Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sevoflurane Baxter, 100%, inhalation vapour, liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Sevoflurane 100%

Excipient with known effect: None

The medicinal product is comprised only of the active substance, see section 6.1.

3 PHARMACEUTICAL FORM

Inhalation vapour, liquid
Clear, colourless liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Induction and maintenance of general anaesthesia in adults and children.

4.2 Posology and method of administration

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

Surgical anaesthesia

The concentration of sevoflurane being delivered from a vaporizer during anaesthesia should be known. This may be accomplished by using a vaporizer calibrated specifically for Sevoflurane.

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

A short acting barbiturate or other intravenous induction agent may be administered followed by inhalation of sevoflurane.

Induction with sevoflurane may be achieved by inhalation of 0.5-1.0% sevoflurane in oxygen (O_2) with or without nitrous oxide (N_2O), increasing by increments of 0.5-1.0% sevoflurane, to a maximum of 8% in adults and children until the required depth of anaesthesia is achieved. In adults inspired concentrations of up to 5% sevoflurane usually produce surgical anaesthesia in less than two minutes. In children, inspired concentrations of up to 7% sevoflurane usually produce surgical anaesthesia in less than two minutes.

Maintenance of anaesthesia
Surgical levels of anaesthesia may be maintained by inhalation of 0.5-3% sevoflurane in O_2 with or without concomitant use of N_2O.

Emergence
Emergence times are generally short following sevoflurane anesthesia. Therefore, patients may require post-operative pain relief earlier.

Elderly
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.

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 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 anesthesia with one of these agents).

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

Sevoflurane should not be used in patients with known or suspected genetic susceptibility to malignant hyperthermia.

Sevoflurane is contraindicated in patients in whom general anesthesia is contraindicated.

4.4 Special warnings and precautions for use

Sevoflurane 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 should be constantly monitored, including electrocardiogram (ECG), blood pressure (BP), oxygen saturation and end tidal carbon dioxide (CO_2.)
The concentration of sevoflurane 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 concentration results in dose-dependent decreases in blood pressure. An excessive reduction in blood pressure may be related to depth of anesthesia and in such instances may be corrected by decreasing the inspired sevoflurane concentration. Due to sevoflurane's insolubility in blood, hemodynamic changes may occur more rapidly than with some other volatile anaesthetics. Recovery from general anaesthesia should be assessed carefully before patients are discharged from the post-anaesthesia care unit.

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

Although recovery of consciousness following sevoflurane 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 (see section 4.7).

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 on the uterus and increase in uterine haemorrhage (see Section 4.6).

Patients undergoing neurosurgical procedures

In patients at risk for elevations of ICP, sevoflurane should be administered cautiously in conjunction with ICP-reducing maneuvers such as hyperventilation.

Seizures

Rare 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 judgment is necessary before sevoflurane is used in patients at risk of seizures. In children the depth of anaesthesia should be limited. EEG may permit the optimization of sevoflurane dose and help avoid the development of seizure activity in patients with a predisposition for seizures (see section 4.4 – Paediatric population).

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. Also 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 concentration and fresh gas flow rate should be adjusted to minimize exposure to Compound A. Sevoflurane 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

Sevoflurane should be administered with caution to patients with impaired renal function (GFR ≤ 60 ml/min); renal function should be monitored postoperatively.

Patients with liver disease

Very rare cases of mild, moderate or serious post-operative liver dysfunction or hepatitis (with or without jaundice) have been reported from post marketing experience. Clinical judgement should be exercised when sevoflurane is used in patients with underlying liver problems or those who are receiving treatment with medications 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 if anaesthesia with intravenous medicinal products or regional anaesthesia is possible (see Section 4.8***).***

Patients with mitochondrial disorders

Caution should be exercised in administering general anesthesia, including sevoflurane, to patients with mitochondrial disorders.

Patient circumstances that warrant consideration

Particular care must be taken when selecting the dosage for hypovolaemic, hypotensive, weakened patients or otherwise hemodynamically compromised, e.g., due to concomitant medications.

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

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 to susceptible patients.

Malignant hyperthermia:

In susceptible individuals, potent inhalation anaesthetic agents 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, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anesthesia, acute hypoxia, hypercapnia and hypovolemia. Fatal outcome of malignant hyperthermia has been reported with sevoflurane. Treatment includes discontinuation of triggering agents (e.g. sevoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Renal failure may appear later, and urine production should be monitored and sustained if possible. Use of inhaled anesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias and death in pediatric patients during the postoperative period.

Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable. 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 hyperkalemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Replacement of dried-out CO_2 absorbens

The exothermic reaction between sevoflurane and CO_2 absorbent lime is reinforced when the CO_2 absorbent lime is dried out, e.g. after a longer period with current of dry gas over the bottle with CO_2 absorbent lime. 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 absorbent lime, specifically those containing potassium hydroxide.. An unexpected delay in increase of inspired concentration of sevoflurane or an unexpected decrease of inspired concentration of sevoflurane compared with the setting of the vaporiser may be a sign of overheating of the CO_2 absorbent lime 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) were observed in the respiratory circuit of an experimental anesthesia machine using desiccated CO_2 absorbents and maximum sevoflurane concentrations (8%) for extended periods of time (≥ 2 hours). Concentrations of formaldehyde observed at the anesthesia 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 physician suspects the CO_2 absorbent lime to be dried-out, this must be replaced before the administration of sevoflurane. The colour indicator on most CO_2 absorbent limes 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)*.

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 judgment should be exercised when using sevoflurane 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 arrhythmia 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 medicinal products and other forms of interaction

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

Nitrous oxide

As with other halogenated volatile anesthetics, the MAC of sevoflurane is decreased when administered in combination with nitrous oxide. The MAC equivalent is reduced approximately 50% in adult and approximately 25% in pediatric patients (see section 4.2 – Maintenance).

Neuromuscular blocking agents

As with other inhalational anesthetic agents, sevoflurane affects both the intensity and duration of neuromuscular blockade by non-depolarizing muscle relaxants. When used to supplement alfentanil-N_2O anesthesia, sevoflurane potentiates neuromuscular block induced with pancuronium, vecuronium or atracurium. The dosage adjustments for these muscle relaxants when administered with sevoflurane are similar to those required with isoflurane. The effect of sevoflurane on succinylcholine and the duration of depolarizing neuromuscular blockade has not been studied.

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

Among non-depolarizing agents, 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 anesthesia, the dose of non-depolarizing muscle relaxants is likely to be reduced compared to that during N_2O/opioid anesthesia. 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 administration is compatible with benzodiazepines and opioids as commonly used in surgical practice.

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

Beta blockers

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

Epinephrine/adrenaline

Sevoflurane is similar to isoflurane in the sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline, the threshold dose of adrenaline producing multiple ventricular arrhythmias has been established at 5 microgram per Kg.

Inducers of CYP2E1

Medicinal products and compounds that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of sevoflurane and lead to significant increases in plasma fluoride concentrations. Concomitant use of sevoflurane 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 and indirect sympathomimetic medicinal products (amphetamines, ephedrine).

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 anesthetics have been reported in patients treated long-term with St John's Wort.

Barbiturates

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited data from the use of sevoflurane in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3); therefore, sevoflurane should be used during pregnancy and in woman of childbearing potential not using contraception only if clearly needed.

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

Caution should be exercised in obstetric anesthesia due to the relaxant effect of sevoflurane on the uterus and increase in uterine hemorrhage.

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

Fertility
Studies in animals have shown reproductive toxicity (see section 5.3). There are no data on effects 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 operating a motor vehicle or hazardous machinery, may be impaired for some time after general anesthesia (see section 4.4).Patients should not drive following sevoflurane anaesthesia for a period determined by the anaesthetist.

4.8 Undesirable effects

Summary of the safety profile

As with all potent inhalational anaesthetics, sevoflurane can produce dose-dependent cardiac respiratory depression. Most of the adverse reactions are mild to moderate in severity and transient in duration. Nausea and vomiting have been reported in the post-operative period – common symptoms following surgery and general anaesthesia – which may be due to the inhalational anaesthetic, other agents administered intra-operatively or post-operatively, or the patient's reaction to the surgical procedure.

The most commonly reported adverse reactions were as follows: In adult patients: hypotension, nausea and vomiting; In elderly patients: bradycardia, hypotension and nausea; and In paediatric patients: agitation, cough, vomiting and nausea.

Tabulated summary of adverse reactions

All reactions, at least possibly related to sevoflurane from clinical trials and post-marketing experience, are displayed in the Table below by MedDRA System Organ Class, Preferred Term and frequency. The following frequency groupings are used: very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000); very rare (<1/10,000), including isolated reports. Post-marketing adverse reactions are reported voluntarily from a population with an unknown rate of exposure. Therefore it is not possible to estimate the true incidence of adverse events and the frequency is "unknown". The type, severity, and frequency of adverse reactions in sevoflurane patients in clinical trials were comparable to adverse reactions in reference-drug patients.

Adverse Reaction Data Derived From Clinical Trials and Post-marketing Experience

Summary of Most Frequent Adverse Drug Reactions in Sevoflurane Clinical Trials and Post-marketing Experience

System Organ Class	**Frequency**	**Adverse Reactions**
Immune system disorders	Unknown	Anaphylactic reaction [1] Anaphylactoid reaction Hypersensitivity [1]
Psychiatric disorders	Very Common Uncommon Unknown	Agitation Confusion Delirium
Nervous system disorders	Common Unknown	Somnolence Dizziness Headache Convulsion [2 3] Dystonia Increased intracranial pressure
Cardiac disorders	Very Common Common Uncommon Unknown	Bradycardia Tachycardia Atrioventricular block complete, Cardiac arrhythmias (including ventricular arrhythmias), atrial fibrillation, extrasystoles (ventricular, supra-ventricular, bigeminy-linked), Cardiac arrest [4] Ventricular fibrillation Torsades de pointes Ventricular tachycardia, Electrocardiogram QT prolonged
Vascular disorders	Very Common Common	Hypotension Hypertension
Respiratory, thoracic and mediastinal disorders	Very Common Common Uncommon Unknown	Cough Respiratory disorder Respiratory depression Laryngospasm Airway obstruction Apnoea Asthma Hypoxia Bronchospasm Dyspnoea [1] Wheezing [1] Breath holding
Gastrointestinal disorders	Very Common Common Unknown	Nausea Vomiting Salivary hypersecretion Pancreatitis

Metabolism And Nutrition Disorders	Unknown	Hyperkalemia
Musculoskeletal connective tissue and bone disorders	Unknown	Muscle rigidity

Hepato-biliary disorders	Unknown	Hepatitis [1 2] Hepatic failure [1 2] Hepatic necrosis [1 2] Jaundice
Renal and Urinary Disorders	Unknown	Tubulointerstitial nephritis
Skin and subcutaneous tissue disorders	Unknown	Dermatitis contact [1] Pruritus Rash [1] Swelling face [1] Urticaria
General disorders and administration site conditions	Common Unknown	Chills Pyrexia Chest discomfort [1] Hyperthermia malignant [1 2] Edema
Investigations	Common Uncommon	Blood glucose abnormal Liver function test abnormal [5] White blood cell count abnormal Blood fluoride increased[1] Serum Creatinine increased
Injury, poisoning and procedural complications	Common	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 postmarketing 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 agents.

Description of selected adverse reactions

Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane 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 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 agents, 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 edema, erythema, urticaria, pruritis bronchospasm, anaphylactic or anaphylactoid reactions have been reported particularly in association with long-term occupational exposure to inhaled anaesthetic agents, including sevoflurane.

In susceptible individuals, potent inhalation anaesthetic agents 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 judgment should be exercised when using sevoflurane 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 medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

Ireland
HPRA Pharmacovigilance
Website: www.hpra.ie

By reporting side effects you can help provide more information on the safety of this medicine.

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 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

Pharmacotherapeutic group: anaesthetics, general; halogenated hydrocarbons.
ATC code: N 01 AB 08

Sevoflurane is a halogenated methyl isopropyl ether inhalational anaesthetic which produces a rapid induction and recovery phase. MAC (minimum alveolar concentration) is age specific (see Section 4.2).

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

5.2 Pharmacokinetic properties

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 until cessation of anaesthesia.

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.

The rapid and extensive pulmonary elimination of sevoflurane minimises the quantity available for metabolism. The metabolism of sevoflurane is not induced by barbiturates.

5.3 Preclinical safety data

Preclinical data on single and repeated dose toxicity of sevoflurane showed no specific organ toxicity.

Reproductive studies: Studies on fertility performed in rats indicated a decrease in implantation and pregnancy rates after repeated exposure to anaesthetic doses. Developmental toxicity studies performed in rats and rabbits did not reveal any teratogenic effect. In sub-anaesthetic concentrations during the perinatal phase rats showed a prolongation of gestation.
A study in male rats has demonstrated decreased sperm motility and concentration as well as increased testicular degeneration after chronic exposure to sevoflurane (1 MAC sevoflurane inhalation for 7 or 14 days) compared to controls.

Published studies in animals (including primates) at doses resulting in light to moderate anaesthesia demonstrate that the use of anaesthetic agents during the period of rapid brain growth or synaptogenesis results in cell loss in the developing brain that can be associated with prolonged cognitive deficiencies. The clinical significance of these nonclinical findings in not known.

Extensive in-vitro and in-vivo mutagenicity studies with sevoflurane yielded negative results. Carcinogenicity studies were not performed.
Effects on circulatory function and oxygen consumption: The results of studies conducted in dogs indicate that sevoflurane does not cause any coronary steal syndrome and does not exacerbate a pre-existing myocardial ischaemia. Animal studies have shown that liver and kidney circulation is maintained well with sevoflurane.

Sevoflurane decreases the cerebral metabolic rate for oxygen ($CMRO_2$) in a fashion analogous to that seen with isoflurane. An approximately 50% reduction of $CMRO_2$ is observed at concentrations approaching 2.0 MAC. Animal studies have demonstrated that sevoflurane does not have a significant effect on cerebral blood flow.

Effects of sevoflurane on the central nervous system: In animals, sevoflurane significantly suppresses electroencephalographic (EEG) activity comparable to equipotent doses of isoflurane. There is no evidence that sevoflurane is associated with epileptiform activity during normocapnia or hypocapnia. In contrast to enflurane, attempts to elicit seizure-like EEG activity during hypocapnia with rhythmic auditory stimuli have been negative.

Compound A: Compound A is a degradation product of sevoflurane, which is generated in CO_2-absorbers. Its concentration increases normally with increasing absorber temperature, sevoflurane concentration and lowering of the fresh gas flow rate.

Studies performed in rats have shown a dose and duration of exposure dependent, reversible, nephrotoxicity (single cell necrosis of the proximal tubule cells). In the rat evidence for nephrotoxicity could be found at 25-50 ppm following 6 and 12 hours exposure. The relevance to humans is unknown.

In clinical studies the highest concentration of Compound A (using soda lime as CO_2 absorbents in the circuit) was 15 ppm in children and 32 ppm in adults. In systems using barium lime as CO_2 absorbents concentrations of up to 61 ppm were found. Although the experience with low-flow anaesthesia is limited, to date there is no evidence of kidney impairment due to Compound A.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

In the clinical setting, through direct contact with CO2 absorbents (Soda lime and barium hydroxide lime), sevoflurane can degrade producing low levels of Compound A (pentafluoroisopropenyl fluoromethyl ether (PIFE)), and trace amounts of Compound B (pentfluoromethoxy isopropyl fluoromethyl ether (PMFE)). The interaction with CO2 absorbents is not unique to sevoflurane. The production of degradants in the anaesthesia circuit results from the extraction of the acidic proton in the presence of a strong base (potassium hydroxide (KOH) and/or sodium hydroxide (NaOH)) forming an alkene (Compound A) from sevoflurane. 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

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

250 ml aluminium bottles, lined with an internal epoxyphenolic resin protective lacquer. The bottles are closed with:

- plastic screw-on caps with a polytetrafluoroethylene (PTFE) laminate inner liner or
- an integrated crimped-on valve closure with stainless steel, nylon, ethylene-propylene copolymer (EPDM) and polyethylene product contact components.Pack sizes of 1 and 6 bottles.Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Sevoflurane 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 the sevoflurane vaporiser. Only vaporisers demonstrated to be compatible with this medicinal product 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 CO2 absorbent is suspected to be desiccated it should be replaced.

7 MARKETING AUTHORISATION HOLDER

Baxter Holding B.V.
Kobaltweg 49
3542CE Utrecht
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA2299/031/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st May 2010
Date of last renewal: 26th June 2014

10 DATE OF REVISION OF THE TEXT

March 2024