Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sevoflurane 100% inhalation vapour, liquid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains sevoflurane 100 % w/v.
The medicinal product is comprised only of the active ingredient.

3 PHARMACEUTICAL FORM

Inhalation vapour, liquid
Clear, colourless, volatile liquid

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Sevoflurane is indicated for induction and maintenance of general anaesthesia in adult and paediatric patients. Use of sevoflurane in dental anaesthesia should be restricted to hospitals or day care units only (see section 4.3).

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
Sevoflurane should be delivered via a vaporiser specifically calibrated for use with sevoflurane so that the concentration delivered can be accurately controlled. MAC (minimum alveolar concentration) values for sevoflurane decrease with age and with the addition of nitrous oxide. The table below indicates average MAC values for different age groups.

Table 1. MAC Values for Adults and Paediatric Patients According to Age

AGE OF PATIENT (YEARS)	SEVOFLURANE IN OXYGEN	SEVOFLURANE IN 65% N_20/35%0_2
0 – 1 months*	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%

* Neonates are full term gestational age. MAC in premature infants has not been determined
@ In 1 - <3 year old paediatric patients, 60%N_2O/40%O_2 was used

Sevoflurane is similar to Isoflurane in the sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline.

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 in oxygen or in combination with oxygen-nitrous oxide mixtures. For induction of anaesthesia inspired concentrations of up to 8% sevoflurane usually produces surgical anaesthesia in less than two minutes in both adults and children.

Maintenance
Surgical levels of anaesthesia may be sustained with concentrations of 0.5 – 3% sevoflurane with or without the concomitant use of nitrous oxide.

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.

4.3 Contraindications

Sevoflurane should not be used in patients with known or suspected sensitivity to sevoflurane or to other halogenated inhalational anaesthetics (e. g. history of hepatotoxicity, usually including elevated liver enzymes, fever, leucocytosis and/or eosinophilia temporally related to anaesthesia with one of these agents).

Sevoflurane is contraindicated in patients with known or suspected genetic susceptibility to malignant hyperthermia.

Sevoflurane is also contraindicated in all patients (adults and children) undergoing dental procedures outside a hospital or day care unit (see section 4.4).

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

4.4 Special warnings and precautions for use

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

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. The concentration of sevoflurane being delivered from a vaporizer must be known exactly. As volatile anaesthetics differ in their physical properties, only vaporisers specifically calibrated for sevoflurane must be used. The administration of general anaesthesia must be individualised based on the patient's response. Hypotension and respiratory depression increase as anaesthesia is deepened.

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.

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

Caution should be exercised in administering general anaesthesia, including sevoflurane, to patients with mitochrondrial disorders.

All patients anaesthetised with sevoflurane should be constantly monitored, including ECG, BP, oxygen saturation and end tidal CO_2, in a setting where full resuscitative equipment is available and with staff fully trained in resuscitative techniques. The presence of additional risk factors should be taken into consideration (see section 4.8).

During the maintenance of anaesthesia, increasing the concentration of sevoflurane produces dose-dependent decreases in blood pressure. Excessive decrease in blood pressure may be related to depth of anaesthesia and in such instances may be corrected by decreasing the inspired concentration of sevoflurane. Particular care must be taken when selecting the dosage for

patients who are hypovolemic, hypotensive, or otherwise hemodynamically compromised, e.g., due to concomitant medications.

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

The recovery from general anaesthesia should be assessed carefully before patients are discharged from the post-anaesthesia care unit. Although recover 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).

Malignant Hyperthermia
In susceptible individuals, potent inhalation anaesthetic agents, including sevoflurane, may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. 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.

In clinical trials, one case of malignant hyperthermia was reported. In addition, there have been postmarketing reports of malignant hyperthermia. Some of these reports have been fatal (see section 4.8).

Treatment includes discontinuation of triggering agents (e.g. sevoflurane), administration of intravenous dantrolene sodium (consult prescribing information for intravenous dantrolene sodium for additional information on patient management), 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 flow should be monitored and sustained if possible.

Perioperative Hyperkalemia
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 post-operative 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.

Hepatic
Very rare cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice have been reported from postmarketing experiences.

Clinical judgement should be exercised when sevoflurane is used in patients with underlying hepatic conditions or under treatment with drugs known to cause hepatic dysfunction (see section 4.8).

It has been reported that previous exposure to halogenated hydrocarbon anaesthetics, especially if the interval is less than 3 months, may increase the potential for hepatic injury.

Replacement of Desiccated CO_2 Absorbents:
Rare cases of extreme heat, smoke, and/or spontaneous fire in the anaesthesia machine have been reported during sevoflurane use in conjunction with the use of desiccated CO_2 absorbent, specifically those containing potassiumhydroxide.An unusually delayed rise or unexpected decline of inspired sevoflurane concentration compared to the vaporizer setting may be associated with excessive heating of the CO_2 absorbent canister.

An exothermic reaction, enhanced sevoflurane degradation, and production of degradation products (see DESCRIPTION above) can occur when 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 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.

The following are clinical findings, which have been reported in association with these rare, isolated events. Failed inhalation induction or inadequate anaesthesia with sevoflurane; patient signs of airway irritation, such as coughing, oxygen desaturation, increased airway pressures, difficult ventilation, severe airway oedema and erythema and elevated carboxyhemoglobin levels have been reported in association with these rare isolated events.

If excessive heat from the CO_2 absorbent canister is noted, the clinical situation should be evaluated and disconnecting the patient from the anaesthesia circuit should be considered.

When a clinician suspects that the CO_2 absorbent may be desiccated, it should be replaced before administration of sevoflurane. The colour indicator of most CO_2 absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant colour change should not be taken as an assurance of adequate hydration. CO_2 absorbents should be replaced routinely regardless of the state of the colour indicator.

Anaesthetic machines should be completely shut off at the end of clinical use, the packaging integrity of new CO_2 absorbents should be verified prior to use and the temperature of CO_2 absorbents canisters monitored during use.

Renal Impairment:
In clinical trials no effect on renal function was observed, including in-patients with pre-existing renal impairment. Because of the small number of patients with renal insufficiency (baseline serum creatinine greater than 1.5 mg/dL) that have been studied, the safety of sevoflurane administration in this group has not been fully established. Therefore, until further experience is obtained, sevoflurane should be used with caution in patients with renal insufficiency.

Sevoflurane produces low levels of Compound A (pentafluoroisopropenyl fluoromethyl ether (PIFE)) and trace amounts of Compound B (pentafluoromethoxy isopropyl fluoromethyl ether (PMFE)), when in direct contact with CO_2 absorbents. Levels of Compound A increase with: increase in canister temperature; increase in anaesthetic concentration; decrease in gas flow rate and increase more with the use of Baralyme rather than Soda lime. (See also Pharmaceutical Particulars.). The concentrations of Compound A found in routine clinical practice are on average 19ppm in adults (maximum 32ppm) with use of Soda lime as the CO_2 absorbent. Although exposure to sevoflurane in low flow systems is limited, there has been no evidence of renal dysfunction attributable to Compound A.

Neurosurgery:
In patients at risk for elevations of ICP, sevoflurane should be administered cautiously in conjunction with ICP-reducing manoeuvres 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 optimisation of sevoflurane dose and help avoid the development of seizure activity in patients with a predisposition for seizures (see section 4.4 - Paediatric population).

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).

4.5 Interaction with other medicinal products and other forms of interaction

Beta-sympathomimetic agents like isoprenaline and alpha- and beta-sympathomimetic agents like adrenaline and noradrenaline should be used with caution during sevoflurane narcosis, due to a potential risk of ventricular arrhythmia.

Non-selective MAO-inhibitors: Risk of crisis during the operation. It is generally recommended that treatment should be stopped 2 weeks prior to surgery.

Sevoflurane may lead to marked hypotension in patients treated with calcium antagonists, in particular dihydropyridine derivates.

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

Concomitant use of succinylcholine with 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 post-operative period

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.

Epinephrine/Adrenaline
Sevoflurane is similar to isoflurane in the sensitisation of the myocardium to the arrhythmogenic effect of exogenously administered adrenaline.

Indirect-acting Sympathomimetics
There is a risk of acute hypertensive episode with the concomitant use of sevoflurane and indirect-acting sympathomimetic products (amphetamines, ephedrine).

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

Verapamil
Impairment of atrioventricular conduction was observed when verapamil and sevoflurane were administered at the same time.

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.

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 administration is compatible with barbiturates as commonly used in surgical practice

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

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

Nitrous oxide
As with other halogenated volatile anaesthetics, 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 – Maintenance).

Neuromuscular Blocking Agents

As with other inhalational anaesthetic agents, sevoflurane affects both the intensity and duration of neuromuscular blockade by non-depolarising muscle relaxants. When used to supplement alfentanil-N2O anaesthesia, 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 depolarising neuromuscular blockade has not been studied.

Dosage reduction of neuromuscular blocking agents during induction of anaesthesia 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-depolarising muscle relaxants; and, (2) during maintenance of anesthesia, the dose of non-depolarising muscle relaxants is likely to be reduced compared to that during N***2***O/opioid anaesthesia. Administration of supplemental doses of muscle relaxants should be guided by the response to nerve stimulation.

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.

Labor 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 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.

Breast-feeding
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

As with other agents, 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 anaesthesia (see section 4.4).

4.8 Undesirable effects

Summary of the safety profile
As with all potent inhaled anaesthetics, sevoflurane may cause dose-dependent cardio- respiratory depression. Most adverse reactions are mild to moderate in severity and are transient in duration.

Nausea,vomiting and delirium have been observed in the postoperative period, common sequelae of surgery and general anaesthesia, which may be due to the inhalational anaesthetic, other agents administered intra-operatively or post-operatively and to the patient's response 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

Table 2. 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	Agitation
Nervous system disorders	Common	Somnolence Dizziness Headache
	Unknown	Convulsion [2 3] Dystonia
Cardiac disorders	Very Common	Bradycardia Tachycardia
	Common	Atrioventricular block complete
	Uncommon	Cardiac arrest [4]
	Unknown	QT prolongation associated with Torsade
Vascular disorders	Very Common	Hypotension
	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Very Common	Cough Respiratory disorder
	Common	Laryngospasm
	Unknown	Bronchospasm Dyspnoea [1] Wheezing [1]
Gastrointestinal disorders	Very Common	Nausea Vomiting
	Common	Salivary hypersecretion
Hepato-biliary disorders	Unknown	Hepatitis [1 2]

		Hepatic failure [1] [2] Hepatic necrosis [1] [2]
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]
Investigations	Common	Blood glucose abnormal Liver function test abnormal [5] White blood cell count abnormal Fluoride increased [1]
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.

Cardic arrhythmias including ventricular arrhythmias have been reported during sevoflurane anaesthesia.

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, or anaphylactic reaction) have been received, 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. 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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

In the event of apparent overdosage, the following action should be taken: discontinue administration of sevoflurane, maintain a patent airway, initiate assisted or controlled ventilation with oxygen and maintain adequate cardiovascular function.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: anaesthetics, general;halogenated hydrocarbons.

ATC Code: N01AB08.

Changes in the clinical effects of sevoflurane rapidly follow changes in the inspired concentration.

Recovery of cognitive function and motor co-ordination have been evaluated compared to reference drug using a meta-analysis of data generated in clinical trials. Patients administered sevoflurane reached criteria required for discharge from the recovery room significantly sooner than those administered reference drug.

Cardiovascular Effects

As with all other inhalation agents sevoflurane depresses cardiovascular function in a dose related fashion.

Nervous System Effects

No evidence of seizure was observed during the clinical development programme.Sevoflurane does not have any stimulating effect on the sympathetic nervous system.

Sevoflurane has minimal effect on ICP (intra-cranial pressure) and preserves CO_2 responsiveness. In patients at risk for elevations of ICP, sevoflurane should be administered cautiously in conjunction with ICP-reducing manoeuvres such as hyperventilation.

5.2 Pharmacokinetic properties

The low solubility of Sevoflurane in blood would suggest that alveolar concentrations should rapidly increase upon induction and rapidly decrease upon cessation of the inhaled agent. This was confirmed in a clinical study where inspired and end-tidal concentrations of halogenated anaesthetics (F_I and F_A) were measured. The F_A/F_I (wash-in) value at 30 minutes for sevoflurane was 0.85 and 0.73 for isoflurane. The wash-in was faster for sevoflurane than isoflurane at all time points. The F_A/F_{AO} (wash-out) value at 5 minutes was 0.15 for sevoflurane and 0.22 for isoflurane.

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 excreted in the urine.

The rapid and extensive pulmonary elimination of sevoflurane minimises the amount of anaesthetic available for metabolism. The metabolism of sevoflurane is not inducible 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 (CMRO2) in a fashion analogous to that seen with isoflurane. An approximately 50% reduction of CMRO2 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 CO2-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 CO2 absorbents in the circuit) was 15 ppm in children and 32 ppm in adults. In systems using barium lime as CO2 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

Sevoflurane is stable when stored under normal room lighting conditions. No discernible degradation of sevoflurane occurs in the presence of strong acids or heat. Sevoflurane 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 inhaled anaesthetics to CO_2 absorbent within the anaesthesia machine. When used as directed with fresh absorbents, degradation of sevoflurane is minimal and degradants are undetectable or non-toxic. Sevoflurane degradation and subsequent degradant formation are enhanced by increasing absorbent temperature, desiccated CO_2 absorbent (especially potassium hydroxide-containing), increased sevoflurane concentration and decreased fresh gas flow. Sevoflurane 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 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, especially those containing potassium hydroxide the formation of formaldehyde, methanol, carbon monoxide, Compound A and perhaps some of its degradants, Compound B, C and D may occur.

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 Type III amber glass bottles sealed with a poly-seal cap, secured with PET film.

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 via a vaporiser calibrated specifically for sevoflurane using a key filling system designed for sevoflurane specific vaporiser or other appropriate sevoflurane specific vaporiser filling system.

Carbon dioxide absorbents should not be allowed to dry out when inhalational anaesthetics are being administered. Some halogenated anaesthetics have been reported to interact with dry carbon dioxide absorbent to form carbon monoxide. However, in order to minimise the risk of formation of carbon monoxide in re-breathing circuits and the possibility of elevated carboxyhaemoglobin levels, CO_2 absorbents should not be allowed to dry out.

There have been rare cases of excessive heat production, smoke and fire in the anaesthetic machine when sevoflurane has been used in conjunction with a desiccated (dried out) CO_2 absorbent. If the CO_2 absorbent is suspected to be desiccated it should be replaced.

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

7 MARKETING AUTHORISATION HOLDER

Chanelle Medical Unlimited Company
Dublin Road
Loughrea
Co. Galway
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0688/036/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th of April 2017
Date of last renewal: 6th of April 2022

10 DATE OF REVISION OF THE TEXT

October 2021