SCHEDULING STATUS: S5

PROPRIETARY NAME AND DOSAGE FORM

ULTANE Liquid

COMPOSITION

Sevoflurane, which is chemically identified as fluoromethyl-2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether.

Lewis Acid Degradation: At least 300 ppm of water is added as a Lewis Acid inhibitor. No other additives or chemical stabilisers are utilised.

PHARMACOLOGICAL CLASSIFICATION

A 2.1 - Anaesthetics

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Sevoflurane is a halogenated anaesthetic given by inhalation. Sevoflurane depresses respiratory function and blood pressure in a dose-related manner.

Sevoflurane is a dose-related cardiac depressant. Sevoflurane does not produce increases in heart rate at doses less than 2 minimum alveolar concentration (MAC).

A study investigating the epinephrine (adrenaline) induced prodysrhythmogenic effect of sevoflurane in adult patients undergoing transsphenoidal hypophysectomy demonstrated that the threshold dose of epinephrine (i.e. the dose at which the first sign of dysrhythmia was observed) producing multiple ventricular dysrhythmias was 5 micrograms/kg.

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

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

Sevoflurane does not affect renal concentrating ability.

Minimum alveolar concentration (MAC):

The minimum alveolar concentration (MAC) is the concentration at which 50 % of the population tested does not move in response to a single stimulus of skin incision.

For MAC equivalents for sevoflurane for various age groups See **DOSAGE AND DIRECTIONS FOR USE**.

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

Tracheobronchial tree secretions are mildly stimulated.

Pharmacokinetic properties

Solubility:

The low solubility of sevoflurane in blood results in a rapid increase in the alveolar concentrations upon induction and a rapid decrease upon cessation of the inhaled agent. In a clinical study the F_A/F_I (washin) value at 30 minutes for sevoflurane was 0,85. The F_A/F_{AO} (washout) value at 5 minutes was 0,15.

Metabolism:

The rapid pulmonary elimination of sevoflurane minimises the amount of anaesthetic available for metabolism. In humans < 5 % sevoflurane absorbed is metabolised 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. No other metabolic pathways for sevoflurane have been identified.

Fluoride Ion:

The defluorination of sevoflurane is not inducible by barbiturates. Fluoride ion concentrations are influenced by the duration of anaesthesia, the concentration of sevoflurane administered, and the composition of the anaesthetic gas mixture. (See **SIDE-EFFECTS**).

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

PRE-CLINICAL SAFETY DATA

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

Fischer 344 rats were anesthetized within two to three minutes after start of exposure to sevoflurane (1,4 %) for up to ten hours. There were no functional or morphologic defects following administration of sevoflurane.

In a Segment I reproduction study, sevoflurane had no significant effects on male or female reproductive capabilities at exposure concentrations of up to 1.0 MAC (2,2 %). Segment II and III studies in rats indicate sevoflurane is not a selective developmental toxicant.

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

Compound A

In Wistar rats the LC_{50} of Compound A was 1050 to1090 ppm in animals exposed for one hour and 400 to 420 ppm in animals exposed for three hours (median lethal concentrations were approximately 1070 and 330 to 490 ppm, respectively). In rats exposed to 30, 60, or 120 ppm of Compound A in an 8-week chronic toxicity study (24 exposures, three hours/exposure), no apparent evidence of toxicity was observed other than loss of body weight in females on the last study day.

Sprague-Dawley rats were administered Compound A via nose-only inhalation exposure in an open system (25, 50, 100 or 200 ppm [0,0025 to 0,02 %] of Compound A). Control groups were exposed to air. The threshold, at which reversible alterations in urinary and clinical parameters indicative of renal changes (concentration-dependent increases in BUN, creatinine, glucose, protein/creatinine ratios and N-acetyl-glucosamidase/creatinine ratios) were observed, was 114 ppm of Compound A. Histological lesions were all reversible.

Since the uptake of inhalational agents in small rodents is substantially higher than in humans, higher levels of drug, Compound A (degradant of sevoflurane) or 2-bromo-2-chloro-1,1-difluoro ethylene (BCDFE) (degradant/metabolite of halothane) would be expected in rodents. Also, the activity of the key enzyme (β-lyase) involved in haloalkene nephrotoxicity is ten-fold greater in the rat than it is in humans.

Compound A concentrations are reported to increase with increasing absorber temperature, increasing sevoflurane concentrations and with decreasing fresh gas flow rates. It has been reported that the concentration of Compound A increases significantly with prolonged dehydration of Baralyme. In the clinical situation, the highest concentration of Compound A in the anaesthesia circuit with soda lime as the CO_2 absorbent was 15 ppm in paediatrics and 32 ppm in adults. However, concentrations to 61 ppm have been observed in patients attached to systems with Baralyme® as the CO_2 absorbent. The level of Compound A at which toxicity occurs in humans is not known. Although exposure to sevoflurane in low flow systems is limited, there has been no evidence of renal dysfunction attributable to Compound A.

Compound B

In the clinical situation, the concentration of Compound B detected in the anaesthesia circuit did not exceed 1,5 ppm. Inhalation exposure to Compound B at concentrations of up to 2400 ppm (0,24 %) for three hours resulted in no adverse effects on renal parameters or tissue histology in Wistar rats.

Carcinogenesis

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

DESCRIPTION OF CLINICAL STUDIES

Efficacy

Numerous clinical studies have been conducted with sevoflurane as the anaesthetic agent for paediatric and adult patients. The results have shown sevoflurane provides smooth, rapid induction of, as well as rapid emergence from, anaesthesia.
Sevoflurane was associated with faster times to induction and to such recovery events as emergence, response to command, and orientation compared to reference drugs.

Adult Anaesthesia

Mask Induction

In adult studies in which mask induction was performed, sevoflurane was demonstrated to provide smooth and rapid induction of anaesthesia.

Maintenance

In 3 outpatient and 25 inpatient studies involving 3591 adult patients (2022 sevoflurane, 1196 isoflurane, 111 enflurane, 262 propofol) sevoflurane was demonstrated to be an effective agent for the maintenance of anaesthesia.

Sevoflurane was demonstrated to be an appropriate agent for use in neurosurgery, Caesarean section, patients undergoing coronary artery bypass surgery (CABG), and non-cardiac patients at risk for myocardial ischaemia.

Paediatric Anaesthesia

In two outpatient and three inpatient studies involving 1498 paediatric patients (837 sevoflurane, 661 halothane), sevoflurane was demonstrated to be an effective agent for the induction and maintenance of anaesthesia.

Mask Induction

In paediatric studies in which mask induction was performed, the induction time was statistically significantly shorter and the incidence of coughing was statistically significantly lower with sevoflurane than with halothane.

Safety

Clinical studies were conducted in a wide variety of patient populations (children, adults, elderly, renally impaired, hepatically impaired, obese, patients undergoing cardiac by-pass surgery, patients treated with aminoglycosides or metabolic inducers, patients exposed to repeat surgeries, patients undergoing surgeries ≥ 6 hours in duration). The results of evaluations of laboratory parameters (e.g., SGPT, SGOT, alkaline phosphatase, total bilirubin, serum creatinine, BUN) as well as investigator-reported incidence of adverse events relating to hepatic and renal function, demonstrated sevoflurane did not have a clinically significant effect on liver or kidney function, nor did it exacerbate pre-existing renal or hepatic impairment within these study populations (see **WARNINGS AND SPECIAL PRECAUTIONS – Hepatic** and **SIDE-EFFECTS**). These studies also demonstrated there were no statistically significant differences between sevoflurane and reference agents in the proportions of patients showing changes in any clinical chemistry parameter.

The impact on renal function was comparable among sevoflurane and the reference drugs, between types of anaesthesia circuits, among flow rates, and between patients with or without inorganic fluoride concentrations ≥ 50 µm.

The incidence of renal dysfunction was < 1 % for both sevoflurane (0,17 %) and reference drugs (0,22 %; isoflurane, halothane, enflurane, propofol) in comparative studies. This overall incidence is consistent with that of a general surgical population. In all cases, an alternate cause or reasonable explanation existed for the renal dysfunction.

Paediatric

Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/sedation drug administration or other factors such as the surgery or underlying illness. In addition, more recent published registry studies did not confirm these findings.

Published animal studies of some anaesthetic/sedation drugs have reported adverse effects on brain development in early life (see **PRE-CLINICAL SAFETY DATA**).

Hepatically Impaired

During clinical development, sevoflurane was effective and well-tolerated when used as the primary agent for the maintenance of anaesthesia in patients with impaired hepatic function, Child-Pugh Class A and B, and sevoflurane did not exacerbate pre-existing hepatic impairment. For hepatic adverse events seen in postmarketing experience, see **WARNINGS AND SPECIAL PRECAUTIONS – Hepatic** and **SIDE-EFFECTS.**

Renally Impaired

Sevoflurane was evaluated in renally impaired patients with baseline serum creatinine ≥1,5 mg/dL (130 µmole/L). Based on the incidence and magnitude of changes in serum creatinine concentrations, sevoflurane did not further deteriorate renal function.

INDICATIONS

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

CONTRA-INDICATIONS

ULTANE should not be used in patients with known or suspected hypersensitivity to **ULTANE** or to other halogenated agents *(e.g. history of hepatotoxicity, usually including elevated liver enzymes, fever, leukocytosis and/or eosinophilia temporally related to anaesthesia with one of these agents).*

ULTANE should not be used in patients with known or suspected genetic susceptibility to malignant hyperthermia (See **WARNINGS AND SPECIAL PRECAUTIONS**).

ULTANE should not be used in patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy. (See **WARNINGS AND SPECIAL PRECAUTIONS**).

WARNINGS AND SPECIAL PRECAUTIONS

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.

ULTANE should be administered only by persons trained in the administration of general anaesthesia. Facilities for maintenance of a patent airway, artificial ventilation and oxygen enrichment and circulatory resuscitation must be immediately available.

Since levels of anaesthesia may be altered easily and rapidly, only vaporisers specifically calibrated for **ULTANE** should be used. Hypotension and respiratory depression increase as anaesthesia is deepened.

Malignant hyperthermia: In susceptible individuals **ULTANE** 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, dysrhythmias, and/or unstable blood pressure. Some of these non-specific signs may also appear during light anaesthesia, acute hypoxia, hypercapnia and hypovolaemia. Fatalities have occurred.

Treatment of malignant hyperthermia includes discontinuation of **ULTANE** administration of intravenous dantrolene sodium and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base abnormalities.
Renal failure may appear later, and urine flow should be monitored and sustained if possible.

Perioperative Hyperkalaemia: Use of inhaled anaesthetic agents, including **ULTANE**, has been associated with increases in serum potassium levels that have resulted in cardiac dysrhythmias and death in paediatric patients during the peri-operative period. Patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy, appear to be most vulnerable (see **CONTRA-INDICATIONS**). Concomitant use of succinylcholine has been associated with most, but not all, of these cases. These patients also experienced significant elevations in serum creatine phosphokinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalaemia and resistant dysrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Reports of QT prolongation, associated with Torsades de Pointes, have been received. Caution should be exercised when administering **ULTANE** to susceptible patients.

Hepatic: Cases of mild, moderate and severe post-operative hepatic dysfunction or hepatitis with or without jaundice have been reported from post-marketing experiences.

Caution should be exercised when **ULTANE** is used in patients with underlying hepatic conditions or under treatment with medicines known to cause hepatic dysfunction. (See **SIDE-EFFECTS**)

It has been reported that previous exposure to halogenated hydrocarbon anaesthetics may increase the potential for hepatic injury.

General: During maintenance of anaesthesia, increasing the concentrations of **ULTANE** 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 **ULTANE**.

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 recovery of consciousness following **ULTANE** administration generally occurs within minutes, the impact on intellectual function for two or three days following anaesthesia has not been studied. Changes in mood may persist for several days following administration.

Replacement of Desiccated CO_2 Absorbents: Cases of extreme heat, smoke and/or spontaneous fire in the anaesthesia machine have been reported during **ULTANE** use in conjunction with the use of desiccated CO_2 absorbent. A delayed rise or unexpected decline of inspired **ULTANE** concentration compared to the vaporiser setting may be associated with excessive heating of the CO_2 canister.

The exothermic reaction that occurs with **ULTANE** and CO_2 absorbents is increased when the CO_2 absorbent becomes desiccated, such as after an extended period of dry gas flow through the CO_2 absorbent canisters. **ULTANE** 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 **ULTANE** concentrations

(8 %) for extended periods of time (≥ 2 hours). *(Compound A is pentafluoroisopropanyl fluoromethyl ether, Compound B is the methoxy addition product formed after reaction of Compound A with methanol, and Compound B can undergo further HF elimination to form Compounds C, D and E).* 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.

When a clinician suspects that the CO_2 absorbent may be dessicated, it should be replaced before administration of **ULTANE**. 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.

Renal Impairment: Because of the small number of patients with renal insufficiency studied (baseline serum creatinine greater than 15 mg/L (133 µmol/L), the safety of **ULTANE** administration in this group has not yet been fully established. Therefore, **ULTANE** should be used with caution in patients with renal insufficiency.

Neurosurgery: In patients at risk for an increase in intracranial pressure, **ULTANE** should be administered cautiously in conjunction with measures to reduce intracranial pressure (such as hyperventilation).

Seizures: Cases of seizures have been reported in association with **ULTANE** use. (See **SIDE-EFFECTS**)

Paediatric use: The use of **ULTANE** 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 factors. Clinical judgement should be exercised when using **ULTANE** in patients who may be at risk for seizures.

Hypersensitivity: Reports of hypersensitivity (including contact dermatitis, rash, dyspnoea, wheezing, chest discomfort, swelling face or anaphylactic reaction) have been received, including cases of association with long-term occupational exposure to **ULTANE**.

Sevoflurane Degradation: **ULTANE** 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, aluminum, 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 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, the formation of formaldehyde, methanol, carbon monoxide, Compound A and perhaps some of its degradants, Compounds B, C, and D may occur.

Effects on ability to drive and use machines

Patients should be advised that performance of activities requiring mental alertness, such as decision making or operating a motor vehicle or hazardous machinery, may be impaired for some time after general anaesthesia**.**

INTERACTIONS

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.

Barbiturates:

ULTANE administration is compatible with barbiturates.

Benzodiazepines and Opioids:

Benzodiazepines and opioids decrease the MAC of **ULTANE. ULTANE** administration is compatible with benzodiazepines and opioids.

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 **ULTANE** and lead to significant increases in plasma fluoride concentrations.

Nitrous oxide:

The MAC of **ULTANE** is decreased when administered in combination with nitrous oxide. The MAC equivalent is reduced approximately 50 % in adult and approximately 25 % in paediatric patients. Altitude may affect the effects of nitrous oxide.

Neuromuscular blocking agents:

ULTANE affects both the intensity and duration of neuromuscular blockade by non-depolarising muscle relaxants. When used to supplement alfentanil N_2O anaesthesia, **ULTANE** potentiates neuromuscular block induced with pancuronium, vecuronium or atracurium. The effect of **ULTANE** 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 **ULTANE** administration.

Among non-depolarising 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, (2) during maintenance of anaesthesia, the dose of non-depolarising muscle relaxants is likely to be reduced compared to that during N_2O/opioid anaesthesia. Administration of supplemental doses of muscle relaxants should be guided by the response to nerve stimulation.

PREGNANCY AND LACTATION

Safety in pregnancy or lactation has not been established. The safety of **ULTANE** in labour and delivery has not been demonstrated. **ULTANE** may be used for anaesthesia during Caesarean section.

Published animal studies of some anaesthetic/sedation drugs have reported adverse effects on brain development in early life (see **PRE-CLINICAL SAFETY DATA**).

ULTANE has relaxant effects on the uterus with the potential risk for uterine bleeding. Caution should be observed when using **ULTANE** during obstetric anaesthesia.

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

DOSAGE AND DIRECTIONS FOR USE

Surgical-anaesthesia:

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

Induction:

Dosage should be individualised and titrated to the desired effect according to the patient's age and clinical status. A short acting intravenous induction agent may be administered, followed by inhalation of **ULTANE**. Induction with **ULTANE** may be achieved in oxygen or in combination with oxygen-nitrous oxide mixtures. Inspired concentrations of up to 8 % **ULTANE** usually produce surgical anaesthesia in less than 2 minutes in both adults and children.

Maintenance:

Surgical levels of anaesthesia may be sustained with concentrations of 0,5 - 3 % **ULTANE** with or without the concomitant use of nitrous oxide.

Elderly: Lesser concentrations of **ULTANE** are normally required to maintain surgical anaesthesia.

MAC values in Adults and Paediatric Patients According to Age		
Age of patient (years)	Sevoflurane in oxygen	Sevoflurane in 65 % N_2O/35 % O_2
0 - 1 month *	3,3 %	
1 - < 6 months	3,0 %	
6 months - < 3 years	2,8 %	2,0 % **
3 - 12	2,5 %	
25	2,6 %	1,4 %
40	2,1 %	1,1 %
60	1,7 %	0,9 %
80	1,4 %	0,7 %
* Neonates are full-term gestational age. MAC in premature infants has not been determined ** In 3 - < 5 year old paediatric patients, 60 % N_2O/40 % O_2 was used.		

Emergence:

Emergence times are generally short following **ULTANE** anaesthesia. Therefore, patients may require postoperative pain relief earlier.

SIDE-EFFECTS

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

Adverse events are displayed in the following tables by System Organ Class and frequency, according to the following convention: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000); and very rare (≤ 1/ 10 000).

CLASSIFICATION OF ADVERSE EVENTS REPORTED WITH SEVOFLURANE USE IN CONTROLLED CLINICAL TRIALS*

System Organ Class	**Frequency**	**Adverse Reactions ** **
Psychiatric disorders	Common	Agitation
Nervous system disorders	Common	Somnolence Dizziness Headache
Cardiac disorders	Very common	Bradycardia
	Common	Tachycardia
	Uncommon	Atrioventricular block complete
	Unknown	QT prolongation associated with Torsade
Vascular disorders	Very common	Hypotension
	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Very common	Cough
	Common	Respiratory disorder Laryngospasm
Gastrointestinal disorders	Very common	Nausea Vomiting
	Common	Salivary hypersecretion

General disorders and administration site conditions	Common	Chills Pyrexia
Investigations	Common	Increased blood glucose Abnormal liver function test Increased white blood cell count Increased fluoride[#]
Injury, poisoning and procedural complications	Common	Hypothermia

[#] Increases in serum inorganic fluoride levels may occur during and after **ULTANE** anaesthesia. Concentrations of inorganic fluoride generally peak within two hours of the end of **ULTANE** anaesthesia and return within 48 hours to pre-operative levels. In clinical trials, elevated fluoride levels were not associated with impairment of renal function.

***** Classification based on the reported incidence of adverse events in controlled clinical trials on sevoflurane use.

** Adverse event terms are listed in MedDRA 8.0 terminology.

CLASSIFICATION OF ADVERSE EVENTS REPORTED WITH SEVOFLURANE USE IN SPECIAL PATIENT GROUPS IN CONTROLLED CLINICAL TRIALS*

USE IN CHILDREN POST-SURGICALLY

System Organ Class	**Frequency**	**Adverse Reactions ****
Psychiatric disorders	Very common	Agitation
Respiratory, thoracic and mediastinal disorders	Very common	Cough

Gastrointestinal disorders	Very common	Vomiting, nausea

USE IN ADULTS

System Organ Class	**Frequency**	**Adverse Reactions ****
Vascular disorders	Very common	Hypotension
Gastrointestinal disorders	Very common	Nausea, vomiting

USE IN ELDERLY PATIENTS

System Organ Class	**Frequency**	**Adverse Reactions ****
Cardiac disorders	Very common	Bradycardia
Vascular disorders	Very common	Hypotension
Gastrointestinal disorders	Very common	Nausea, vomiting

***** Classification based on the reported incidence of adverse events in controlled clinical trials on sevoflurane use in children post-surgically, adults and elderly patients.

** Adverse event terms are listed in MedDRA 8.0 terminology.

Post-marketing reports

Adverse reactions have been spontaneously reported during post-approval use of **ULTANE**. These events are reported voluntarily from a population of an unknown rate of exposure. Therefore it is not possible to estimate the true incidence of adverse events or establish a causal relationship to **ULTANE** exposure.

Immune system disorders

Anaphylactic reaction, anaphylactoid reaction.

Nervous system disorders

Convulsion, dystonia

Seizure-like activity may occur on less frequent occasions following **ULTANE** administration. Reported events were of short duration and there was no evidence of any abnormality during emergence from anaesthesia or in the post-operative period.

Cardiac disorders

Cardiac arrest

There have been reports of QTc prolongation and cardiac arrest in the setting of **ULTANE** use.

Respiratory, thoracic and mediastinal disorders

Bronchospasm.

Hepato-biliary disorders

Cases of post-operative hepatitis have been reported. In addition, there have been post-marketing reports of hepatic failure and hepatic necrosis associated with the use of **ULTANE**. However, the actual incidence and relationship of **ULTANE** to these events cannot be established with certainty.

Skin and sub-cutaneous tissue disorders

Pruritus, rash, urticaria.

General disorders and administration site conditions

Malignant hyperthermia

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

In the event of apparent overdosage, the following action should be taken:

Discontinue administration of **ULTANE**, maintain a patent airway, initiate assisted or controlled ventilation with oxygen and maintain adequate cardiovascular function.

IDENTIFICATION

ULTANE is a clear, colourless liquid.

PRESENTATION

ULTANE is supplied in 100 ml or 250 ml amber glass or amber 250 ml polyethylene naphthalate (PEN) bottles.

STORAGE INSTRUCTIONS

Store at room temperature (below 25 °C).

Protect from light.

Keep out of reach of children.

REGISTRATION NUMBER

29/2.1/0748

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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