# PROFESSIONAL INFORMATION

**SCHEDULING STATUS S5**

## 1. NAME OF THE MEDICINE

SEVOFLURANE BAXTER (Liquid for inhalation)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sevoflurane 100 %.

Excipient with known effect: None

SEVOFLURANE BAXTER is comprised only of the active substance (see section 6.1).

## 3. PHARMACEUTICAL FORM

SEVOFLURANE BAXTER is a clear, colourless liquid for inhalation.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

SEVOFLURANE BAXTER is indicated for induction and maintenance of general anaesthesia in adult and paediatric patients for inpatient and outpatient surgery.

### 4.2 Posology and method of administration

**Posology**

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

Surgical anaesthesia:

The concentration of SEVOFLURANE BAXTER being delivered from a vaporiser during anaesthesia should be known. This may be accomplished by using a vaporiser calibrated specifically for SEVOFLURANE BAXTER.

*Anaesthesia induction:*

Dosage should be individualised and titrated to the desired effect according to the patient's age and clinical status.

A short acting intravenous induction medicine may be administered, followed by inhalation of SEVOFLURANE BAXTER.

Induction with SEVOFLURANE BAXTER may be achieved in oxygen or in combination with oxygen-nitrous oxide mixtures. Inspired concentrations of up to 8 % SEVOFLURANE BAXTER usually produce surgical anaesthesia in less than 2 minutes in both adults and children.

*Maintenance of anaesthesia:*

Surgical levels of anaesthesia may be maintained by inhalation of 0,5 - 3 % SEVOFLURANE BAXTER in $O_2$ with or without concomitant use of nitrous oxide.

**Table 1**

**MAC values in Adults and Paediatric Patients According to Age**

| Age of patient (years) | Sevoflurane in oxygen | Sevoflurane in 65 % $N_2O$ / 35 % $O_2$ |
|---|---|---|
| 0 – 1 month* | 3,3 % | |
| 1 – < 6 months | 3,0 % | |
| 6 months – < 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 % |

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|---|
| * Neonates are full-term gestational age. MAC in premature infants has not been determined. |
| ** In 3 – < 5 year old paediatric patients, 60 % $N_2O$/40 % $O_2$ was used. |

*Emergence:*

Emergence times are generally short following SEVOFLURANE BAXTER anaesthesia. Therefore, patients may require post-operative pain relief earlier.

**Special populations**

*Elderly:*

Lesser concentrations of SEVOFLURANE BAXTER are normally required to maintain surgical anaesthesia.

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

*Paediatric population:*

Refer to Table 1 for MAC values for paediatric patients according to age when used in oxygen with or without concomitant use of nitrous oxide.

**4.3 Contraindications**

SEVOFLURANE BAXTER should not be used in patients with known or suspected hypersensitivity to sevoflurane or to other halogenated anaesthetics (e.g. history of liver function disorder, fever or leucocytosis of unknown cause after anaesthesia with one of these medicines).

SEVOFLURANE BAXTER should not be used in patients with a history of confirmed hepatitis due to a halogenated inhalational anaesthetic or a history of unexplained moderate to severe hepatic dysfunction with jaundice, fever and eosinophilia after anaesthesia with sevoflurane.

SEVOFLURANE BAXTER should not be used in patients with known or suspected genetic susceptibility to malignant hyperthermia (see section 4.4).

SEVOFLURANE BAXTER should not be used in patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy (see section 4.4).

SEVOFLURANE BAXTER is contraindicated in patients in whom general anaesthesia is contraindicated.

**4.4 Special warnings and precautions for use**

General

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

SEVOFLURANE BAXTER should be administered only by persons trained in the administration of general anaesthesia. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and circulatory resuscitation must be immediately available. All patients anaesthetised with SEVOFLURANE BAXTER should be constantly monitored, including electrocardiogram (ECG), blood pressure (BP), oxygen saturation and end tidal carbon dioxide ($CO_2$).

The concentration of SEVOFLURANE BAXTER 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 anaesthesia is deepened.

During maintenance of anaesthesia, increasing the SEVOFLURANE BAXTER concentration results in dose-dependent decreases in blood pressure. An excessive reduction in blood pressure may be related to depth of anaesthesia and in such instances may be corrected by decreasing the inspired concentration of SEVOFLURANE BAXTER. Due to sevoflurane’s insolubility in blood, hemodynamic changes may occur more rapidly than with some other volatile anaesthetics. Particular care must be taken when selecting the dosage for hypovolaemic, hypotensive, weakened patients or otherwise

hemodynamically compromised, e.g., due to concomitant medications. Recovery from general anaesthesia should be assessed carefully before patients are discharged from the post-anaesthesia care unit.

Emergence is generally rapid following SEVOFLURANE BAXTER anaesthesia; therefore, patients may require early postoperative pain relief.

Although recovery of consciousness following SEVOFLURANE BAXTER administration generally occurs within minutes, the impact on intellectual function for two or three days following anaesthesia has not been studied. As with other anaesthetics, small changes in moods may persist for several days following administration.

Patients should be advised that performance of activities requiring mental alertness, such as driving of a motor vehicle or operating hazardous machinery, may be impaired for up to days after general anaesthesia (see section 4.7). Patients should be advised not to take any legal/contractual decisions for 24 hours after receiving anaesthetic. Alcohol should also be avoided for the same time period.

Patients with coronary disease

As with all anaesthetics, maintenance of haemodynamic stability is important in order to avoid myocardial ischaemia in patients with coronary artery disease.

Patients undergoing obstetrical procedures

Caution should be exercised in obstetric anaesthesia due to the relaxant effect of SEVOFLURANE BAXTER on the uterus and increase in uterine haemorrhage (see section 4.6).

Patients undergoing neurosurgical procedures

In patients at risk for elevations of an increase in intracranial pressure, SEVOFLURANE BAXTER should be administered cautiously in conjunction with intracranial pressure reducing measures such as hyperventilation.

Seizures

Cases of seizures have been reported in association with sevoflurane use.

Use of sevoflurane has been associated with seizures occurring in children and young adults as well as older adults with and without predisposing risk factors. Clinical judgement is necessary before SEVOFLURANE BAXTER is used in patients at risk of seizures. In children the depth of anaesthesia should be limited. EEG may permit the optimization of the SEVOFLURANE BAXTER dose and help avoid the development of seizure activity in patients with a predisposition for seizures (see section 4.4 – Paediatric population).

Replacement of dried-out $CO_2$ absorbents

The exothermic reaction between sevoflurane and $CO_2$ absorbent is reinforced when the $CO_2$ absorbent is dried out, e.g. after a longer period with current of dry gas over the bottle with $CO_2$ absorbent. Rare cases have been reported of extreme heat, smoke and/or spontaneous fire from the anaesthesia vaporiser during use of sevoflurane together with dried-out $CO_2$ absorbent, specifically those containing potassium hydroxide. An unexpected delay in increase of inspired concentration of SEVOFLURANE BAXTER or an unexpected decrease of inspired concentration of SEVOFLURANE BAXTER compared with the setting of the vaporiser may be a sign of overheating of the $CO_2$ absorbent bottle.

An exothermic reaction, enhanced sevoflurane degradation, and production of degradation products can occur when the $CO_2$ absorbent becomes desiccated, such as after an extended period of dry gas flow through the $CO_2$ absorbent canisters. Sevoflurane degradants (methanol, formaldehyde, carbon monoxide, and Compounds A, B, C, and D - Compound A is pentafluoroisopropanyl fluoromethyl ether, Compound B is the methoxy addition product formed after reaction of Compound A with methanol, and Compound B can undergo further HF elimination to form Compounds C, D and E) were observed in the respiratory circuit of an experimental anaesthesia machine using desiccated $CO_2$ absorbents and maximum sevoflurane concentrations (8 %) for extended periods of time (≥ 2 hours). Concentrations of formaldehyde observed at the anaesthesia 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.

If the treating doctor suspects the $CO_2$ absorbent to be dried-out, this must be replaced before the administration of SEVOFLURANE BAXTER. The colour indicator on most $CO_2$ absorbents does not necessarily change when dried-out. Therefore, the absence of marked changed of colour should not be taken as a secure sign of sufficient hydration. $CO_2$ absorbents must be replaced regularly irrespective of the colour indicator (see section 6.6).

Patients with renal injury

Although data from controlled clinical studies at low flow rates are limited, findings taken from patient and animal studies suggest there is a potential for renal injury, which is presumed due to Compound A. Animal and human studies demonstrate that sevoflurane administered for more than 2 MAC hours and at fresh gas flow rates of < 2 l/min may be associated with proteinuria and glycosuria (see section 5.1).

The level of Compound A exposure at which clinical nephrotoxicity might be expected to occur has not been established. Consider all of the factors leading to Compound A exposure in humans, especially duration of exposure, fresh gas flow rate, and concentration of sevoflurane.

Inspired SEVOFLURANE BAXTER concentration and fresh gas flow rate should be adjusted to minimize exposure to Compound A. SEVOFLURANE BAXTER exposure should not exceed 2 MAC hours at flow rates of 1 to < 2 l/min. Fresh gas flow rates <1 l/min are not recommended.

Patients with renal impairment

The safety of sevoflurane in patients with renal insufficiency (baseline serum creatinine greater than 15 mg/l (133 µmol/l)) has not yet been fully established. SEVOFLURANE BAXTER should therefore be administered with caution to patients with impaired renal function (GFR ≤ 60 ml/min) and renal function should be monitored postoperatively.

Patients with liver disease

Cases of mild, moderate or serious post-operative liver dysfunction or hepatitis (with or without jaundice) have been reported from post marketing experience. Caution should be exercised when

SEVOFLURANE BAXTER is used in patients with underlying liver problems or those who are receiving treatment with medicines known to cause liver dysfunction. In patients who have experienced hepatic injury, jaundice, unexplained fever or eosinophilia after administration of other inhalation anaesthetics, it is recommended to avoid administration of SEVOFLURANE BAXTER if anaesthesia with intravenous medicines or regional anaesthesia is possible (see section 4.8).

Patients with repeated exposures to halogenated hydrocarbons, including sevoflurane, within a relatively short interval may have an increased risk of hepatic injury.

Patients with mitochondrial disorders

Caution should be exercised in administering general anaesthesia, including SEVOFLURANE BAXTER, to patients with mitochondrial disorders.

Hypersensitivity

Reports of hypersensitivity (including contact dermatitis, rash, dyspnoea, wheezing, chest discomfort, swelling face or anaphylactic reaction) have been received, including cases of association with long-term occupational exposure to sevoflurane (see section 4.3 and 4.8).

Malignant hyperthermia

In susceptible individuals, SEVOFLURANE BAXTER may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. Rare cases of malignant hyperthermia have been reported with the use of sevoflurane (see also section 4.8). The clinical syndrome is signalled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnoea, cyanosis, dysrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anaesthesia, acute hypoxia, hypercapnia and hypovolemia. Fatal outcome of malignant hyperthermia has been reported with sevoflurane.

Treatment includes discontinuation of triggering medicines (e.g. sevoflurane), administration of intravenous dantrolene sodium, 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 production should be monitored and sustained if possible.

Perioperative hyperkalaemia

Use of inhaled anaesthetic medicines, including sevoflurane, has been associated with rare increases in serum potassium levels that have resulted in cardiac dysrhythmias and death in paediatric patients during the postoperative period.

Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable (see section 4.3). 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 hyperkalaemia and resistant dysrhythmias is recommended, as is subsequent valuation for latent neuromuscular disease.

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|---|
| 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 BAXTER to susceptible patients (see section 4.8). |

**Paediatric population**

The use of sevoflurane has been associated with seizures. Many have occurred in children and young adults starting from 2 months of age, most of whom had no predisposing risk factors. Clinical judgement should be exercised when using SEVOFLURANE BAXTER in patients who may be at risk for seizures (see section 4.4 – Seizures).

Rapid emergence in children may briefly evoke a state of agitation and hinder cooperation (in about 25 % of anaesthetised children).

Isolated cases of ventricular dysrhythmias were reported in paediatric patients with Pompe's disease.

Dystonic movements, which disappear without treatment, are seen in children who have received sevoflurane for anaesthesia induction. The relationship to sevoflurane is uncertain.

Down syndrome

A significantly higher prevalence and degree of bradycardia has been reported in children with Down syndrome during and following sevoflurane induction.

**4.5 Interaction with other medicines and other forms of interaction**

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

*Nitrous oxide:*

The minimum alveolar concentration (MAC) of SEVOFLURANE BAXTER is decreased when administered in combination with nitrous oxide. The MAC equivalent is reduced approximately 50 % in adult and approximately 25 % in paediatric patients (see section 4.2 – Maintenance). Altitude may affect the effects of nitrous oxide.

*Neuromuscular blocking medicines:*

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

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

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

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

*Benzodiazepines and opioids:*

Benzodiazepines and opiates are expected to decrease the MAC of sevoflurane to the same manner as other inhaled anaesthetics. SEVOFLURANE BAXTER administration is compatible with benzodiazepines and opioids as commonly used in surgical practice.

Opioids such as fentanyl, alfentanil and sufentanil, when combined with SEVOFLURANE BAXTER, may lead to a synergistic fall in heart rate, blood pressure and respiratory rate.

*Beta blockers:*

SEVOFLURANE BAXTER may increase the negative ionotropic, chronotropic and dromotropic effects of beta blockers through blockade of cardiovascular compensation mechanisms.

*Adrenaline (Epinephrine):*

SEVOFLURANE BAXTER is similar to isoflurane in the sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline (epinephrine), the threshold dose of

adrenaline (epinephrine) producing multiple ventricular dysrhythmias has been established at 5 microgram per kg.

*Inducers of CYP2E1:*

Medicines and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of SEVOFLURANE BAXTER and lead to significant increases in plasma fluoride concentrations. Concomitant use of SEVOFLURANE BAXTER and isoniazid can potentiate the hepatotoxic effects of isoniazid.

*Indirect-acting sympathomimetics:*

There is a risk of acute hypertensive episode with the concomitant use of SEVOFLURANE BAXTER and indirect sympathomimetic medicines (e.g. amphetamines, adrenaline (ephedrine)).

Beta-sympathomimetic medicines like isoprenaline and alpha- and beta- sympathomimetic medicines like adrenaline (epinephrine) and noradrenaline (norepinephrine) should be used with caution during SEVOFLURANE BAXTER narcosis, due to a potential risk of ventricular dysrhythmia.

*Verapamil:*

Atrioventricular impairment of conduction was observed when verapamil and sevoflurane were administered at the same time.

*St John's Wort:*

Severe hypotension and delayed emergence from anaesthesia with halogenated inhalational anaesthetics have been reported in patients treated long-term with St John's Wort.

*Barbiturates:*

SEVOFLURANE BAXTER administration is compatible with barbiturates, propofol and other commonly used intravenous anaesthetics. Lower concentrations of SEVOFLURANE BAXTER may be required following use of an intravenous anaesthetic.

*Non-selective MAO-inhibitors:*

Due to the risk of crisis during the operation; it is generally recommended that treatment should be stopped 2 weeks prior to surgery.

*Calcium antagonists:*

SEVOFLURANE BAXTER may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivatives.

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

*Succinylcholine:*

Concomitant use of succinylcholine with inhaled anaesthetic medicines has been associated with rare increases in serum potassium levels that have resulted in cardiac dysrhythmias and death in paediatric patients during the post-operative period.

**4.6 Fertility, pregnancy and lactation**

*Pregnancy:*

Safety in pregnancy has not been established. There is no or limited data on the use of sevoflurane in pregnant women. SEVOFLURANE BAXTER may be used for anaesthesia during Caesarean section, but only if clearly needed.

Studies in animals have shown that anaesthetics may present with reproductive toxicity, including adverse effects on brain development in early life (see section 5.3).

*Labour and delivery:*

In a clinical trial, the safety of sevoflurane was demonstrated for mothers and infants when used for anaesthesia during Caesarean section. The safety of SEVOFLURANE BAXTER in labour and vaginal delivery has not been demonstrated.

Caution should be exercised in obstetric anaesthesia due to the relaxant effect of SEVOFLURANE BAXTER on the uterus and increase in uterine haemorrhage.

*Breastfeeding:*

It is not known whether sevoflurane is excreted in human milk. Caution should be exercised when SEVOFLURANE BAXTER is administered to a breastfeeding woman.

*Fertility:*

Studies in animals have shown adverse effects on fertility. There is no data on the effects of sevoflurane on fertility in humans.

**4.7 Effects on ability to drive and use machines**

Patients should be advised that performance of activities requiring mental alertness, such as decision making, operating a motor vehicle or hazardous machinery, may be impaired for some time after general anaesthesia (see section 4.4). Patients should not drive or operate hazardous machinery following SEVOFLURANE BAXTER anaesthesia for a period determined by the anaesthetist.

**4.8 Undesirable effects**

SEVOFLURANE BAXTER can produce dose-dependent cardiac respiratory depression. Most of the undesirable effects are mild to moderate in severity and transient in duration. Nausea, vomiting and delirium have been reported in the post-operative period – common symptoms following surgery and general anaesthesia, which may be due to the inhalational anaesthetic, other medicines administered intra-operatively or post-operatively, or the patient's reaction to the surgical procedure.

The following undesirable effects have been observed with sevoflurane use:

| **System Organ Class** | **Frequency** | **Undesirable effect** |
|---|---|---|
| Immune system disorders | Frequency unknown | Anaphylactic reaction [1] Anaphylactoid reaction Hypersensitivity [1] |

| | | |
|---|---|---|
| Blood and lymphatic system disorders | Less frequent | Leucopenia<br>Leucocytosis |
| Metabolism and nutrition disorders | Frequency unknown | Hyperkalaemia |
| Psychiatric disorders | Frequent | Agitation |
| | Less frequent | Confusion |
| Nervous system disorders | Frequent | Dizziness<br>Somnolence<br>Headache |
| | Frequency unknown | Convulsion [2, 3]<br>Dystonia<br>Increased intracranial pressure |
| Cardiac disorders | Frequent | Bradycardia<br>Tachycardia |
| | Less frequent | Atrioventricular block complete<br>Cardiac dysrhythmias (including ventricular dysrhythmias)<br>Atrial fibrillation<br>Extrasystoles (ventricular, supra-ventricular, bigeminy-linked) |
| | Frequency unknown | Cardiac arrest [4]<br>Ventricular fibrillation<br>Torsades de pointes<br>Ventricular tachycardia<br>Electrocardiogram QT prolonged |
| Vascular disorders | Frequent | Hypotension<br>Hypertension |
| | Frequent | Cough<br>Respiratory disorder |

| | | |
|---|---|---|
| Respiratory, thoracic and mediastinal disorders | | Respiratory depression<br>Laryngospasm<br>Airway obstruction |
| | Less frequent | Apnoea<br>Asthma<br>Hypoxia |
| | Frequency unknown | Bronchospasm<br>Dyspnoea [1]<br>Wheezing [1]<br>Breath holding<br>Pulmonary oedema |
| Gastrointestinal disorders | Frequent | Nausea<br>Vomiting<br>Salivary hypersecretion |
| | Frequency unknown | Pancreatitis |
| Hepato-biliary disorders | Frequency unknown | Hepatitis [1, 2]<br>Hepatic failure [1, 2]<br>Hepatic necrosis [1, 2]<br>Jaundice |
| Skin and subcutaneous tissue disorders | Frequency unknown | Dermatitis contact [1]<br>Pruritus<br>Rash [1]<br>Swelling face [1]<br>Urticaria |
| Musculoskeletal connective tissue disorders | Frequency unknown | Muscle rigidity<br>Muscle twitching |
| Renal and Urinary Disorders | Less frequent | Urinary retention<br>Glycosuria |

| | | |
|---|---|---|
| | Frequency unknown | Tubulointerstitial nephritis |
| General disorders and administration site conditions | Frequent | Chills<br>Pyrexia |
| | Frequency unknown | Chest discomfort [1]<br>Hyperthermia malignant [1, 2]<br>Oedema |
| Investigations | Frequent | Blood glucose abnormal<br>White blood cell count abnormal<br>Liver function test abnormal [5]<br>Blood fluoride increased [1]<br>AST increased |
| | Less frequent | Serum creatinine increased<br>ALT increased<br>Blood lactate dehydrogenase increased |
| Injury, poisoning and procedural complications | Frequent | Hypothermia |

[1] See section 4.8 – Description of selected adverse reactions.

[2] See section 4.4.

[3] See section 4.8 – Paediatric population.

[4] There have been very rare post-marketing reports of cardiac arrest in the setting of sevoflurane use.

[5] Occasional cases of transient changes in hepatic function tests were reported with sevoflurane and reference medicines.

*Description of selected adverse reactions*

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

Rare reports of post-operative hepatitis exist. In addition, there have been rare post-marketing reports of hepatic failure and hepatic necrosis associated with the use of potent volatile anaesthetic medicines, including sevoflurane. However, the actual incidence and relationship of sevoflurane to these events cannot be established with certainty (see section 4.4).

Rare reports of hypersensitivity (including contact dermatitis, rash, dyspnoea, wheezing, chest discomfort, swelling face, eyelid oedema, erythema, urticaria, pruritus, bronchospasm, anaphylactic or anaphylactoid reactions) have been reported particularly in association with long-term occupational exposure to inhaled anaesthetic medicines, including sevoflurane (see section 4.4).

In susceptible individuals, potent inhalation anaesthetic medicines may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia (see section 4.4).

*Paediatric population*

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. Several cases reported no concomitant medications, and at least one case was confirmed by electroencephalography (EEG). Although many cases were single seizures that resolved spontaneously or after treatment, cases of multiple seizures have also been reported. Seizures have occurred during, or soon after sevoflurane induction, during emergence, and during post-operative recovery up to a day following anaesthesia. Clinical judgement should be exercised when using SEVOFLURANE BAXTER in patients who may be at risk for seizures (see section 4.4).

*Reporting of suspected adverse reactions:*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

**4.9 Overdose**

Symptoms of overdose include respiratory depression and circulatory insufficiency.

In the event of apparent overdosage the following action should be taken: SEVOFLURANE BAXTER administration should be discontinued and supportive measures provided: the patient's airway should be maintained and artificial or controlled ventilation with pure oxygen should be instituted, along with measures to maintain stable cardiovascular function.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacological classification: A 2.1 Anaesthetics

Pharmacotherapeutic group: anaesthetics, general; halogenated hydrocarbons.

ATC code: N 01 AB 08

SEVOFLURANE BAXTER is a halogenated methyl isopropyl ether inhalational anaesthetic which produces a rapid induction and recovery phase. Minimum alveolar concentration (MAC) is age specific (see section 4.2).

SEVOFLURANE BAXTER produces loss of consciousness, reversible abolition of pain and motor activity, diminution of autonomic reflexes, respiratory and cardiovascular depression. These effects are dose-dependent.

Sevoflurane has a low blood/gas partition coefficient (0,65) leading to a rapid recovery from anaesthesia.

Cardiovascular effects: SEVOFLURANE BAXTER may produce concentration-related decrease of blood pressure. SEVOFLURANE BAXTER produces a sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered epinephrine. This sensitisation is similar to that produced by isoflurane.

SEVOFLURANE BAXTER is a dose-related cardiac depressant. It does not produce increases in heart rate at doses less than 2 MAC.

Animal studies have shown that regional blood flow (e.g. hepatic, renal, cerebral, coronary circulations) is well maintained with sevoflurane.

Sevoflurane has minimal effect on neurodynamics or ICP (intracranial pressure) and preserves $CO_2$ responsiveness.

Sevoflurane does not affect renal concentrating ability.

*Minimum alveolar concentration* (*MAC):*

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 BAXTER for various age groups see section 4.2.

The MAC of sevoflurane in oxygen was determined to be 2,05 % for a 40-year-old adult. MAC decreases with age and with the addition of nitrous oxide.

Tracheobronchial tree secretions are not excessively stimulated.

**5.2 Pharmacokinetic properties**

*Solubility*

Sevoflurane is weakly soluble in blood and tissue, resulting in the rapid achievement of a sufficient alveolar concentration to produce anaesthesia and a subsequent rapid elimination upon cessation of anaesthesia. In a clinical study the $F_A/F_I$ (washin) value at 30 minutes for sevoflurane was 0,85. The $F_A/FA_O$ (washout) value at 5 minutes was 0,15.

*Metabolism*

The rapid and extensive pulmonary elimination of sevoflurane minimises the quantity available for metabolism. In humans, < 5 % of sevoflurane absorbed is metabolised in the liver to hexafluoroisopropanol (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 in the urine. No other metabolic pathways for sevoflurane have been identified.

*Fluoride Ion:*

The defluorination of SEVOFLURANE BAXTER is not inducible by barbiturates. Fluoride ion concentrations are influenced by the duration of anaesthesia, the concentration of SEVOFLURANE BAXTER administered, and the composition of the anaesthetic gas mixture (see section 4.8).

Serum inorganic fluoride concentrations after sevoflurane anaesthesia have been reported to be dose dependent and reach about 10 to 20 µmol/l (after 1 to 2 MAC hours), 20 to 40 µmol/l (after 2 to 7 MAC hours) and may be as high as 20 to 90 µmol/l with prolonged exposure.

**5.3 Preclinical safety data**

Sevoflurane has a low order of acute toxicity in rats, mice, rabbits, dogs and monkeys. Anaesthesia induction was smooth and rapid, with no struggling, signs of gasping or other undesirable reactions. Deaths from exposure to lethal concentrations were due to respiratory arrest. Exposure was not associated with any specific organ toxicity or developmental toxicity in laboratory animals.

Published studies in pregnant and juvenile animals suggest that the use of anaesthetic and sedation medicines that block NMDA receptors and/or potentiate GABA activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. These studies included anaesthetic medicines from a variety of medicine classes. The clinical significance of these nonclinical findings is yet to be determined.

*Carcinogenesis:*

Studies on carcinogenesis have not been performed. No mutagenic effect was noted in the Ames test and no chromosomal aberrations were induced in cultured mammalian cells.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

None

### 6.2 Incompatibilities

SEVOFLURANE BAXTER is stable when stored under normal room lighting conditions. No discernible degradation of SEVOFLURANE BAXTER occurs in the presence of strong acids or heat. SEVOFLURANE BAXTER is not corrosive to stainless steel, brass, aluminium, nickel-plated brass, chrome-plated brass, or copper beryllium alloy.

Chemical degradation can occur upon exposure of SEVOFLURANE BAXTER to $CO_2$ absorbent within the anaesthesia machine. When used as directed with fresh absorbents, degradation of SEVOFLURANE BAXTER is minimal, and degradants are undetectable or non-toxic. SEVOFLURANE BAXTER degradation and subsequent degradant formation are enhanced by increasing absorbent temperature, desiccated $CO_2$ absorbent, increased SEVOFLURANE BAXTER concentration and decreased fresh gas flow.

SEVOFLURANE BAXTER can undergo alkaline degradation by two pathways. The first results from the loss of hydrogen fluoride with the formation of pentafluoroisopropanyl fluoromethyl ether (PIFE or more commonly known as Compound A). The second pathway for degradation of SEVOFLURANE BAXTER occurs only in the presence of desiccated $CO_2$ absorbents and leads to the dissociation of sevoflurane into hexafluoroisopropanol (HFIP) and formaldehyde. HFIP is inactive, non-genotoxic, rapidly glucoronidated, cleared, and has toxicity comparable to sevoflurane.

Formaldehyde is present during normal metabolic processes. Upon exposure to a highly desiccated absorbent, formaldehyde can further degrade into methanol and formate. Formate can contribute to the formation of carbon monoxide, in the presence of high temperature. Methanol can react with Compound

A to form the methoxy addition product Compound B. Compound B can undergo further HF elimination to form Compounds C, D, and E. With highly desiccated absorbents, the formation of formaldehyde, methanol, carbon monoxide, Compound A and perhaps some of its degradants, Compounds B, C, and D may occur.

No dose adjustment or change in clinical practice is necessary when rebreathing circuits are used.

Higher levels of Compound A are obtained when using barium hydroxide lime rather than soda lime.

**6.3 Shelf life**

- 4 years when packed in aluminium bottles sealed with screw-on polypropylene caps.
- 2 years when packed in aluminium bottles sealed with integrated crimped-on valve closures.

**6.4 Special precautions for storage**

Store at or below 30 °C.

Store in the original packaging.

The bottle cap should be replaced securely after use.

**KEEP OUT OF THE OF REACH OF CHILDREN.**

**6.5 Nature and contents of container**

SEVOFLURANE BAXTER is supplied in aluminium bottles containing 250 ml sevoflurane. The bottles are lined with an internal protective lacquer (consisting of an epoxy phenolic resin in a solvent application vehicle). The aluminium bottles are sealed with either screw-on polypropylene caps or integrated crimped-on valve closures. The aluminium bottles may be presented in external polyvinylchloride (PVC) decorative sleeves.

Pack sizes of 1 and 6 bottles are available.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

*Special precautions for handling:*

SEVOFLURANE BAXTER should be administered with a vaporiser calibrated specifically for sevoflurane. Filling occurs directly from the bottle via an integrated valve or, in case of a bottle without integrated valve, with the use of an appropriate adaptor designed specifically to fit the sevoflurane vaporiser. Only vaporisers demonstrated to be compatible with this medicine should be used for administration.

Sevoflurane has been found to undergo degradation in the presence of strong Lewis acids that may be formed on metal or glass surfaces under harsh conditions, and the use of vaporisers that contain such strong Lewis acids, or that may form them under conditions of normal use, must be avoided.

Carbon dioxide absorbents should not be allowed to dry out when inhalational anaesthetics are being administered. If the $CO_2$ absorbent is suspected to be desiccated it should be replaced (see section 4.4).

*Special precautions for disposal:*

Any unused medicine or waste material should be disposed of in accordance with local requirements.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

Baxter Healthcare South Africa (Pty) Ltd

The Campus – Eden Gardens

57 Sloane & Cnr Main Road ~~Rd~~

Bryanston

2021

South Africa

**8. REGISTRATION NUMBER**

49/2.1/0432

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

~~To be allocated by SAHPRA upon registration~~ 06-April-2022

**10. DATE OF REVISION OF THE TEXT**

Not applicable.