SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Sevofluran Piramal 100% inhalation vapour, liquid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each bottle contains 100% (V/V) sevoflurane.

3. PHARMACEUTICAL FORM
Inhalation vapour, liquid

Clear, colourless, liquid

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Induction and maintenance of general anaesthesia in adult and paediatric patients of all ages, including full term neonates (see section 4.2 for age details).

4.2 Posology and method of administration
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.

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

Anaesthesia induction
Dose 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 medicinal product 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.

In hypovolemic, hypotonic or debilitated patients, particular care should be taken to dose, and there must be opportunities for oxygen delivery and resuscitation.

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.

Age dependence of MAC in sevoflurane		
Age (years)	**Sevoflurane in oxygen**	**Sevoflurane in 65% nitrous oxide/35% oxygen***
< 3	3.3 to 2.6%	2.0%
3 to < 5	2.5%	not measured
5 to 12	2.4%	not measured
25	2.5%	1.4%
35	2.2%	1.2%

40	2.05%	1.1%
50	1.8%	0.98%
60	1.6%	0.87%
80	1.4%	0.70%
* in children: 60% nitrous oxide/40% oxygen		

Emergence
Emergence times are generally short following sevoflurane anaesthesia. 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 nitrus oxide.

Renal insufficiency
Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 133 μmol/litre) studied, the safety of sevoflurane administration in this group has not been fully established. Therefore, sevoflurane should be used with caution in patients with renal insufficiency.

Method of administration
Inhalation use. Sevoflurane has to be administered either via face mask or via endotracheal tube. Sevoflurane should be delivered via a vaporizer specifically calibrated for use with sevoflurane so that the concentration delivered can be accurately controlled.

4.3 Contraindications
Hypersensitivity to sevoflurane or other halogenated anaesthetics (e.g. history of liver function disorder, fever or leucocytosis of unknown cause after anaesthesia with one of these medicinal products).

Patients with a history of confirmed hepatitis due to a halogenated inhalational anesthetic or a history of unexplained moderate to severe hepatic dysfunction with jaundice, fever, and eosinophilia after anaesthesia with sevoflurane.

Patients with known or suspected genetic susceptibility to malignant hyperthermia.

Patients in whom general anaesthesia is contraindicated.

4.4 Special warnings and precautions for use
All patients anaesthetised with sevoflurane should be constantly monitored, including electro-cardiogram (ECG), blood pressure (BP), oxygen saturation and end tidal carbon dioxide (CO_2).

Sevoflurane causes respiratory depression, which may be augmented by narcotic premedication or other agents causing respiratory depression. Respiration should be supervised and assisted as appropriate.

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

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. Small changes in moods may persist for several days following administration (see section 4.7).

Patients with coronary disease
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 (intracranial pressure), 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).

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 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 and serious post-operative liver dysfunction or hepatitis with or without jaundice have been reported from post marketing experience.

Clinical judgment is necessary before sevoflurane is used in patients with underlying liver problems or under treatment with medicinal products known to cause hepatic 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 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 used in administering general anesthesia, including sevoflurane, to patients with mitochondrial disorders.

Patient circumstances that warrant consideration
Particular care must be taken when selecting the dose for patients who are hypovolaemic, hypotensive, or otherwise hemodynamically compromised, e.g., due to medicinal products administered concomitantly.

Sevoflurane should be used with caution in patients with myasthenia gravis.

Like other halogenated anaesthetics, sevoflurane may cause cough during induction.

There have been isolated reports of QT prolongation, very rarely associated with torsade de pointes (in exceptional cases fatal). Therefore, sevoflurane should be used with caution in susceptible patients.

Malignant hyperthermia
In susceptible individuals, potent inhalation anaesthetics 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, arrhythmias, and/or unstable blood pressure. Some of these nonspecific signs may also appear during light anaesthesia, acute hypoxia, hypercapnia and hypovolaemia. Fatal outcome of malignant hyperthermia has been reported with sevoflurane.

Treatment includes discontinuation of triggering medicinal products (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 anesthetics 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.

Perioperative hyperkalaemia
Use of inhaled anaesthetic agents has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias 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. 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 arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Replacement of dried-out CO_2 absorbens
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 ($\geq$ 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).

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 have been reported in paediatric patients with Pompe's disease.

Dystonic movements, which disappear without treatment, have been observed 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 is considered to be safe and effective when administered concurrently with a wide variety of medicinal products commonly encountered in surgical situations such as central nervous system medicinal products, autonomic medicinal products, skeletal muscle relaxants, anti-infective medicinal products including aminoglycosides, hormones and synthetic substitutes, blood derivatives and cardiovascular medicinal products, including epinephrine.

Nitrous oxide

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 paediatric patients (see section 4.2).

Neuromuscular blocking medicinal products
Sevoflurane affects both the intensity and duration of neuromuscular blockade by non-depolarizing muscle relaxants. When used to supplement alfentanil-N2O anesthesia, sevoflurane potentiates neuromuscular block induced with pancuronium, vecuronium or atracurium. The dose 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.

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

Among non-depolarizing medicinal products, vecuronium, pancuronium and atracurium interactions have been studied. In the absence of specific guidelines: for endotracheal intubation, the dose of non-depolarizing muscle relaxants should be reduced. 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 opioids 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.

MAO inhibitors
With non-selective MAO inhibitors, there is a risk for intraoperative collapse during surgery. It is recommended that treatment is completed two weeks prior to surgery.

Isoniazid
Interactions (risk of potentiation of the hepatotoxic effects of isoniazid metabolites) have been observed with the simultaneous use of isoniazid and halogenated inhalation anaesthetics and cannot be ruled out with sevoflurane.

In most cases, there is no reason to discontinue treatment with other vital drugs prior to general anaesthesia. It is sufficient if the anaesthetist is informed about them.

Calcium antagonists
Sevoflurane may lead to marked hypotension in patients treated with calcium channel blockers, especially dihydropyridine derivatives.

Due to the risk of an additive negative inotropic effect, calcium antagonists should only be used with caution together with inhalation anaesthetics.

4.6 Fertility, pregnancy and lactation

Pregnancy
Reproduction studies in rats and rabbits at doses up to 1 MAC have revealed no evidence of harm to the fetus due to sevoflurane. There are no adequate and well-controlled studies in pregnant women; therefore, sevoflurane should be used during pregnancy 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 labor 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. There are hints for a reduced fertility and implantation rate in rats following the repeated application of anaesthetic doses (see section 5.3).

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 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

Sevoflurane can produce dose-dependent cardiac respiratory depression. Most of the adverse reactions 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 medicinal products 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)

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 "not known" (frequency cannot be estimated from the available data). 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	Not known	Anaphylactic reaction[1], anaphylactoid reaction, hypersensitivity[1]
Metabolism and nutrition disorders	Not known	Hyperkalemia
Psychiatric disorders	Very common Uncommon	Agitation Confusion
Nervous system disorders	Common Not known	Somnolence, dizziness, headache Convulsion[2, 3], dystonia, increased intracranial pressure
Cardiac disorders	Very common Common	Bradycardia Tachycardia

	Uncommon Not known	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 Not known	Cough Respiratory disorder, respiratory depression, laryngospasm, airway obstruction Apnoea, asthma, hypoxia Bronchospasm, dyspnoea[1], wheezing[1], breath holding
Gastrointestinal disorders	Very common Common Not known	Nausea, vomiting Salivary hypersecretion Pancreatitis
Hepato-biliary disorders	Unknown	Hepatitis[1, 2], hepatic failure[1, 2], hepatic necrosis[1, 2], jaundice
Skin and subcutaneous tissue disorders	Unknown	Contact dermatitis, pruritus, rash[1], swelling face[1], urticaria
Musculoskeletal connective tissue and bone disorders	Unknown	Muscle -rigidity
Renal and urinary disorders	Unknown	Tubulointerstitial nephritis
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

Other adverse effects
There may be very rare cases of spasmodic movements after sevoflurane anaesthesia. Such events were short-lived and there were no signs of illness during recovery from anaesthesia or after surgery.

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 anaesthetics 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 use of medicinal products, 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 the national reporting system listed in Appendix V.

4.9 Overdose
Symptoms of overdose include respiratory depression and circulatory insufficiency.

In the event of apparent overdose 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: N01AB08

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.

Nervous system effects
In patients with normal intracranial pressure (ICP), sevoflurane had minimal effect on ICP and preserved CO_2 responsiveness.

The safety of sevoflurane has not been investigated in patients with a raised ICP.
In patients at risk for elevations of ICP, sevoflurane should be administered cautiously in conjugation with ICP-reducing manoeuvres such as hyperventilation.

5.2 Pharmacokinetic properties

The low solubility of sevoflurane in blood should result in alveolar concentrations which rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent.

In humans <5% of the absorbed sevoflurane is metabolised. The rapid and extensive pulmonary elimination of sevoflurane minimises the amount of anaesthetic available for metabolism. Sevoflurane is defluorinated via cytochrome P450(CYP)2E1 resulting in the production of hexafluoroisopropanol (HFIP) with release of inorganic fluoride and carbon dioxide (or a one carbon fragment). HFIP is then rapidly conjugated with glucuronic acid and excreted in the urine.

The metabolism of sevoflurane may be increased by known inducers of CYP2E1 (e.g. isoniazid and alcohol), but it is not inducible by barbiturates. Transient increases in serum inorganic fluoride levels may occur during and after sevoflurane anaesthesia. Generally, concentrations of inorganic fluoride peak within 2 hours of the end of sevoflurane anaesthesia and return within 48 hours to pre-operative levels.

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

Acute and subchronic toxicity
Preclinical data on acute and subchronic toxicity of sevoflurane show that it elicits a dose-dependent depression of the respiration and of the cardiovascular system, without resulting in a specific organ toxicity.In monkeys, a slight, reversible increase in liver enzymes was detected following repeated administration. Hints for nephrotoxicity of sevoflurane degradation products were evaluated in specific studies (see below).

Reproductive and developmental toxicity
At maternally toxic doses, reduced weight, delayed ossification and an increased occurrence of small skeletal anomalies was observed in the progeny of rats. Teratogenic effects did not occur. There are hints for a reduced fertilisation and implantation rate in rats following repeated application of anaesthetic doses.

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.

Mutagenicity/carcinogenicity
Extensive *in-vitro* and *in-vivo* studies with sevoflurane on mutagenicity yielded negative results. Carcinogenicity studies are not available.

Compound A
In Wistar rats, the LC_{50} of Compound A, a degradation product of sevoflurane which is formed in CO_2-absorbents, amounted to 1050 to 1090 ppm following a 1- hour exposure and 400 to 420 ppm following a 3-hour exposure. In an eight-week, chronic study (24 exposures for 3 h each) there was no toxicological finding besides a weight reduction in female rats.

In a further study with Wistar rats, there were hints for nephrotoxicity following an exposure of 6 to 12 hours at 25 to 50 ppm.

In Sprague-Dawley rats, the threshold value for reversible changes of parameters of kidney function (e.g. blood urea levels, creatinine, glucose) amounted to 114 ppm. All histo-morphological changes were reversible.

Since the absorption of inhaled compounds is considerably higher in small rodents than in humans, usually higher levels of drug substance or of Compound A (pentafluorisopropenylfluormethylether, PIFE) are expected. The activity of ß-lyase, a key enzyme which is involved in the nephrotoxicity of haloalkenes, is 10-fold higher in small rodents than in humans.

Concentrations of Compound A usually increase with increasing absorber temperature and sevoflurane concentration as well following reduction of fresh air inflow. In clinical studies, the highest concentration of Compound A (when using soda lime as a CO_2-absorbents in the circuit system) amounted to 15 ppm in children and 32 ppm in adults. However, concentrations of up to 61 ppm have been measured in systems using barium lime as CO_2 absorbents. The threshold value for toxicity in humans is not known. Although the experience with low-flow anaesthesia is still limited, until now there is no hint for a disturbance of kidney function elicited by Compound A.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
None

6.2 Incompatibilities
In the clinical setting, through direct contact with CO_2 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 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.

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

6.3 Shelf life
3 years

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Type III, 250 ml amber coloured glass bottles (with or without an external PVC coating). The bottles are provided with an LDPE yellow-coloured collar and closed with a two components screw cap (outer phenolic cover with LDPE liner).

Type III, 250 ml amber coloured glass bottles (with or without an external PVC coating) with a multicomponent screw cap (HDPE, ethylene propylene diene rubber (EPDM) o-rings/gaskets and stainless steel spring) attached to the bottle with an aluminium crimp ring.

Pack sizes of 1 and 6 bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER
<To be completed nationally>

8. MARKETING AUTHORISATION NUMBER(S)
<To be completed nationally>

9. DATE OF FIRST AUTHORISATION
<To be completed nationally>

10. DATE OF REVISION OF THE TEXT
2024-10-03