not freeze.

Packaging.

250 ml in aluminum bottles, hermetically sealed with U-Fill adapters for contactless vaporizer refilling. 1 bottle in a cardboard box.

Release category. By prescription.

Manufacturer.

LLC "Yuria-Pharm".

Location of the manufacturer and address of its place of business.

Ukraine, Cherkasy region, Cherkasy city, Kobzarska st., 108. Tel.: (044) 281-01-01.