PRODUCT MONOGRAPH

Pr SUPRANE

(desflurane, USP) 100% v/v
Liquid for Inhalation

Inhalation Anesthetic

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Canada L5N 0C2

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Pr SUPRANE
(desflurane, USP)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Inhalation	Volatile Liquid, 100% v/v (desflurane, USP)	None

INDICATIONS AND CLINICAL USE

Adults

SUPRANE (desflurane) is indicated as an inhalation agent for maintenance of general anesthesia following induction with agents other than SUPRANE (desflurane) in adults.

SUPRANE (desflurane) is not recommended for mask induction of anesthesia in adults because of a high incidence of moderate to severe upper airway adverse events (see **ADVERSE REACTIONS**).

Geriatrics (> 65 years of age)

The minimum alveolar concentration (MAC) of SUPRANE (desflurane) decreases with increasing patient age. The dose should be adjusted accordingly (see **WARNINGS AND PRECAUTIONS**, **Special Populations**, **Geriatrics**).

Pediatrics

SUPRANE (desflurane) is indicated as an inhalation agent for maintenance of general anesthesia following induction with agents other than SUPRANE (desflurane) and subsequent endotracheal intubation in pediatric patients.

SUPRANE (desflurane) is not recommended for mask induction of anesthesia in pediatric patients because of a high incidence of moderate to severe upper airway adverse events (see **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS**, **Special Populations, Pediatrics**, and **ADVERSE REACTIONS**).

CONTRAINDICATIONS

- When general anesthesia is contraindicated.
- Known sensitivity to SUPRANE (desflurane), other halogenated anesthetics, or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.
- Patients with a history of hepatitis due to a halogenated inhalational anesthetic or in whom liver dysfunction, jaundice or unexplained fever, leucocytosis, or eosinophilia has occurred after a previous halogenated anesthetic administration (see **WARNINGS AND PRECAUTIONS**, **Hepatic/Biliary/Pancreatic**).
- Known or suspected genetic susceptibility to malignant hyperthermia or in patients with a history of malignant hyperthermia (see **WARNINGS AND PRECAUTIONS**, **Malignant Hyperthermia (MH)**).
- Desflurane is contraindicated for use as an inhalation induction agent in pediatric patients because of the frequent occurrence of cough, breath holding, apnea, laryngospasm and increased secretions (see **INDICATIONS**, **Pediatrics**).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Administration only by qualified individuals trained in general anesthesia using a vaporizer specific to SUPRANE (desflurane) in adequately equipped facilities (see **General** section below);
- SUPRANE (desflurane) can react with desiccated carbon dioxide absorbents to produce carbon monoxide resulting in elevated carboxyhemoglobin levels (see **General** section below);
- SUPRANE (desflurane) may trigger Malignant Hyperthermia in susceptible individuals and fatal outcomes have been reported (see **Malignant Hyperthermia** section below);
- SUPRANE (desflurane) use may lead to Perioperative Hyperkalemia in patients with neuromuscular disorders (see **Perioperative Hyperkalemia** section below);
- In pediatric patients, SUPRANE (desflurane) is not recommended for induction of anesthesia because of moderate to severe upper airway adverse events observed in clinical studies (see **CONTRAINDICATIONS** and **Special Populations**, **Pediatrics**).

General

SUPRANE (desflurane) should be administered only by persons trained in the administration of general anesthesia, using a vaporizer specifically designed and designated for use with SUPRANE (desflurane). Facilities and equipment for maintenance of a patent airway, artificial ventilation, oxygen enrichment and circulatory resuscitation must be immediately available. Hypotension and respiratory depression increase as anesthesia is deepened.

Safe Use of CO_2 Absorbents

SUPRANE (desflurane) can react with desiccated carbon dioxide (CO_2) absorbents to produce carbon monoxide, which may result in elevated levels of carboxyhemoglobin in some patients. In clinical practice, cases of elevated carboxyhemoglobin have been reported in association with SUPRANE (desflurane). Case reports suggest that barium hydroxide lime and soda lime become desiccated when fresh gases are passed through the CO_2 absorbent canister at high flow rates over many hours or days. When a clinician suspects that CO_2 absorbent may be desiccated, it should be replaced before the administration of SUPRANE (desflurane). The color indicator of most CO_2 absorbents does not necessarily change as a result of desiccation. Therefore, the lack of significant color change should not be taken as an assurance of adequate hydration. CO_2 absorbents should be replaced routinely regardless of the state of the color indicator.

As with other inhalational anesthetic agents, the use of CO_2 absorbents without strong bases is preferable.

SUPRANE (desflurane) is not recommended for mask induction as it causes a high incidence of laryngospasm, coughing, breath holding, apnea, increase in secretions and oxyhemoglobin desaturation (see **ADVERSE REACTIONS**).

As with any inhalation agent, the use of SUPRANE (desflurane) proportionately decreases the concentration of all other gases administered concurrently, including oxygen (O_2). For example, the addition of 10% SUPRANE (desflurane) to 70% nitrous oxide (N_2O) and 30% O_2 reduces the O_2 concentration to 27%.

Nitrous oxide diminishes the inspired concentration of SUPRANE (desflurane) required to reach a desired level of anesthesia (see **DOSAGE AND ADMINISTRATION**, **Table 6**).

Cardiovascular

Caution should be exercised when administering SUPRANE (desflurane) to susceptible patients. SUPRANE (desflurane), like other inhalation anesthetic agents, may prolong the QT interval in adults and children. This effect is exacerbated by some of the patient's disease conditions or concomitant

medications (e.g., patients with congenital Long QT Syndrome or patients taking drugs that can prolong the QT interval).

In healthy volunteers, in the absence of concomitant N_2O and/or opioid administration, sudden step increases in the end-tidal concentration of SUPRANE (desflurane) may cause transient increases in sympathetic activity with associated increases in heart rate and blood pressure. The hemodynamic changes are more common at concentrations ≥ 6% and more severe with large (≥ 1%), sudden increments. Without treatment, and without further increases in SUPRANE (desflurane) concentration, these increases in heart rate and blood pressure resolve in approximately 4 minutes. At the new, higher end-tidal SUPRANE (desflurane) concentration blood pressure is likely to be lower and heart rate higher than at the previous, lower steady-state SUPRANE (desflurane) concentration. The transient increases of heart rate and blood pressure are less if the end-tidal concentration of SUPRANE (desflurane) is increased in increments of 1% or less. However, if during the transiently increased heart rate and blood pressure the end-tidal concentration of SUPRANE (desflurane) is again rapidly increased, further increase of heart rate and blood pressure may result. Administration of sympatholytic drugs (fentanyl, alfentanil, esmolol, clonidine) prior to a sudden step increase of SUPRANE (desflurane) blunts or blocks the increase in heart rate and blood pressure. The sympathetic response is not obtunded by intravenous or endotracheal lidocaine or by intravenous propofol (see ACTION AND CLINICAL PHARMACOLOGY).

When SUPRANE (desflurane) is used in the clinical setting, the following should be considered:

- **In patients with or at risk of coronary artery disease, maintenance of normal hemodynamics is important to avoid myocardial ischemia. Marked increases in pulse rate, mean arterial pressure and levels of epinephrine and norepinephrine are associated with a rapid increase in desflurane concentrations. SUPRANE (desflurane) should not be used as the sole anesthetic in patients with or at risk of coronary artery disease or in patients where increases in heart rate or blood pressure are undesirable. Rapid inhaled induction of anesthesia with SUPRANE (desflurane) alone, without concomitant administration of an opioid, in patients with coronary artery disease, has been associated with an increased incidence of myocardial ischemia. SUPRANE (desflurane), when given in conjunction with opioids for maintenance of anesthesia in patients with coronary artery disease, has not produced an incidence of ischemia different from that produced by other anesthetics. Thus, when SUPRANE (desflurane) is to be used in patients with coronary artery disease, it should always be used in combination with other medications, such as intravenous opioids or hypnotics, and it should not be used for induction (see ACTION AND CLINICAL PHARMACOLOGY).**

- **When changing the depth of anesthesia, rapid increases in the end-tidal concentration of SUPRANE (desflurane) should be avoided and the end-tidal concentration increased in small increments of 1% or less. It is not necessary to deliver concentrations of SUPRANE (desflurane) far in excess of the desired end-tidal concentration ("overpressurization" technique) due to the low blood and tissue solubilities of SUPRANE (desflurane) and the resulting rapid equilibrium of alveolar concentration with inspired and delivered concentrations; thus the transient and self-limiting increases in heart rate and blood pressure may be avoided.**

- **During maintenance of anesthesia, increases in heart rate and blood pressure occurring after rapid incremental increases in end-tidal concentration of SUPRANE (desflurane) may not represent inadequate anesthesia. The changes due to sympathetic activation resolve in approximately 4 minutes. Increases in heart rate and blood pressure occurring before or in the absence of a rapid increase in SUPRANE (desflurane) concentration, may be interpreted as light anesthesia. Thus, in such patients, incremental increases of 0.5 – 1.0% end-tidal SUPRANE (desflurane) may attenuate these signs of light anesthesia, as may concomitant administration of analgesics. Should raised heart rate and blood pressure persist, then other causes should be sought.**

There are no data regarding the cardiovascular effects of SUPRANE (desflurane) in hypovolemic and hypotensive patients.

Endocrine and Metabolism

As with other halogenated anesthetic agents, there is some elevation of glucose intraoperatively. This factor should be taken into consideration, especially in diabetic patients. (See **ADVERSE REACTIONS**, **Abnormal Hematologic and Clinical Chemistry Findings**).

Malignant Hyperthermia (MH):

SUPRANE (desflurane) anesthesia is contraindicated in subjects known to be susceptible to MH. In susceptible individuals, SUPRANE (desflurane) anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. Some of these nonspecific signs may also appear during light anesthesia, acute hypoxia, hypercapnia and hypovolemia. An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO_2 absorption system (hot canister). PaO_2 and pH may decrease, and

hyperkalemia and a base deficit may appear. Treatment includes discontinuation of SUPRANE (desflurane), 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 derangements. Renal failure may appear later, and urine flow should be monitored and sustained if possible. Fatal outcome of malignant hyperthermia has been reported with desflurane**.**

Pheochromocytoma/neuroblastoma: There are insufficient data on the use of SUPRANE (desflurane) in patients with pheochromocytoma and neuroblastoma. Since SUPRANE (desflurane) can cause stimulation of the sympathetic nervous system, its use is not recommended in patients with these conditions (see **WARNINGS AND PRECAUTIONS**).

Hepatic/Biliary/Pancreatic

SUPRANE (desflurane) is contraindicated in patients with a history of hepatitis due to a halogenated inhalational anesthetic or in whom liver dysfunction, jaundice or unexplained fever, leucocytosis, or eosinophilia has occurred after a previous halogenated anesthetic administration.

Cases of mild, moderate, and severe postoperative hepatic dysfunction or hepatitis with or without jaundice, including fatal hepatic necrosis and hepatic failure, have been reported with SUPRANE (desflurane). As with other halogenated anesthetics, SUPRANE (desflurane) may cause sensitivity hepatitis in patients who have been sensitized by previous exposure to a halogenated anesthetic. Such reactions may also occur after the first exposure to SUPRANE (desflurane).

Although the mechanism by which this occurs is still unclear, data from studies on halothane suggests that metabolism by cytochrome P450 2E1 (CYP2E1) catalyzes formation of trifluoroacetylated haptens, which may be implicated as target antigens in the mechanism of halothane-induced hepatitis. Although other halogenated anesthetics are believed to be metabolized to a much lesser degree by the CYP2E1 system (20% by halothane compared to 0.01% desflurane), the reported hepatic injuries share similarities with that associated with halothane.

In patients with pre-existing hepatic abnormalities or under treatment with drugs known to cause hepatic abnormalities, clinical judgment should be exercised and appropriate alternative general anesthesia should be considered. Specialized care is recommended when a patient presents with any postoperative hepatic dysfunction after receiving a halogenated inhalational anesthetic.

Neurologic

Although recovery of consciousness following desflurane administration generally occurs within minutes, the impact on intellectual function for two or three days following anesthesia has not been studied. As with other anesthetics, small changes in mood may persist for several days following

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

Peri-Operative Considerations

As with all halogenated anesthetics, repeated anesthesia within a short period of time should be approached with caution.

Since awakening is rapid with SUPRANE (desflurane), as with other rapidly-acting anesthetic agents, care should be taken that appropriate analgesia has been administered to the patient at the end of the procedure or early in the post-anesthesia care unit stay. Rapid awakening with pain may be associated with agitation, particularly in pediatric patients.

Respiration and cardiovascular function must be monitored closely and supported when necessary.

There is no information of the effects of desflurane following anesthesia on the ability to operate an automobile or other heavy machinery. However, patients should be advised that the ability to perform such tasks may be impaired after general anesthesia.

Perioperative Hyperkalemia: Use of inhaled anesthetic agents, including desflurane, has been associated with rare increases in serum potassium levels that have resulted in cardiac arrhythmias, some fatal, in patients during the postoperative period. Patients with latent as well as overt muscular dystrophies, 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 creatinine kinase levels and, in some cases, changes in urine consistent with myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state. Early and aggressive intervention to treat the hyperkalemia and resistant arrhythmias is recommended, as is subsequent evaluation for latent neuromuscular disease.

Neurosurgery: Due to the limited number of patients studied, the safety of SUPRANE (desflurane) has not been established and is not recommended for use in neurosurgical procedures (see **CLINICAL TRIALS**).

Special Populations

SUPRANE should only be used in pregnant women, including women in labour and delivery, or young children when its benefits outweigh potential risks. Patients should be followed up post-operatively after exposure to SUPRANE as appropriate to identify potential adverse effects (See **TOXICOLOGY**, **Reproductive Toxicology**).

Pregnant Women: Due to the limited number of patients studied, the safety of SUPRANE (desflurane) has not been established for use in obstetric procedures. Volatile inhalational anesthetics, including SUPRANE (desflurane), inhibit uterine contraction and reduce uteroplacental blood flow. There are no adequate data from the use of SUPRANE (desflurane) in pregnant women.

Nursing Women: There are no adequate data from the use of SUPRANE (desflurane) in lactating women. SUPRANE (desflurane) is not recommended for use in lactating women unless the benefits outweigh the risks.

Pediatrics: SUPRANE (desflurane) is contraindicated for induction in pediatric patients because of a high incidence of moderate to severe upper airway adverse events, including coughing (72%), breathholding (63%), laryngospasm (50%), oxyhemoglobin desaturation (SpO_2 < 90%) (26%) and increased secretions (21%) observed in clinical studies. After induction of anesthesia with agents other than SUPRANE (desflurane) and subsequent tracheal intubation, SUPRANE is indicated for maintenance of anesthesia in pediatric patients.

Desflurane should be used with caution in children with asthma or a history of recent upper airway infection due to the potential for airway narrowing and increases in airway resistance.

SUPRANE (desflurane) should not be used for maintenance of anesthesia in non-intubated pediatric patients due to an increased incidence of respiratory adverse reactions, including coughing, laryngospasm and secretions, especially with removal of the laryngeal mask airway (LMA) under deep anesthesia in pediatric patients 6 years old or younger. The safety of SUPRANE (desflurane) has not been investigated in non-intubated pediatric patients younger than 2 years of age due to increased incidence of respiratory events observed in the 2 – 16 year age group.

The minimum alveolar concentration (MAC) of SUPRANE (desflurane) in pediatric patients is higher than that in young adults (see **DOSAGE AND ADMINISTRATION**). In pediatric patients, emergence from anesthesia may evoke a brief state of agitation that may hinder cooperation. Several studies in the literature have reported frequent agitation upon emergence from SUPRANE (desflurane) anesthesia in children. These studies varied with regards to the age of patients, surgical procedures, anesthetic techniques, pain management strategies, adjuvant medications and assessment tools for emergence agitation. It is unknown whether this is related to SUPRANE (desflurane) or to the rapid transition from anesthesia to consciousness.

Geriatrics (> 65 years of age): The MAC in geriatric patients is approximately 70% of the adult dose in 100% oxygen and 40% the adult dose in 60% nitrous oxide (see **DOSAGE AND ADMINISTRATION**, **Table 6**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious reported adverse events in alphabetical order are apnea, bronchospasm, cardiac arrest, hepatic failure, hyperkalemia, hypotension, malignant hyperthermia, and respiratory depression.

The most frequent adverse events (incidence > 10%) are cough, nausea, vomiting, salivary hypersecretion and oxyhemoglobin desaturation.

All of the adverse events that are listed in this section may result in the need for clinical diagnosis or treatment.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse event information is derived from controlled clinical trials. The studies were conducted using a variety of premedications, other anesthetics, and surgical procedures of varying length. Of the 1,843 patients exposed to SUPRANE (desflurane) in clinical trials, 1,209 were used in estimating the incidence of adverse events below. Of these, 370 adults and 152 children were induced with SUPRANE (desflurane) alone and 687 patients were maintained principally with SUPRANE (desflurane). Frequencies reflect the percent of patients with the event and each patient was counted once for each type of adverse event. They are listed by organ class, then by decreasing frequency.

Table 1 –Treatment-Emergent Adverse Events with Incidence ≥ 1% - Induction (use as a mask inhalation agent)

Induction (use as a mask inhalation agent)			
System Organ Class (SOC)	**Adverse Event (Preferred MedDRA Term)**	**Incidence (%)**	
		Adult Patients (N=370)	**Pediatric Patients (N=152)**
GASTROINTESTINAL DISORDERS	**Increased secretions**	9	21
INFECTIONS AND INFESTATIONS	**Pharyngitis**	4	-
PSYCHIATRIC DISORDERS	**Breath holding**	27	63
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	**Coughing**	34	72
	Apnea	15	-
	Laryngospasm	8	50
	Oxyhemoglobin desaturation (SpO_2 < 90%)	8	26
	Bronchospasm	-	3

Table 2 – Treatment-Emergent Adverse Events with Incidence ≥ 1% - Maintenance or Recovery

	Maintenance or Recovery (Incidence ≥ 1%)	
System Organ Class (SOC)	**Adverse Event (Preferred MedDRA Term)**	**Incidence (%)**
		Adult and *Pediatric Patients (N=687)
CARDIAC DISORDERS	**Bradycardia**	1
	Hypertension	1
	Nodal arrhythmia	1
	Tachycardia	1
EYE DISORDERS	**Conjunctivitis (conjunctival hyperemia)**	2
GASTROINTESTINAL DISORDERS	**Nausea**	27
	Vomiting	16
	Increased salivation	1
INFECTIONS AND INFESTATIONS	**Pharyngitis**	1
NERVOUS SYSTEM DISORDERS	**Headache**	1
PSYCHIATRIC DISORDERS	**Breath holding**	2
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS	**Apnea**	7
	Cough increased	4
	Laryngospasm	3

* Includes data for intubated pediatric patients

Table 3 – Treatment-Emergent Adverse Events with Incidence > 1% - Maintenance in Non-intubated Pediatric Patients

Maintenance in Non-intubated Pediatric Patients (face mask or LMA used; N=300) All Respiratory Events* (>1% of All Pediatric Patients)				
	All Ages (N=300)	2-6 yr (N=150)	7-11 yr (N=81)	12-16 yr (N=69)
Any respiratory events	39%	42%	33%	39%
Airway obstruction	4%	5%	4%	3%
Breath-holding	3%	2%	3%	4%
Coughing	26%	33%	19%	22%
Laryngospasm	13%	16%	7%	13%
Secretion	12%	13%	10%	12%
Non-specific desaturation	2%	2%	1%	1%

*Minor, moderate and severe respiratory events

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Treatment-emergent adverse events with incidence less than 1% and reported in 3 or more patients, regardless of severity (N=1,843)

Cardiac Disorders: Myocardial Infarction, Myocardial Ischemia, Arrhythmia, Bigeminy

General Disorders: Fever

Musculoskeletal, Connective Tissue and Bone Disorders: Myalgia

Nervous System Disorders: Dizziness

Psychiatric Disorders: Agitation

Respiratory, Thoracic, and Mediastinal Disorders: Hypoxia, Asthma, Dyspnea

Skin and Appendages: Pruritus

Vascular Disorders: Vasodilation, Hemorrhage

See **WARNINGS AND PRECAUTIONS** for information regarding pediatric use and malignant hyperthermia.

Abnormal Hematologic and Clinical Chemistry Findings

Transient elevations in glucose and white blood cell count may occur as with the use of other anesthetic agents. Abnormal liver function tests were observed in < 1% of patients. Hepatitis has been reported very rarely.

Post-Market Adverse Events

In addition to the treatment-emergent adverse events noted in clinical trials, the following adverse events have been reported in the post-marketing experience. These adverse events are listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity.

Blood and Lymphatic System Disorders: Coagulopathy

Metabolism and Nutrition Disorders: Hyperkalemia, Hypokalemia, Metabolic acidosis

Nervous System Disorders: Convulsion

Eye Disorders: Ocular icterus

Cardiac Disorders: Cardiac arrest, Torsade de pointes, Ventricular failure, Ventricular hypokinesia, Atrial fibrillation

Vascular Disorders: Malignant hypertension, Hemorrhage, Hypotension, Shock

Respiratory, Thoracic and Mediastinal Disorders: Respiratory arrest, Respiratory failure, Respiratory distress, Bronchospasm, Hemoptysis

Gastrointestinal Disorders: Pancreatitis acute, Abdominal pain

Hepatobiliary Disorders: Hepatic failure, Hepatic necrosis, Hepatitis, Cytolytic hepatitis, Cholestasis, Jaundice, Hepatic function abnormal, Liver disorder

Skin and Subcutaneous Tissue Disorder: Urticaria, Erythema

Musculoskeletal, Connective Tissue, and Bone Disorders: Rhabdomyolysis

General Disorders and Administration Site Conditions: Hyperthermia malignant, Asthenia, Malaise

Investigations: Electrocardiogram ST-T change, Electrocardiogram T wave inversion, Transaminases increased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood bilirubin increased, Coagulation test abnormal, Ammonia increased

Injury, Poisoning, and Procedural Complications: Agitation postoperative (see **WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics)**

Additional “Injury, Poisoning, and Procedural Complications” reactions due to accidental exposures

to non-patients: Dizziness, Migraine, Tachyarrhythmia, Palpitations, Eye burns, Blindness transient, Encephalopathy, Ulcerative keratitis, Ocular hyperemia, Visual acuity reduced, Eye irritation, Eye pain, Fatigue, Accidental exposure, Skin burning sensation, Drug administration error

Electrocardiogram QT Prolonged

SUPRANE (desflurane), like other inhalation anesthetic agents may cause QT prolongation. See **WARNINGS AND PRECAUTIONS**, **Cardiovascular**.

DRUG INTERACTIONS

Serious Drug Interactions

- In Patients with latent as well as overt muscular dystrophies, particularly Duchenne Muscular Dystrophy, concomitant use with succinylcholine is associated with hyperkalemia and cardiac arrhythmias (see **WARNINGS AND PRECAUTIONS**).

Overview

The minimum alveolar concentration (MAC) for desflurane is reduced by concomitant N_2O, intravenous fentanyl, or intravenous midazolam administration. Commonly used muscle relaxants are potentiated by desflurane.

Drug-Drug Interactions

Concentration of Other Gases: The MAC for desflurane is reduced by concomitant N_2O administration (see **DOSAGE AND ADMINISTRATION**, **Table 6**).

Neuromuscular Relaxants: SUPRANE (desflurane) potentiates the effect of depolarizing and nondepolarizing neuromuscular relaxants. During desflurane anesthesia, when compared to nitrous oxide/opioid anesthesia, the requirements for depolarizing and nondepolarizing agents are reduced by 30% and 50%, respectively. Anesthetic concentrations of desflurane at equilibrium reduce the ED95 of succinylcholine by approximately 30% and that of atracurium and pancuronium by approximately 50% compared to N_2O/opioid anesthesia. The doses of pancuronium, atracurium, suxamethonium and vecuronium needed to produce 95% depression in neuromuscular transmission (ED95) at different concentrations of desflurane are reported in Table 4. The ED95 of vecuronium is 14% lower with desflurane than isoflurane. Additionally, recovery from neuromuscular blockade is longer with desflurane than with isoflurane.

Table 4: Dosage (mg/kg) of Muscle Relaxant causing 95% Depression in Neuromuscular Transmission

Desflurane Concentration	Pancuronium	Atracurium	Suxamethonium	Vecuronium
0.65 MAC 60% N_2O/O_2	0.026	0.133	N/A	N/A
1.25 MAC 60% N_2O/O_2	0.018	0.119	N/A	N/A
1.25 MAC 100% O_2	0.022	0.120	0.360	0.019

N/A – No data available

Sedatives and Analgesics: Patients anesthetized with different concentrations of desflurane (administered as desflurane/Oxygen alone) who received increasing doses of intravenous fentanyl or intravenous midazolam showed a reduction in the anesthetic requirements or MAC. Results are reported in Table 5. It is possible that there will be a similar influence on MAC with other opioid and sedative drugs.

Table 5: Effect of Fentanyl or Midazolam on Desflurane MAC

Medication	*MAC (%)	%MAC Reduction
No Fentanyl	6.33 - 6.35	-
Fentanyl (3 mcg/kg)	3.12 - 3.46	46 - 51
Fentanyl (6 mcg/kg)	2.25 - 2.97	53 - 64
No Midazolam	5.85 - 6.86	-
Midazolam (25 mcg/kg) **	4.93	15.7
Midazolam (50 mcg/kg) **	4.88	16.6

* Includes values for ages 18 - 65 years

** Includes data for ages 31-65 years for Midazolam

Beta Blockers: Concomitant use of beta blockers may exaggerate the cardiovascular effects of inhalational anesthetics, including hypotension and negative inotropic effects.

Monoamine Oxidase Inhibitors (MAO): Concomitant use of MAO inhibitors and inhalational anesthetics may increase the risk of hemodynamic instability during surgery or medical procedures.

Other Drugs: The effects of SUPRANE (desflurane) on the disposition of other drugs has not been determined. No clinically significant adverse interactions with commonly used pre-anesthetic drugs, or drugs used during anesthesia (intravenous agents, and local anesthetic agents) were reported in clinical trials.

Inducers of CYP2E1: Therapeutic products and other agents that increase the activity of cytochrome P450 isoenzyme CYP2E1, such as isoniazid and alcohol, may increase the metabolism of desflurane and lead to significant increases in plasma fluoride concentrations. Moreover, CYP2E1 metabolic pathways may be involved in the rare hepatotoxic effects observed with halogenated anesthetics, therefore, a concomitant use of CYP2E1 inducers may potentiate this risk in susceptible patients.

Indirect-acting sympathomimetics: amphetamines and their derivatives, psychostimulants, appetite suppressants, ephedrine and its derivatives can increase the risk of peri-operative hypertension. In patients undergoing elective surgery, treatment should ideally be discontinued several days before surgery.

Drug-Lifestyle Interactions

There is no information on the effects of desflurane following anesthesia on the ability to operate an automobile or other heavy machinery. However, patients should be advised that the ability to perform such tasks may be impaired for at least 24 hours after general anesthesia.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Issues such as whether or not to premedicate and the choice of premedicant(s) must be individualized. In clinical trials, patients scheduled to be anaesthestized with desflurane frequently received i.v. pre-anesthetic medication, such as opioids and/or benzodiazepines.
- SUPRANE (desflurane) is potentiated by benzodiazepines and opioids (see **DRUG INTERACTIONS**).
- Nitrous oxide diminishes the inspired concentration of SUPRANE (desflurane) required to reach a desired level of anesthesia (see **DOSAGE AND ADMINISTRATION**, **Table 6**).
- SUPRANE (desflurane) decreases the required doses of neuromuscular blocking agents (see **Table 4**). If added relaxation is required, supplemental doses of muscle relaxants may be used. (See **DRUG INTERACTIONS**.)
- SUPRANE (desflurane) is not recommended for mask induction as it causes a high incidence of laryngospasm, coughing, secretions, breath holding, apnea, increase in secretions and oxyhemoglobin desaturation (see **ADVERSE REACTIONS**).

- After induction in adults with an intravenous drug such as thiopental or propofol, SUPRANE (desflurane) can be started at approximately 0.5-1 MAC, whether the carrier gas is O_2 or N_2O/O_2.
- No dosage adjustments are required in patients with renal and hepatic impairment. Hepatic dysfunction has been reported after SUPRANE (desflurane) use (see **ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings**).
- **Blood pressure and heart rate should be monitored carefully during maintenance as part of the evaluation of depth of anesthesia.**
- **In patients with coronary artery disease, maintenance of normal hemodynamics is important to avoid myocardial ischemia. SUPRANE (desflurane) should not be used as the sole anesthetic in patients with or at risk of coronary artery disease or in patients where increases in heart rate or blood pressure are undesirable. Rapid inhaled induction of anesthesia with SUPRANE (desflurane) alone, without concomitant administration of an opioid, in patients with coronary artery disease, has been associated with an increased incidence of myocardial ischemia. SUPRANE (desflurane), when given in conjunction with opioids for maintenance of anesthesia in patients with coronary artery disease, has not produced an incidence of ischemia different from that produced by other anesthetics. Thus, when SUPRANE (desflurane) is to be used in patients with coronary artery disease, it should always be used in combination with other medications, such as intravenous opioids or hypnotics, and it should not be used for induction (see ACTION AND CLINICAL PHARMACOLOGY).**

Recommended Dose and Dosage Adjustment

Adults: Surgical levels of anesthesia in adults may be maintained with concentrations of 2.5-8.5% SUPRANE (desflurane) with or without the concomitant use of nitrous oxide.

Pediatrics: SUPRANE (desflurane) should not be used for maintenance of anesthesia in non-intubated pediatric patients due to an increased incidence of respiratory adverse reactions, including coughing, laryngospasm and secretions, especially with removal of the laryngeal mask airway (LMA) under deep anesthesia in patients 6 years old or younger. The safety of SUPRANE (desflurane) has not been investigated in non-intubated pediatric patients younger than 2 years of age due to increased incidence of respiratory events observed in the 2 – 16 year age group.

Surgical anesthesia is maintained with concentrations of 5.2-10% SUPRANE (desflurane) in children with or without the concomitant use of nitrous oxide.

Geriatrics: Geriatric patients require approximately 70% the adult dose in 100% oxygen and approximately 40% the adult dose in 60% nitrous oxide.

During the maintenance of anesthesia with inflow rates of 2 L/min or more, the alveolar concentration of SUPRANE (desflurane) will usually be within 10% of the inspired concentration.

During the maintenance of anesthesia, increasing concentrations of SUPRANE (desflurane) produce dose-dependent decreases in blood pressure. Excessive decreases in blood pressure may be due to depth of anesthesia and in such instances may be corrected by decreasing the inspired concentration of SUPRANE (desflurane).

Concentrations of SUPRANE (desflurane) exceeding 1 MAC may increase heart rate. Thus with this drug, an increased heart rate may not serve reliably as a sign of inadequate anesthesia.

The MAC of desflurane decreases with increasing patient age. The dose of desflurane should be adjusted accordingly. Table 6 provides mean relative potency based on age in ASA physical status I and II patients.

Table 6 – Effect of Age on MAC of SUPRANE (desflurane) Mean ± SD (percent atmospheres)

AGE	N*	100% Oxygen	N*	60% Nitrous Oxide / 40% Oxygen
2 weeks	6	9.2 ± 0.0	-	-
10 weeks	5	9.4 ± 0.4	-	-
9 months	4	10.0 ± 0.7	5	7.5 ± 0.8
2 years	3	9.1 ± 0.6	-	-
3 years	-	-	5	6.4 ± 0.4
4 years	4	8.6 ± 0.6	-	-
7 years	5	8.1 ± 0.6	-	-
25 years	4	7.3 ± 0.0	4	4.0 ± 0.3
45 years	4	6.0 ± 0.3	6	2.8 ± 0.6
70 years	6	5.2 ± 0.6	6	1.7 ± 0.4

* N = number of cross over pairs (using up-and-down method of quantal response).

When changing the depth of anesthesia, rapid increases in the end-tidal concentration of SUPRANE (desflurane) should be avoided and the end-tidal concentration increased in small increments of 1% or less. It is not necessary to deliver concentrations of SUPRANE (desflurane) far in excess of the desired end-tidal concentration ("overpressurization" technique) due to the low blood and tissue solubilities of SUPRANE (desflurane) and the resulting rapid equilibrium of alveolar concentration with inspired and delivered concentrations; thus the transient and self-limiting increases in heart rate and blood pressure may be avoided.

During maintenance of anesthesia, increases in heart rate and blood pressure occurring after rapid incremental increases in end-tidal concentration of SUPRANE (desflurane) may not represent inadequate anesthesia. The changes due to sympathetic activation resolve in approximately 4 minutes. Increases in heart rate and blood pressure occurring before or in the absence of a rapid increase in SUPRANE (desflurane) concentration may be interpreted as light

anesthesia. Thus, in such patients, incremental increases of 0.5-1.0% end-tidal SUPRANE (desflurane) may attenuate these signs of light anesthesia, as may concomitant administration of analgesics. Should raised heart rate and blood pressure persist, then other causes should be sought.

Administration

SUPRANE (desflurane) is administered by inhalation. Deliver SUPRANE (desflurane) from a vaporizer specifically designed and designated for use with SUPRANE (desflurane). The administration of general anesthesia must be individualized based on the patient's response.

SUPRANE (desflurane) should only be administered by persons trained in the administration of general anesthesia using a vaporizer specifically designed and designated for use with desflurane.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre for the most current information.

Signs and Symptoms: Marked hypotension, tachycardia, apnea, deepening of anesthesia, cardiac and/or respiratory depression in spontaneously breathing patients, and cardiac depression in ventilated patients in whom hypercapnia and hypoxia may occur only at a late stage.

Treatment: Stop drug administration. Support respiration and circulation as required per standard clinical practice.

ACTION AND CLINICAL PHARMACOLOGY

Pharmacodynamics

Desflurane is a volatile inhalational anesthetic whose low solubility (blood/gas partition coefficient equals 0.42) permits rapid variation in anesthetic depth. If anesthesia is maintained with inflow rates of greater than 2 L/min, the alveolar concentration is usually within 10% of the inspired concentration. It is not necessary to deliver concentrations of desflurane far in excess of the desired end-tidal concentration ("overpressurization" technique) due to the low blood and tissue solubilities of desflurane and the resulting rapid equilibrium of alveolar concentration with inspired and delivered concentrations (see **WARNINGS AND PRECAUTIONS**).

Since awakening is rapid, care should be taken that appropriate analgesia has been administered to the patient at the end of the procedure or early in the post-anesthesia care unit.

MAC varies widely with age. In 45 year old patients, MAC is 6.0% in 100% oxygen and 2.8% in 60% nitrous oxide (see **Table 1**).

SUPRANE (desflurane) is not useful for mask induction as it causes an unacceptably high incidence of laryngospasm, coughing, secretions, breath holding and apnea (see **ADVERSE REACTIONS**).

Desflurane is a profound respiratory depressant, producing a progressive decrease in tidal volume and increase in arterial carbon dioxide tension. Apnea is common at concentrations above 1.5 MAC (Minimum Alveolar Concentration). This depression may be partly reversed by surgical stimulation. Nitrous oxide diminishes the inspired concentration of desflurane required to reach a desired level of anesthesia. (See **DOSAGE AND ADMINISTRATION**, **Table 6**.)

Desflurane potentiates the effect of depolarizing and nondepolarizing neuromuscular relaxants. When compared to nitrous oxide/opioid anesthesia, the requirements for depolarizing and nondepolarizing agents are reduced by 30% and 50%, respectively.

Desflurane, like other volatile anesthetics, induces malignant hyperthermia in genetically susceptible swine (see **WARNINGS AND PRECAUTIONS**).

Hemodynamic Effects

Cardiovascular Effects: In healthy male volunteers, desflurane produces a progressive decrease in blood pressure (15% at 1.2 MAC), due mainly to vasodilation, and an increase in heart rate (15% at 1.2 MAC) when administered in oxygen or 60% nitrous oxide during controlled ventilation at normocapnia. The cardiac output was unchanged at 1.7 MAC in oxygen, but decreased 20% at 1.2 MAC in 60% nitrous oxide. Similar changes were seen during spontaneous ventilation.

Effect on Sympathetic Activity: Constant or slowly increasing concentrations of desflurane blunt or block sympathetic responses to noxious stimuli. The increased heart rate response to hypotension is reduced in this setting. However, rapid changes to concentrations above 6%, as well as rapid changes above 6% can result in tachycardia and hypertension. The physiology of this response is unknown. In unpremedicated volunteers, desflurane can unpredictably induce transient (~ 4 minutes) increases in sympathetic activity, heart rate and blood pressure. The hemodynamic changes are more common at concentrations ≥ 6% and more severe with large (≥ 1%), sudden increments. A single clinical study of coronary artery bypass graft (CABG) patients showed similar effects (see **CLINICAL TRIALS**, Cardiovascular Surgery). This transient cardiovascular response can be blunted substantially by fentanyl (1.5 μg/kg), alfentantil (10 or 20 μg/kg), or clonidine 4 μg/kg as a premedication. Esmolol decreases the heart rate, but not blood pressure. The sympathetic stimulation is not obtunded by intravenous or endotracheal lidocaine or by intravenous propofol.

Desflurane does not alter the human myocardial arrhythmogenic threshold for epinephrine (approximately 7 μg/kg).

Pharmacokinetics

Desflurane is a volatile liquid inhalation anesthetic minimally biotransformed in the liver in humans. Less than 0.02% of the desflurane absorbed can be recovered as urinary metabolites (compared to 0.2% for isoflurane). Due to the volatile nature of desflurane in plasma samples, desflurane pharmacokinetics has been investigated using the *wash-in-wash-out* profile of desflurane as a surrogate of plasma pharmacokinetics. Eight healthy male volunteers first breathed 70% N_2O/30% O_2 for 30 minutes and then a mixture of desflurane 2.0%, isoflurane 0.4%, and halothane 0.2% for another 30 minutes. During this time, inspired and end-tidal concentrations (F_I and F_A) were measured. The F_A/F_I (*wash-in*) value at 30 minutes for desflurane was 0.91, compared to 1.00 for N_2O, 0.74 for isoflurane, and 0.58 for halothane. The *wash-in* rates for halothane and isoflurane were similar to literature values. The *wash-in* was faster for desflurane than for isoflurane and halothane at all time points. The F_A/F_{AO} (*wash-out*) value at 5 minutes was 0.12 for desflurane, 0.22 for isoflurane, and 0.25 for halothane. The *wash-out* for desflurane was more rapid than that for isoflurane and halothane at all elimination time points. By 5 days, the F_A/F_{AO} for desflurane is 1/20th of that for halothane or isoflurane.

Absorption: Desflurane is an anesthetic gas with a blood/gas partition coefficient of 0.424. As such it has the lowest blood/gas partition coefficient of the halogenated anesthetic agents. Its rate of absorption is primarily dependent upon and is governed by the mechanics of gas law and patient ventilation. In a crossover clinical study, desflurane demonstrated a faster wash-in and wash-out than either halothane or isoflurane.

Distribution: Inhalation anesthetics may alter the protein binding characteristics for some drugs, eg. diazepam. This may result in an increase in the free:protein bound ratio for these drugs, potentially affecting both their pharmacokinetics and pharmacodynamics, and enhancing their clinical effect.

Even poorly soluble, desflurane is widely distributed in the body. It partitions well into perfused tissues, muscles and to a lesser extent fat. Based on intermediate calculations done for the mammillary model presented in a study that compared the kinetics and metabolism of desflurane against isoflurane and halothane in volunteers, the volumes of these compartments are:

Vessel Rich Group	32 ± 10 L
Muscle Group	5.7 ± 1.6 L
4th Compartment	11 ± 3 L
Fat Group	2.1± 0.4 L

Metabolism: Approximately 0.02% of absorbed desflurane is metabolized. In normal volunteers, there was no increase in serum or urine fluoride concentrations. Studies in patients with chronic renal insufficiency and patients undergoing renal transplantation showed no effects on renal function.

Excretion: Desflurane is almost exclusively eliminated by transfer from the blood into the alveolar

gas in the lung and subsequent exhalation. Desflurane is minimally metabolized and a study of percutaneous transmission does not suggest that it accounts for a significant fraction of elimination.

Special Populations and Conditions

Pediatrics: In a clinical safety trial conducted in children aged 2 to 16 years (mean 7.4 years), following induction with another agent, SUPRANE (desflurane, USP) and isoflurane (in N_2O/O_2) were compared when delivered via face mask or laryngeal mask airway (LMA) for maintenance of anesthesia, after induction with intravenous propofol or inhaled sevoflurane, in order to assess the relative incidence of respiratory adverse events (see **ADVERSE REACTIONS**, **Table 3**).

SUPRANE (desflurane, USP) was associated with higher rates (compared with isoflurane) of coughing, laryngospasm and secretions with an overall rate of respiratory events of 39%. Of the pediatric patients exposed to desflurane, 5% experienced severe laryngospasm (associated with significant desaturation; *i.e.* SpO_2 of <90% for >15 seconds, or requiring succinylcholine), across all ages, 2-16 years old. Individual age group incidences of severe laryngospasm were 9% for 2-6 years old, 1% for 7-11 years old, and 1% for 12-16 years old. Removal of LMA under deep anesthesia (MAC range 0.6 – 2.3 with a mean of 1.12 MAC) was associated with a further increase in frequency of respiratory adverse events as compared to awake LMA removal or LMA removal under deep anesthesia with the comparator. The frequency and severity of non-respiratory adverse events were comparable between the two groups.

The incidence of respiratory events under these conditions was highest in children aged 2-6 years. Therefore, similar studies in children under the age of 2 years were not initiated.

See **WARNINGS AND PRECAUTIONS**, **Special Populations**, Pediatrics and **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment**, Pediatrics.

Geriatrics: The minimum alveolar concentration (MAC) of desflurane decreases with increasing patient age. The dose should be adjusted accordingly. The average MAC for desflurane in a 70 year old patient is two-thirds the MAC for a 20 year old patient.

Hepatic Insufficiency: Nine patients receiving desflurane were compared to eleven patients receiving isoflurane, all with chronic hepatic disease (viral hepatitis, alcoholic hepatitis, or cirrhosis). No differences in hematological or biochemical tests, including hepatic enzymes and hepatic function evaluation, were seen. Hepatic dysfunction has been reported after desflurane use. A causal relationship may or may not exist.

Renal Insufficiency: Concentrations of 1-4% desflurane in nitrous oxide/oxygen have been used in patients with chronic renal or hepatic impairment and during renal transplantation surgery.

Because of minimal metabolism, a need for dose adjustment in patients with renal and hepatic impairment is not to be expected.

Ten patients receiving desflurane (N=10) were compared to 10 patients receiving isoflurane, all with chronic renal insufficiency (serum creatinine 1.5-6.9 mg/dL). No differences in hematological or biochemical tests, including renal function evaluation, were seen between the two groups. Similarly, no differences were found in a comparison of patients receiving either desflurane (N=28) or isoflurane (N=30) undergoing renal transplant.

STORAGE AND STABILITY

Store at or below 30°C (86°F).

SPECIAL HANDLING INSTRUCTIONS

Emergency Overview: Concentrations of anesthetic in the air would have to reach approximately 2-3% before people would be expected to experience significant dizziness.

Principle routes of exposure include:

Skin contact – May cause skin irritation. In case of contact, immediately flush skin with plenty of water. Remove contaminated clothing and shoes. Seek medical attention if irritation develops.

Eye contact – May cause eye irritation. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Seek medical attention if irritation develops.

Ingestion – No specific hazards other than therapeutic effects. Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. If large quantities of this material are swallowed, seek medical attention immediately.

Inhalation – If individuals smell vapors, or experience dizziness or headaches, they should be moved to an area with fresh air. Individuals could also experience the following: Cardiovascular effects: may include fluctuations in heart rate, changes in blood pressure, chest pain. Respiratory effects: may include shortness of breath, bronchospasms, laryngospasms, respiratory depression. Gastrointestinal effects: may include nausea, upset stomach, loss of appetite. Nervous System effects: may include ataxia, tremor, disturbance of speech, lethargy, headache, dizziness, blurred vision.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SUPRANE (desflurane) is supplied in 250 mL amber glass bottles or 310 mL aluminum bottles, containing 240 mL desflurane at 100% v/v concentration.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

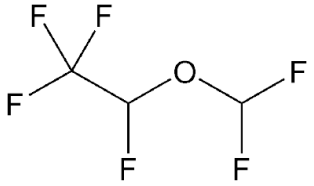
Drug Substance

Proper name: desflurane

Chemical name: (±)-2-Difluoromethyl 1,2,2,2-tetrafluoroethyl ether

Molecular formula and molecular mass: $C_3H_2F_6O$, 168.04

Structural formula:



Physicochemical properties: Desflurane is a non-flammable, colourless, volatile liquid

Partition coefficients at 37°C :

Blood/Gas	0.424
Olive Oil/Gas	18.7
Brain/Gas	0.54

Mean component/gas partition coefficients

Polypropylene (Y piece)	6.4
Polyethylene (circuit tube)	16.2
Latex rubber (bag)	19.3
Latex rubber (bellows)	10.4
Polyvinylchloride (endotracheal tube)	34.7

Vapour Pressure:

669 mm Hg @ 20°C
731 mm Hg @ 22°C
757 mm Hg @ 22.8°C
764 mm Hg @ 23°C
798 mm Hg @ 24°C
869 mm Hg @ 26°C

CLINICAL TRIALS

The safety and efficacy of SUPRANE (desflurane) have been established in large, multicentre clinical trials in adult outpatients (ASA I, II and III), in cardiovascular surgery (ASA II, III and IV) patients, in elderly (ASA II and III) patients and in pediatric (ASA I and II) patients.

Ambulatory Surgery

SUPRANE (desflurane) was compared to isoflurane in multicentre studies (21 sites) of 792 ASA physical status I, II or III patients aged 18-76 years (median 32). SUPRANE (desflurane) with or without nitrous oxide or other anaesthetics was generally well tolerated. Patients receiving SUPRANE (desflurane) emerged significantly faster than those receiving isoflurane, and there were no differences in the incidence of nausea and vomiting.

Cardiovascular Surgery

SUPRANE (desflurane) was compared to isoflurane, sufentanil or fentanyl for the anaesthetic management of CABG, abdominal aortic aneurysm, peripheral vascular and carotid endarterectomy surgery in 7 studies at 15 centres involving a total of 558 patients (ASA physical status II, III and IV).

Cardiac Studies

The effects of SUPRANE (desflurane) in patients undergoing CABG surgery were investigated in three studies.

Using echocardiography in addition to Holter monitoring to detect myocardial ischemia, one study compared SUPRANE (desflurane) with sufentanil in groups of 100 patients each. The opiod group received a small dose of thiopental, and sufentanil, 5-10 μg/kg followed by an infusion of 0.07 μg/kg/min, and no halogenated inhaled anaesthetic. The SUPRANE (desflurane) group received no opioid for induction of anaesthesia, and after intravenous thiopental had a rapid inhaled induction of anaesthesia with SUPRANE (desflurane) concentrations exceeding 10% end-tidal. The SUPRANE (desflurane) group had increases in heart rate (HR) and mean arterial pressure (MAP) during induction of anaesthesia and a 13% incidence of myocardial ischemia during induction of anaesthesia which was greater than the zero incidence during induction in the sufentanil group. During the precardiopulmonary bypass period, more SUPRANE (desflurane) patients required cardiovascular adjuvants to control hemodynamics than the sufentanil patients. During maintenance of anaesthesia, the sufentanil group had myocardial ischemia of greater duration and intensity than did the SUPRANE (desflurane) group. There were no differences in incidence of myocardial infarction or death between the two groups.

The second study compared SUPRANE (desflurane) with fentanyl in groups of 26 and 25 patients, respectively. The fentanyl group received 50 μg/kg and no halogenated inhaled anaesthetic. The SUPRANE (desflurane) group received fentanyl 10 μg/kg and a maximum SUPRANE (desflurane) concentration of 6%. The groups did not differ in the incidence of electrocardiographic changes suggestive of ischemia, myocardial infarction, or death.

In the third study, investigators compared SUPRANE (desflurane) with isoflurane in groups of 57 and 58 patients, respectively. Both groups were given up to 10 μg/kg fentanyl during induction of anaesthesia. The mean end-tidal anaesthetic concentrations prior to coronary bypass were 6% SUPRANE (desflurane) or 0.9% isoflurane. SUPRANE (desflurane) and isoflurane provided clinically acceptable anaesthesia prior to and after coronary bypass. A sub-analysis was performed for data

collected at one of the study centres. At this centre SUPRANE (desflurane) was administered to 21 patients and 20 patients received isoflurane. Both groups were given fentanyl 10 μg/kg; during induction of anaesthesia the maximum end-tidal anaesthetic concentrations were 6% SUPRANE (desflurane) or 1.4% isoflurane. The groups had similar incidences of ischemia (as detected by Holter monitoring), myocardial infarction, and death.

In the SUPRANE (desflurane) versus sufentanil study, investigators increased SUPRANE (desflurane) concentration rapidly to 10.2% end-tidal, without having administered any opioid, thereby increasing HR and MAP and observing a 13% incidence of myocardial ischemia in their patients with coronary artery disease. These rapid increases in SUPRANE (desflurane) concentration without pretreatment with an opioid, have been demonstrated to increase sympathetic activity, HR and MAP in volunteers. The other studies avoided these increases in HR and MAP by applying lower SUPRANE (desflurane) concentrations (less than 1 MAC), and by administering substantial doses of fentanyl (10 and 50 μg/kg) as part of the induction technique.

Peripheral Vascular Studies

Four randomized, open-label trials were conducted to assess the hemodynamic stability of patients administered SUPRANE (desflurane) versus isoflurane for maintenance anaesthesia in peripheral vascular surgeries. These studies are summarized below.

Type of Surgery	**Desflurane / O_2**		**Isoflurane / O_2**	
	# of pts.	**mean dose (%)**	**# of pts.**	**mean dose (%)**
Abdominal aorta	25	5.2	29	0.74
Peripheral vascular	24	2.9*	24	0.43*
Carotid endarterectomy	31	4.4	30	0.7
	15	6.1	15	0.65

*desflurane and isoflurane administered with 60% N_2O

In all patients, the volatile anaesthetics were supplemented with fentanyl. Blood pressure and heart rate were controlled by changes in concentrations of the volatile anaesthetics or opiods and cardiovascular drugs, if necessary. No differences were found in the cardiovascular outcome (death, myocardial infarction, ventricular tachycardia or fibrillation, heart failure) for desflurane and isoflurane in these studies.

SUPRANE (desflurane) should not be used as the sole anaesthetic in patients with or at risk of coronary artery disease or in patients where increases in the heart rate or blood pressure are undesirable (see WARNINGS AND PRECAUTIONS).

Geriatric Surgery

SUPRANE (desflurane) plus nitrous oxide was compared to isoflurane plus nitrous oxide in a multicentre study (6 sites) of 203 ASA physical status II or III elderly patients, aged 57-91 years (median 71). Heart rate and arterial blood pressure remained within 20% of preinduction baseline values during administration of SUPRANE (desflurane) 0.5-7.7% (average 3.6%) with 50-60% nitrous oxide. Maintenance and recovery cardiovascular measurements did not differ from those during isoflurane plus nitrous oxide administration, nor did the postoperative incidence of nausea and vomiting. The most common cardiovascular adverse event was hypotension for both isoflurane (6%) as well as SUPRANE (desflurane) (8%).

Neurosurgery

SUPRANE (desflurane) was studied in 38 patients aged 26-76 years (median 48 years), ASA physical status II or III undergoing neurosurgical procedures for intracranial lesions. Due to the limited number of patients studied, the safety of SUPRANE (desflurane) has not been established and is not recommended for use in neurosurgical procedures.

Pediatric Surgery

SUPRANE (desflurane) was compared to halothane, with or without nitrous oxide, in 235 patients aged 2 weeks to 12 years (median 2 years), ASA physical status I or II. The concentration of SUPRANE (desflurane) required for maintenance of anaesthesia is age dependent (see **DOSAGE AND ADMINISTRATION**, **Table 6**). Changes in blood pressure during maintenance of and recovery from anaesthesia were similar between SUPRANE (desflurane) N_2O/O_2 and halothane/N_2O/O_2. Heart rate during maintenance of anaesthesia was approximately 10 beats/min faster with SUPRANE (desflurane) than with halothane. There were no differences in the incidences of nausea and vomiting between SUPRANE (desflurane) and halothane.

DETAILED PHARMACOLOGY

Preclinical pharmacological investigations of desflurane indicate that it has a cardiorespiratory profile similar to that of isoflurane and, although it is not as potent in terms of inspired concentration, induction and recovery from anaesthesia are more rapid than with isoflurane.

1. Anaesthetic Activity

Potency was assessed as Loss of Righting (LOR) in 50% of mice, and as Minimum Alveolar Concentration (MAC) required to prevent gross purposeful movement in response to a noxious stimulus in rats, rabbits, dogs and pigs. Across all the species, isoflurane was four to five times more potent than desflurane. However, desflurane was an effective (100%) anaesthetic in all species tested. As with other anaesthetics, MAC decreased with decreasing body temperature. In rats, a 42% decrease accompanied a 10°C (38°C to 28°C) decrease in rectal temperature, but MAC returned to its original value when the animals became normothermic again. In contrast, MAC in normothermic rats

was unaffected by a duration of anaesthesia of up to 5 hours. MAC for desflurane is also reduced during pregnancy in rats. Time to onset of anaesthesia for desflurane and isoflurane at equi-efficacious concentrations in the rat and mouse appears similar for both anaesthetics; however, recovery was always more rapid for desflurane in all species. The low potency of desflurane is in accord with its low oil/gas solubility (18.7 vs. 97.8 for desflurane and isoflurane, respectively). Its low blood/gas solubility (0.42 vs. 1.4 for desflurane and isoflurane, respectively), accounts for rapid recovery from anaesthesia.

Desflurane (at 0.02, 0.03 and 0.04 mL/kg) was ineffective as an anaesthetic or an analgesic when given intravenously to rats.

2. Cardio-respiratory Effects

A. Spontaneously Breathing Animals

In both dogs and pigs, desflurane and isoflurane (1 MAC for 3 hours) produced similar changes in arterial pressure, heart rate, ECG, end-tidal pCO_2, respiratory rate and tidal volume.

B. Ventilated Animals

In both dogs and pigs, desflurane and isoflurane (1.25 – 2 MAC) produced dose-dependent decreases in arterial pressure, heart rate, cardiac output and dP/dt, (cardiac contractility) and increases in right atrial pressure and systemic vascular resistance. Compared to isoflurane, desflurane produced significantly greater decreases in dP/dt, mean arterial pressure, and significantly greater increases in right atrial pressure and hematocrit. Therefore, although desflurane and isoflurane appear to have similar haemodynamic profiles, the greater desflurane induced changes in dP/dt and mean arterial pressure may indicate that it has a greater cardiac depressive action than isoflurane, when examined under these experimental conditions. No cardiac arrhythmias were observed in either species with either drug.

In pigs, equi-MAC multiples of desflurane and isoflurane similarly caused dose-related decreases in mean arterial blood pressure, stroke volume, oxygen consumption, cardiac output, heart rate, left ventricular minute work, and increases in right- and left-heart filling pressures. For both anaesthetics, the plasma renin activity (PRA) and arginine-vasopressin (AVP) plasma concentrations varied directly with anaesthetic concentrations, and inversely with mean arterial pressure. Both anaesthetics were associated with increased AVP, but PRA was increased to a greater extent with desflurane than with isoflurane at 0.75 and 1.5 MAC. While these two agents similarly affect humoral mechanisms influencing blood pressure (large elevations of AVP and PRA during anaesthesia), arterial pressures remained below conscious levels.

In addition, studies were conducted to evaluate the potential for isoflurane or desflurane to produce 'coronary steal' (a shunting of blood from one region of the myocardium to another, in the absence of a change in perfusion pressure) in chronically instrumented dogs with critical coronary artery stenoses. Both desflurane and isoflurane caused dose-related decreases in arterial pressure and dP/dt and no change in heart rate or coronary blood flow in the constricted left coronary artery. Neither agent caused 'coronary steal'. In contrast, adenosine (a known dilator of coronary arterioles), did produce coronary steal in this preparation.

Desflurane (0.5 – 2.0 MAC) produced significant, dose-related decreases in arterial pressure, cerebral vascular resistance, cerebral O_2 consumption and systemic vascular resistance, and increases in cerebral blood flow in dogs. The highest dose of desflurane was associated with a significant decrease in cardiac output and cerebral blood flow. However, if arterial pressure was maintained with an infusion of phenylephrine, cerebral blood flow did not decrease. Heart rates were similar at all doses of desflurane tested. It was concluded that desflurane is a cerebral vasodilator similar to other volatile anaesthetics, and a cerebral metabolic depressant similar to isoflurane. These characteristics are consistent with those of agents which decrease $CMRO_2$ and may impart some degree of protection from cerebral ischemia.

3. Cardiorespiratory Safety

A. Spontaneously Breathing Animals

Both desflurane and isoflurane caused concentration dependent decreases in mean arterial pressure, pulse pressure, arterial pH, and increases in arterial and end-tidal pCO_2 in dogs. These two anaesthetics produced apneic episodes at similar MAC multiples. However, mean arterial pressure at apnea was significantly higher for desflurane than isoflurane. Atrial arrest, pulse pressure of less than 10 mm Hg, and abolition of the QRS complex are three different potentially lethal sequelae of large concentrations of anaesthetic, which may or may not occur independently of the others. The MAC multiple for atrial arrest, pulse pressure less than 10 mm Hg (pp < 10 mm Hg), and abolition of the QRS complex (no QRS) was significantly lower for isoflurane than for desflurane; the fatal-anaesthetic-to-MAC ratios of desflurane for pp<10 mm Hg and no QRS were significantly higher than those of isoflurane.

B. Ventilated Animals

Administration of increasing concentrations of desflurane or isoflurane to mechanically ventilated dogs and pigs caused concentration dependent decreases in mean arterial pressure and cardiac output. Heart rate changes were minimal or absent in both species. Species differences were evident between the anaesthetics with respect to the fatal anaesthetic concentrations. In dogs, there were no differences between the anaesthetics regarding the MAC multiple at which cardiac arrhythmias (i.e., no QRS or

heart block) developed, and death (pulse pressure <10 mm Hg) occurred, nor were differences evident between the fatal-anaesthetic-to-MAC ratios.

In ventilated pigs, both desflurane and isoflurane decreased mean blood pressure and cardiac output as a linear function of anaesthetic concentration. Values for these variables for isoflurane were greater than those for desflurane at concentrations exceeding 1.5 MAC. Fatal-Anaesthetic-Concentration-to-MAC ratio (FAR) was defined as the ratio of the concentration at which death occurred (lack of arterial pulse form) to MAC, and were determined to be 2.45 vs. 3.02 for desflurane and isoflurane, respectively. Therefore, in mechanically ventilated pigs, the margin of safety for desflurane was less than for isoflurane. However, cardiovascular collapse occurred at a higher concentration of desflurane than did inhibition of spontaneous respiration, indicating that death due to cardiovascular collapse is unlikely to occur in spontaneously breathing animals.

4. Electroencephalographic Changes

Electroencephalographic (EEG) changes were evaluated in normocapnic and hypocapnic pigs anaesthetized with 0.8, 1.2, and 1.6 MAC concentrations of desflurane and isoflurane. Four animals were also anaesthetized with 1.2 MAC of enflurane. At equipotent doses, desflurane and isoflurane caused similar changes in the EEG parameters (waveform amplitude and frequency). No EEG or gross motor seizures were observed. In contrast, all pigs exposed to enflurane exhibited both EEG and gross motor seizures during hypocapnia.

In dogs, increasing concentrations of desflurane initially produce EEG changes commonly associated with increasing depth of anaesthesia, i.e., decreasing frequency and increasing amplitude progressing to burst suppression. However, at 2 MAC, periodic poly-spiking appeared after about 20 minutes of exposure. These changes did not occur in pigs when desflurane was administered at levels sufficient to produce significant (1.5 MAC) or complete (1.7 MAC) suppression of EEG.

5. Drug Interactions

A. Cardiovascular Effects of Epinephrine

Following anaesthesia with either desflurane, isoflurane, or halothane (0.7 – 1.2 MAC) graded infusions of epinephrine (0.2 - 4.0 μg/kg/min) were instituted until premature ventricular contractions (PVCs) were observed in chronically instrumented pigs. Epinephrine infusions increased mean aortic blood pressure similarly during all the anaesthetics. However, at the highest MAC multiple for all the anaesthetics, significantly higher blood pressure was observed during halothane than was observed during either isoflurane or desflurane. At all rates of infusion, heart rate was lower during halothane than during the other agents. The rates of epinephrine infusion that produced PVCs were similar during desflurane and isoflurane, but these rates were significantly greater than those required to trigger arrhythmias during halothane.

B. Cardiovascular Effects with Anaesthetic Adjuvants

The cardiovascular effects of desflurane and isoflurane in combination with agents commonly used in anaesthetic practice were evaluated in ventilated pigs. No significant cardiovascular effects were produced by the co-administration of succinylcholine, edrophonium plus atropine, or fentanyl. Atracurium caused a small increase in the stroke volume of animals anaesthetized with isoflurane, but it had no effect on those exposed to desflurane. Nitrous oxide produced no cardiovascular changes when added to desflurane. However, the addition of nitrous oxide to isoflurane caused a significant increase in systemic vascular resistance, and decreases in stroke volume and cardiac output. Thiopental in combination with both anaesthetics caused significant changes in stroke volume and cardiac output, and it lowered aortic blood pressure in animals exposed to desflurane.

C. EEG Effects with Anaesthetic Adjuvants

The electroencephalographic (EEG) effects of desflurane and isoflurane (1.2 MAC) in combination with several adjuvant drugs (fentanyl, naloxone, succinylcholine, nitrous oxide, thiopental, edrophonium, atracurium, and atropine) were evaluated in ventilated pigs. Neither cerebral irritability nor epileptogenicity were observed at any time. Both thiopental and fentanyl increased cerebral depression (as indicated by increased burst suppression and decreased burst-compensated spectral edge frequency), but in the case of fentanyl this was only significant during anaesthesia with desflurane. Fentanyl-induced cerebral depression was reversible with naloxone; thiopental-induced cerebral depression was not. There were no differences between the EEG responses produced by: succinylcholine, nitrous oxide, edrophonium, or atropine during isoflurane or desflurane anaesthesia.

6. Malignant Hyperthermia

Pigs bred to be susceptible to malignant hyperthermia (MH) were confirmed for this susceptibility by exposure to halothane. Responders were subsequently exposed to one and two MAC concentrations of desflurane. Normal pigs responded to desflurane, with only a decrease in arterial pressure and heart rate. By contrast, two MH-susceptible animals developed unequivocal symptoms of MH (elevated end-tidal CO_2, increased $PaCO_2$, decreased blood pH, and a rising core temperature), two had equivocal symptoms and two did not respond.

TOXICOLOGY

Acute Toxicity

1. Rodent Studies

Acute inhalation exposure of mice (Crl:CD-1[ICR]BR strain) and rats (Crl:CD[SD]BR strain) to concentrations of desflurane were conducted using a head-only exposure chamber. Animals were

held in place in plastic restraint tubes which were equipped with warming coils through which flowed water, thermostatically controlled to about body temperature. Groups of ten animals (five male, five female) were exposed to desflurane at single chamber concentrations ranging from 10.0 to 15.0% v/v in mice and 13.0 to 20.0% v/v in rats. Groups of ten animals (five male, five female) exposed under similar conditions to an atmosphere of oxygen, served as control groups. Survivors of the 4 hour exposure period were observed for 14 days.

All groups became anaesthetized during desflurane exposure. Post exposure clinical signs common to both species included ataxia, shallow respiration/laboured breathing, unconsciousness/prostration, piloerection and wet fur/fur staining. Some signs are consistent with recovery from anaesthesia while others are commonly seen in animals held in plastic restraint tubes during exposure. These signs regressed rapidly post exposure in the survivors.

Species	**LC_{50} % v/v (95% Confidence Limits)**
Mice	
Male	13.8*
Female	12.5 (11.5 – 15.0)
Rat	
Male	15.9 (14.0 – 19.5)
Female	15.4*

*Data do not establish the existence of a linear probit relationship at the 5% significance level; therefore 95% confidence limits cannot be calculated.

Most deaths occurred during exposure or shortly thereafter. The most frequent observations during macroscopic examination of major tissues and organs of animals that died were red or dark lungs (mice and rats) and dark liver (rats). These findings were considered to be non-specific congestion associated with cardiopulmonary failure during exposure. There were no treatment-related findings in animals surviving to study termination.

2. Cardiovascular Safety – Dogs and Swine

The cardiovascular safety and actions of high concentrations of desflurane and isoflurane were examined in beagle dogs and swine (Landrace crossbreed).

Anaesthesia was included by face mask administration of desflurane or isoflurane in oxygen, and tracheal intubation was performed. Body temperature was maintained at or near the awake value and animals were mechanically ventilated with frequency adjusted to maintain normocapnia (except for studies in beagle dogs, where spontaneous respiration was allowed, in order to examine the onset of anaesthetic-induced apnea). Animals were initially equilibrated at approximately 1.0 MAC. Measurements of cardiovascular parameters were made after maintaining a stable end-tidal

anaesthetic concentration for 15 minutes. Anaesthetic concentration was then increased by 0.25 (dogs) or 0.35 – 0.4 MAC (swine), and after 15 minutes of stable end-tidal concentration, cardiovascular measurements were repeated. This process was repeated until the animal died.

As anaesthetic concentrations were increased during mechanical ventilation in both species, cardiovascular parameters (blood pressure, heart rate, cardiac output, right atrial, pulmonary artery pressure and arterial pulmonary wedge pressure) progressively declined. Both desflurane and isoflurane produced a dose-dependent decrease in mean arterial pressure. In swine, cardiac output and blood pressure decreased as a linear function of end-tidal anaesthetic concentration.

Studies in spontaneously breathing dogs demonstrated that increasing the concentrations of either isoflurane or desflurane produce a decrease in arterial pressure and arterial pH as well as increases in arterial and end-tidal pCO_2. Minimal changes in heart rate were observed prior to apnea. There was no significant difference in the relative MAC levels of the two agents at which apnea occurred (2.38 ± .07 and 2.50 ± .10 MAC for desflurane and isoflurane, respectively). At apnea there were no differences for arterial pCO_2 or heart rate between the anaesthetics; however, the mean arterial pressure was significantly greater during desflurane than during isoflurane.

Arterial pCO_2 levels and arterial pH remained at normal levels until pulse pressure fell below 10 mm Hg in dogs. Mixed venous pO_2 and the ratio of oxygen transport to oxygen consumption did not decrease below those observed in conscious swine until end-tidal desflurane reached 2.0 MAC or isoflurane reached 2.4 MAC. At these and greater concentrations, values for these variables declined sharply.

Fatal Concentrations of Desflurane and Isoflurane in Ventilated Dogs and Swine

Species/ Anaesthetic	MAC (% v/v)	Fatal Concentration (% v/v)	FAR*
Dog			
Desflurane	7.20 (0.41)	19.35 (0.86)	2.69 (0.12)
Isoflurane	1.41 (0.04)	3.35 (0.10)	2.38 (0.07)
Swine			
Desflurane	9.80 (0.30)	23.90 (0.06)	2.45 (0.11)
Isoflurane	2.07 (0.08)	6.22 (0.23)	3.02 (0.13)

Values represent Mean (S.E.M.)

*Fatal anaesthetic concentration-to-MAC ratio.

Fatality in spontaneously breathing dogs and swine as a function of anaesthetic concentration was closely comparable for desflurane and isoflurane. Anaesthetic-induced cardiovascular collapse (death) was defined as pulse pressure below 10 mm Hg in dogs and lack of pulsatile pressure in swine. Fatal anaesthetic concentration-to-MAC ratios (%v/v = in O_2) for desflurane and isoflurane were similar within and between species, in spontaneously breathing animals.

Subchronic Toxicology

1. Eight Week Subchronic Inhalation Toxicity Study in Rats

Two eight week rat (Crl:CD[SD]BR strain) subchronic inhalation toxicity studies were conducted. The initial study utilized five treatment groups (10 animals/sex/group) including the: Oxygen Control exposure, isoflurane Control exposure and desflurane Low exposure, desflurane Mid exposure and desflurane High exposure groups. Test agent exposure concentrations, 1.38 and 5.6% (v/v), represent 1.0 MAC (Minimum Alveolar Concentration) of isoflurane and desflurane, respectively. Cumulative exposures were 72 MAC-hours for the isoflurane Control and desflurane High dose groups, 36 MAC-hours for the desflurane Mid dose group and 12 MAC-hours for the desflurane Low dose group.

Due to a system malfunction and acute overexposure during week 7 of study which resulted in the mortality of a significant number of desflurane High dose animals, a second rat subchronic study which utilized two treatment groups (10 animals/sex/group) was initiated. The two groups were: 1) an oxygen Control group; 2) a desflurane High dose group (72 MAC-hours cumulative exposure). No mortalities occurred in this study. Mortalities in the initial study consisted of one desflurane High dose animal which died due to a restraint tube-related asphyxiation, one desflurane Mid dose animal which died but showed no notable necropsy findings and six desflurane High dose animals that died resulting from system malfunction and acute overexposure.

There was no treatment-related effect on body weight gain after repeated anaesthetic exposure; however, reduced food consumption was noted in several groups and appeared to be due to the physical restraint and increased handling rather than a response to anaesthetic treatment.

Blood and urine samples, collected periodically during the study, did not demonstrate treatment-related findings for haematology, clinical chemistry or urinalysis investigations. No adverse ophthalmic changes were observed at study termination.

Group mean testes and epididymal weights were significantly reduced in the isoflurane Control and the desflurane Mid and High exposure groups and were associated with microscopic changes ranging from minimal loss of spermatocytes to spermatogenic arrest. The sharply focal and unilateral occurrence of these changes and the known sensitivity of the rat testes to cyclic temperature changes suggest that this was not a treatment-related effect. Similar changes in the oxygen control rats which did not receive external heating suggest that prolonged restraint also produces pressure and temperature changes. No other organ weight or microscopic changes were noted.

2. 8 Week Subchronic Inhalation Toxicity Study in Dogs

Groups of five beagle dogs per sex were allocated to five treatment groups and exposed three times/week for eight consecutive weeks to the appropriate test atmosphere.

Treatment Group	Test Agent Exposure Concentrations (% v/v)	MAC* Level	Exposure (hours/day)
Oxygen Control	0	0	2.5
Isoflurane-Low	1.7	1.2	2.5
Isoflurane-High	2.3	1.6	1.9
Desflurane-Low	9.9	1.2	2.5
Desflurane-High	13.2	1.6	1.9

*Minimum Alveolar Concentration

Under this exposure regimen, all anaesthetized groups received a minimum of 72 MAC-hours of anaesthetic exposure and animals in the oxygen control group received a minimum of 60 hours of exposure to oxygen.

Anaesthesia with desflurane or isoflurane was induced by nose cone, a tracheal tube was inserted and the animal was transferred to its anaesthesia station. Mechanical ventilation was used and minute volume was adjusted to maintain expired pCO_2 between 4 and 6%. Rectal temperature was recorded and body temperature maintained between 37-39°C during the exposure with a water heated thermal blanket. Oxygen control exposures were conducted in a 4.5 m^3 (Hinner's style) chamber. Animals were exposed (whole body) to an atmosphere of 95% oxygen for 2.5 hours on exposure days.

There was no morbidity or mortalities. All animals survived until scheduled necropsy. Animals recovered uneventfully from each anaesthesia exposure. Occasional emesis, loose stool, and diarrhea were noted during the study. No clinical significance is attributed to the loose stool or diarrhea observations. Emesis occurred primarily after feeding and not in relation to anaesthetic exposure.

No toxicologically meaningful changes in body weights were observed during the study. Ophthalmic examinations performed prior to study initiation and during the eighth week of study found no toxicologic effect of treatment. Haematology, clinical chemistry and urinalysis results collected during weeks 1, 4 and 8 of study showed no effects which were interpreted as related to either desflurane or isoflurane exposure.

Statistically significant differences between absolute or relative organ weight means of either desflurane or isoflurane exposed dogs, compared to oxygen Controls, were rare or inconsistent. Therefore, it was concluded that neither desflurane nor isoflurane had any effect on organ or final body weights.

No changes interpreted as related to either desflurane or isoflurane exposures were found during gross or microscopic evaluation. Mucosal plaques overlying laryngeal cartilages and focal or multifocal

areas of chronic tracheal irritation were found in several dogs exposed to isoflurane and desflurane. These reactions were considered to be a typical response to chronic epithelial injury secondary to tracheal intubation.

Reproductive Toxicology

1. Fertility and General Reproductive Performance in Rats

Groups of 50 Crl:CD VAF/Plus rats (15 study, 5 spare males and 30 females) were randomly assigned to one control and three treatment groups. The F_0 males were exposed for 63 days prior to mating. Exposure of the F_0 females initiated 14 days prior to mating and was continued until the day prior to sacrifice with the exception of the period from gestation day 21 through lactation day 4 in order to prevent parturition in the exposure chamber. The F_1 offspring, though exposed to desflurane in utero and through nursing as neonates, were otherwise untreated.

The desflurane Low, Mid and High exposure groups received daily 1 MAC (Minimum Alveolar Concentration) anaesthetic exposures of desflurane for 0.5, 1 and 4 hours/day, respectively. The control group was exposed to identical chamber conditions (60% oxygen) as were treated groups; however, test agent was not added.

All animals exposed to desflurane were anaesthetized within a few minutes of initiation of exposure and throughout the exposure period. Parental survival in the control group was 100%. Parental survival and body weight were adversely affected by treatment in a dose-related manner at all three exposure levels.

Estrous cycle observations, the copulatory index, the mean copulatory intervals and the mean gestation lengths for the F_0 treated animals were comparable to those of the Control group animals. A statistically significant increase in men postimplantation loss, and correspondingly, a decrease in the mean number of viable embryos were observed in the High exposure litters in comparison to the Control group at gestation day 13 uterine examinations. No adverse effects on the mean numbers of implantations or corpora lutea were present at the High exposure level. Slight reductions in the F_0 male and female fertility and the F_0 female pregnancy indices relative to Control were noted at the High exposure level. A reduced mean number of live pups at lactation day 0 was observed in the High exposure group; however, offspring survival indices through lactation day 21 were comparable to Control values. Significantly decreased mean pup weights relative to the Control group were noted for the High exposure group throughout lactation. No adverse effects were noted for these experimental endpoints in the Mid and Low desflurane exposure groups.

2. Developmental Toxicity Study in Rats

Groups of 25 mated female Crl:CD VAF/Plus rats were randomly assigned to one control and three treatment groups. Gravid females were exposed from days 6 through 15 of gestation.

The desflurane Low, Mid and High exposure groups received daily 1 MAC (Minimum Alveolar Concentration) anaesthetic exposure of desflurane for 0.5, 1 and 4 hours/day, respectively. The control group was exposed to identical chamber conditions (60% oxygen) as were treated groups; however, test agent was not added.

All animals exposed to desflurane were anaesthetized within a few minutes of initiation of exposure and throughout the exposure period. Other than one animal in the desflurane Mid exposure group which died on gestation day 6, survival was 100% for the Control and treatment groups. Significantly reduced maternal body weight gains were noted for the overall treatment and gestation periods for the desflurane High exposure group compared to the Control group. Maternal body weight gains for the desflurane Low and Mid exposure groups were comparable to the Control group.

Dams in the desflurane High exposure group had an increased postimplantation loss compared to animals in the Control group, thus resulting in a significant decrease in the number of viable fetuses per dam in this group.

In addition, a single dam of this group had resorptions only. Both male and female fetal body weights were significantly decreased in the desflurane High exposure group while only male fetal body weights were significantly decreased in the desflurane Mid exposure group.

All other Caesarean section parameters for the remaining exposure groups were comparable to control values. No teratogenic effect was noted among any of the treatment groups.

3. Developmental Toxicity Study in New Zealand White Rabbits

Groups of 16 inseminated New Zealand White SPF rabbits were randomly assigned to 2 control (Ambient and Chamber controls) and 3 treatment groups. Gravid females were exposed from days 6 through 18 of gestation.

The desflurane Low, Mid and High exposure groups received daily 1 MAC (Minimum Alveolar Concentration) anaesthetic exposures for 0.5, 1 and 3 hours/day respectively. The Chamber Control group was exposed to identical chamber conditions (60% oxygen) as were treated groups; however, test agent was not added. The Ambient Control group was transported to the chamber exposure room but remained in their normal colony room cages, thus providing a control for possible handling and chamber related stress.

All animals exposed to desflurane were anaesthetized within a few minutes of initiation of exposure and throughout the exposure period. One animal in the Chamber Control group died due to stomach erosions. All other animals for the remaining Control and treatment groups survived. Animals in the High exposure group had maternal weight loss for the overall exposure period (gestation day 6 to 19) due to losses incurred immediately after treatment initiation (gestation day 6-12 treatment subinterval). Animals in the remaining treatment groups and in the Chamber Control group displayed weight loss or inhibited gains during gestation; however, when compared to the Ambient Control

group these weight differences were not marked and were considered to reflect the stress induced by the chamber environment.

Although the change did not attain statistical significance, a slight decrease in the number of viable fetuses per litter at the High exposure level may have resulted from treatment. Whole litter resorptions (2 per group) in the Chamber Control and each treatment group and increased postimplantation losses compared to Ambient Control in the Chamber Control and the High exposure groups were considered to reflect the effects of the chamber environment rather than effects caused by treatment. No teratogenic effect was observed among any of the exposed groups.

4. Perinatal and Postnatal Study in Rats

Groups of 25 mated female Crl:CD VAF/Plus rats were randomly assigned to 1 control and 3 treatment groups. Gravid females were exposed from gestation day 15 through lactation day 21.

The desflurane Low, Mid and High exposure groups received daily 1 MAC (Minimum Alveolar Concentration) anaesthetic exposures of desflurane for 0.5, 1 and 4 hours/day, respectively. The Control group was exposed to identical chamber conditions (60% oxygen) as were treated groups; however, test agent was not added.

All animals exposed to desflurane were anaesthetized within a few minutes of initiation of exposure and throughout the exposure period. Survival was 100% for animals in the Control, desflurane Low and desflurane Mid exposure groups. Four mortalities occurred during exposures in the desflurane High exposure group. Significantly reduced maternal body weight gains were found for the desflurane High exposure group during the gestation day 15-20 treatment subinterval. This inhibited weight gain continued through lactation day 7 and was considered a result of treatment. Decreased weight gains were also noted for animals of the desflurane Low and Mid exposure groups; however, the lack of dose-response relationship in these groups suggests that they were not a result of treatment.

Pup survival in all treated groups were comparable to the control group throughout lactation. Pup observations during lactation were comparable between the Control and treatment groups with the exception of pup size where significantly lower weight resulting from treatment were noted throughout lactation for desflurane High exposure group pups compared to Control pups. Pup body weights in the remaining desflurane treatment groups were comparable to the Control group. There were no malformations or developmental variations observed which were associated with desflurane treatment.

5. Perinatal Developmental Toxicity Studies

Studies in rodents demonstrate that the use of anesthetic agents during the period of rapid brain growth or synaptogenesis results in widespread neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis. Based on comparisons

across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

In primates, three hours exposure to an anesthetic regimen that produced a light surgical plane of anesthesia did not increase neuronal cell loss; however, treatment regimens of five hours or longer increased neuronal cell loss.

Data in rodents and in primates suggest that the neuronal and oligodendrocyte cell losses are associated with subtle but prolonged cognitive deficits in learning and memory. (see WARNINGS AND PRECAUTIONS, Special Populations).

Genotoxicity Studies

1. In Vitro Genotoxicity Studies

A four test mutagenicity battery was utilized to test the potential of desflurane to cause gene mutations or chromosomal damage. The three test performed were: Bacterial Reverse Gene Mutation Assay (Ames Test), Chinese Hamster Ovary Mutation Assay, Human Lymphocyte Metaphase Chromosomal Analysis and Mouse Micronucleus Test. No evidence of mutagenicity or clastogenicity was found.

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PART III: CONSUMER INFORMATION

[Pr] SUPRANE
(desflurane, USP) **100% v/v**
Liquid for Inhalation

This leaflet is part III of a three-part "Product Monograph" published when SUPRANE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SUPRANE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
SUPRANE is an inhaled general anesthetic used during surgery.

What it does:
SUPRANE maintains unconsciousness, muscle relaxation, and loss of sensation over the entire body while surgery is being performed.

When it should not be used:
- If you have been told that you are allergic to desflurane or other inhaled general anesthetics, or components of the container.
- If you have a history of liver inflammation (hepatitis) due to the use of an inhaled general anesthetic, or have experienced unexplained liver problems (for example jaundice with fever) after a previous use of an inhaled general anesthetic.
- If you or any member of your family has experienced a condition called malignant hyperthermia (a genetic disorder that causes rapid raise in body temperature) during an operation.

What the medicinal ingredient is:
Desflurane, USP.

What the important nonmedicinal ingredients are:
The finished product is composed solely of the active ingredient, desflurane, USP.

What dosage forms it comes in:
SUPRANE is available as a volatile liquid that is 100% v/v in concentration.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- SUPRANE should only be administered by qualified individuals trained in general anesthesia in an adequately equipped facility;
- SUPRANE may trigger a rise in blood potassium or body temperature. You may experience stiff muscles, changes in blood pressure, rapid breathing, a bluish colour to lips or fingers, rapid or irregular heart rate. Trained health care professionals will take care of you if this happens.

You should talk to your anaesthesia professional prior to surgery if you are aware of any of the following conditions:

- If you have been told that you are allergic to desflurane or other inhaled general anesthetics, or components of the container.
- You are pregnant or could be pregnant.
- You are breast-feeding.
- You are taking or have recently taken any other medicines, even those not prescribed.
- You have previously had general anesthesia, particularly if repeated over a short period of time.
- You are suffering from any illness, other than those connected with your operation, such as diabetes, severe headaches, cancer, problems with your nerves or muscles (especially muscular dystrophy), nausea or vomiting.
- You or a member of your family suffers from malignant hyperthermia (a genetic disorder that causes rapid raise in body temperature).
- You suffer from a heart, liver, or kidney problem.
- If your child who needs anesthetics has asthma or has recently had an upper respiratory (airway) infection.

Recovery of consciousness following SUPRANE administration generally occurs within minutes. As with other anesthetics, small changes in moods may persist for several days following administration.

Performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anesthesia. Do not drive a motor vehicle or operate hazardous machinery for at least 24 hours after having a general anesthetic.

INTERACTIONS WITH THIS MEDICATION

Serious Drug Interactions

- Tell your healthcare professional if you have muscular diseases (especially muscular dystrophy), and:
  - You are taking potassium, and/or
  - You have heart problems, especially irregular heart beats

Tell your doctor, nurse or pharmacist about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drugs that may interact with SUPRANE include:

Other anesthetics, tranquillizers (e.g. benzodiazepines) and narcotics (e.g. opioids), nitrous oxide gas, muscle relaxants (e.g. pancuronium), beta blockers (e.g. to treat high blood pressure), Monoamine Oxidase Inhibitors (MAO) inhibitors (e.g. to treat depression) and indirect-acting sympathomimetics (e.g. amphetamines, stimulants and appetite suppressants).

PROPER USE OF THIS MEDICATION

Usual dose:
Your anesthetist will decide what dose of SUPRANE you will receive. The dose will vary depending on your age, weight, and the type of operation that you are having.

You will receive another anesthetic to make you go to sleep before receiving SUPRANE by inhalation.

Overdose:
This will be handled by the anesthetist.

In case of drug overdose (especially if you have accidentally come in contact with SUPRANE on your skin, in your eyes, by swallowing it or by breathing it in), contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects include headache, cough, nausea, vomiting, and excessive production of saliva.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

After exposure to SUPRANE, you should contact your physician or anesthesia professional if you have any of the following reactions:

Agitation

Difficulty breathing/choking/shortness of breath, wheezing

Decreased oxygen in your blood: shortness of breath, bluish colour to lips or fingers.

Elevated Rise in Blood Glucose, if measured

Heart Attack

High or low Blood Pressure

Bleeding

Slow, rapid or irregular Heartbeat

Dizziness

Jaundice: yellow colour to skin and eyes, dark urine

Mild to Severe Allergic reactions

Rash, hives, severe itching

Severe muscle pain or sore throat

Sudden fever with stiffness, pain and weakness in your muscles

This is not a complete list of side effects. For any unexpected effects while taking SUPRANE, contact your doctor or pharmacist.

HOW TO STORE IT

SUPRANE should only be administered in an adequately equipped facility. SUPRANE must be kept out of reach and sight of children. It is stored at or below 30°C (86°F).

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Baxter Corporation, at 1-888-719-9955.

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